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Effective Strategy of the Combination of High-Intensity Focused Ultrasound and Transarterial Chemoembolization for Improving Outcome of Unresectable and Metastatic Hepatoblastoma: a Retrospective Cohort Study[1]

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Abstract

The combination of high-intensity focused ultrasound (HIFU) and transarterial chemoembolization (TACE) has been experimentally performed in a variety of malignant tumors, and its validity has not yet been evaluated for hepatoblastoma (HB). We evaluated the disease-response rate, resection rate, and toxicity in children with unresectable or metastatic HB (stage III and stage IV HB) after sequential treatment with TACE plus HIFU in a controlled clinical trial. The 35 patients with unresectable or metastatic HB were nonrandomly assigned to HIFU ablation ($n = 12$) or C5V chemotherapy ($n = 23$). The rates of complete resection, tumor response, and treatment toxicity were evaluated for both regimens. Nine patients who received C5V and 10 patients who received TACE plus HIFU became operable ($P = .02$). The 3-year event-free survival and overall survival rates were 43.03% and 56.68% in the C5V group and 38.57% and 57.86% in the TACE plus HIFU group, respectively. Acute grade 3 or 4 adverse events, including neutropenia, thrombocytopenia, and anemia, were more frequent in patients treated with C5V therapy than in patients receiving TACE plus HIFU. HIFU ablation achieved a higher rate of complete resection and a lower rate of severe complications compared with C5V treatment in children with advanced HB (Chinese Clinical Trials Registry No. ChiCTR-PRCH-08000182).

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Introduction

Hepatoblastoma (HB) is the most common pediatric primary liver malignancy. The curative therapy for HB requires surgical resection. However, only half of newly diagnosed patients can be treated with surgery at initial presentation [1,2]. Metastatic and unresectable disease at diagnosis portends an extremely poor prognosis, and patients rarely achieve long-term survival with chemotherapy and aggressive surgical resection of all tumor sites [3,4]. Several clinical trials have shown that systemic chemotherapy effectively improves response and survival of patients with unresectable and metastatic HB by reducing the incidence of local recurrence and ultimately increasing tumor resectability [5,6]. However, systemic therapy increases toxicity, and systemic chemotherapy regimens must be stopped due to adverse events such as neutropenia and nephrotoxicity [7,8]. Previous studies have shown that the event-free survival (EFS) of patients with unresectable disease remains

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unsatisfactory at approximately 50%. The survival of patients with metastatic disease is also unsatisfactory [9,10], and the relative resistance of this neoplasm to present therapeutic regimens suggests that new treatment approaches are required. It is possible that the current strategy of treatment must be redesigned.

High-intensity focused ultrasound (HIFU) is an extracorporeal method used to treat primary solid tumors and metastatic disease [11–13]. Compared with conventional therapies, HIFU significantly reduces local, regional, and systemic side effects and provides additional therapeutic options in cases when conventional therapies fail [14,15]. Extracorporeal Magnetic Resonance (MR)-guided HIFU devices have been approved by the Food and Drug Administration (FDA) in the United States for the clinical treatment of uterine fibroids, and ultrasound-guided HIFU devices have also been used in Europe to treat both benign and malignant tumors after obtaining Conformite Europeenne (CE) approval [16,17].

Transarterial chemoembolization (TACE) is a widely used treatment for patients with large-volume solid tumors. TACE is usually used in combination with ablative therapies to exterminate residual tumor cells [18]. HIFU combined with TACE has been used empirically for many years, and a small number of retrospective, uncontrolled reports suggest benefits of this therapy [19]. We previously performed HIFU combined with TACE to treat unresectable disease, including HB, at our institute [19]. In the current study, chemotherapy and TACE plus HIFU regimens were nonrandomly compared in patients with stage III and stage IV HB. Herein, we report the clinical features, tumor response, adverse events, and treatment outcomes for a cohort of patients from our institute with advanced pediatric HB treated by these regimens.

Materials and Methods

Patients

From August 2006 to November 2011, there are 45 children with stage III and stage IV HB diagnosed in our institute. The patients were eligible for study inclusion if they were younger than 5 years old at diagnosis and had biopsy-proven HB that was either unresectable or metastatic at presentation and previously untreated. Among them, 10 cases were excluded because of lost to follow-up and more than 5 years old. The remaining 35 cases were included in this study. The TACE plus HIFU ablation in our institute was initiated in March 2009, and 12 patients received HIFU and TACE treatment protocols. For chemotherapy, 23 patients were included from August 2006 to November 2011. A determination of serum alpha-fetoprotein (AFP) concentration values was mandatory at diagnosis. Human investigations were performed after approval by the Human Investigations Committee of Chongqing Medical University and in accordance with an assurance filed with and approved by the Department of Health and Human Services of Chongqing Medical University. Open or closed surgical biopsy was also mandatory for obtaining an accurate diagnosis before chemotherapy, except for patients in whom the surgical risk was considered unacceptable and unequivocal clinical findings had already been obtained (HB-compatible images and an elevated AFP level). The pretreatment assessment of the primary tumor was performed using abdominal ultrasonography and computed tomography (CT) with contrast medium, magnetic resonance imaging with contrast enhancement, or both methods. The presence of lung metastases was assessed by a chest X-ray (posteroanterior and lateral views) and lung CT scan. Infants with pure fetal HB at the initial biopsy were excluded because these tumors appear to have a different biology [20].

Study Design

The study design details and requirements are described in Figure 1. After the diagnosis of HB, patients initially received two cycles of a modified C5V regimen (cisplatin: 100 mg/m^2 per dose D1; 5-fluorouracil: 600 mg/m^2 per dose D3; vincristine: 1.5 mg/m^2 per dose D3) at 21-day intervals. Patients were then reevaluated for response and surgical resection after two courses of chemotherapy. If the tumor was considered to be unresectable, then the patients were divided to two treatment groups: the control group (n = 23), in which further four cycles of C5V chemotherapy were performed, and the TACE plus HIFU group (n = 12), which was suggested to undergo TACE plus HIFU ablation. A detailed description of the TACE plus HIFU treatment procedure was provided by Wang et al. [19] After the TACE plus HIFU treatments were completed, four C5V cycles were administered. Thus, each patient was scheduled to receive a maximum of six cycles of the C5V regimen.

TACE Procedures

TACE was performed in all patients before HIFU ablation. Depending on the tumor size, location, and arterial supply and its satellite lesions, the tumor-feeding arteries were selectively embolized using a 3-F to 5-F tracker catheter. Either 100 mg/m^2 of carboplatin (Qilu Pharmaceutical Factory, Jinan, China) or 10 to 15 mg/m^2 of adriamycin (Pfizer, Nerviano, Italy) was mixed in 3 to 8 ml of iodized oil (Lipiodol; Huaihai Pharmaceutical Factory, Shanghai, China), and the mixed suspension was slowly injected into the tumor-feeding arteries with fluoroscopic guidance. Embolization of the feeding arteries of all tumors was performed with the use of a 1 mm × 1 mm × 10 mm gelatin sponge (Gelfoam; 3rd Pharmaceutical Factory of Nanjing, Nanjing, China) in all patients after injecting the embolization suspension.

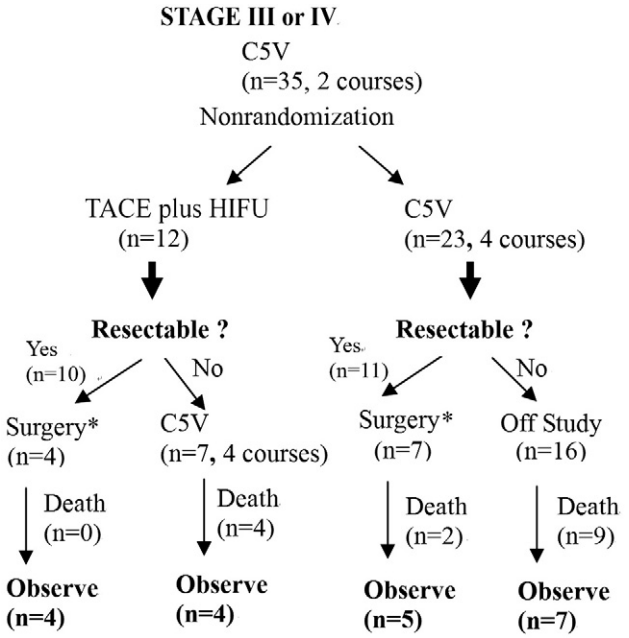

Figure 1. Flow diagram of the enrollment, treatment, and outcome of the 35 patients with HB. *Six patients with TACE plus HIFU ablation and four patients treated with C5V refused surgery to remove the residual tumor.

HIFU Ablation

HIFU ablation procedure was performed 2 to 3 weeks after TACE. The Model-JC 200 HIFU System [Chongqing Haifu (HIFU) Tech Co, Ltd, Chongqing, China] was used in all cases and has been described previously [19]. Briefly, the device consisted of a 12-cm diameter, single-element, piezo-ceramic transducer with acoustic lenses of varying focal lengths, driven at 0.8 MHz to produce therapeutic ultrasound energy, and an ultrasound imaging device (Esaote DU3, Genova, Italy) mounted to guide the transducer in real time. After general anesthesia was induced, the patient was accurately positioned to put the targeted lesion in contact with the degassed water. The coaxial US imaging device was used to establish three-dimensional images of the entire tumor, and the target tumor was divided into parallel slices of 5-mm separation. Then, with movement of the integrated transducer, the tumor was completely ablated from the deep to shallow regions and repeated section by section to achieve entire tumor ablation. Dependent on the size of targeted tumors, HIFU exposure time varied from 30 to 202 min and acoustic power ranged from 181 to 256 W. There was no second HIFU ablation performed in this series.

Follow-Up Response Evaluation

Serum AFP levels and appropriate imaging studies, including CT of the chest and abdomen, were performed before therapy and after every additional cycle of chemotherapy. The tests were then repeated to monitor the disease every 2 months for 2 years and then every 3 months for 2 years. After 2 years, the tests were repeated annually. The tumor response was assessed using the Response Evaluation Criteria in Solid Tumors version 1.1. Complete resection was defined as resection of all tumor sites on the basis of surgical findings and postsurgical images. Any patient who died was considered to have experienced an overall survival (OS) event, regardless of the cause of death. The patients who did not experience an event were censored on the date of last contact.

Treatment Toxicity

Patients were monitored weekly by physical examination, complete blood cell counts, and liver function tests. Approximately 1 month after completion of HIFU, the patients were evaluated by physical examination, blood chemistry analysis, and CT. A follow-up was performed monthly by telephone interviews with patients after HIFU. The acute toxicities associated with combined treatment were graded using the National Cancer Institute Common Toxicity Criteria version 3.0. The individual incidents of various toxicities were graded on a scale of 1 to 4, according to common toxicity criteria. Severe acute toxicity was defined as grade 3 or 4 infection, stomatitis, febrile neutropenia, or all of these events according to the National Cancer Institute Common Toxicity Criteria. The limits for toxicity grades depended on both patient age and the particular organ system involved.

Statistical Methods

The statistical analysis was conducted with current data as of December 2012. We reviewed the post-recurrence or post-progression outcome of patients to elucidate the role of HIFU. The ratio differences between the two treatment regimens were analyzed using Fisher exact test. The statistical significance of any observed difference between the mean values of the control and treatment groups was evaluated with an unpaired Student's t test. We also reviewed the outcomes (EFS) of patients according to their treatment assignment. The Kaplan-Meier method was used to estimate survival curves, and the difference between the treatment and control groups was evaluated using a log-rank test. All data were analyzed by three investigators. All statistical procedures were performed using GraphPad Prism software (San Diego, CA).

Results

Patient and Tumor Characteristics

At the time of analysis, the intention-to-treat sample consisted of the 45 eligible and evaluable patients. Ten patients were excluded from the study because they lacked proper documentation. Sixty-six percent (n = 23) of patients were assigned to receive C5V, whereas 34% (n = 12) of patients were assigned to receive TACE plus HIFU. Six patients without response to the initial course of chemotherapy were treated with TACE plus HIFU ablation by recommendation. Six patients were treated with TACE plus HIFU ablation due to parental request. Tumor staging revealed that stage III (9 of 12, 75%, C5V patients and 15 of 23, 65.2%, TACE plus HIFU patients) was more common than stage IV disease. The male-to-female ratio was 2.3:1 in the C5V treatment group and 2:1 in the TACE plus HIFU treatment group. The patient ages ranged from 3 months to 4 years. The tumor diameters varied from 6.1 to 19.3 cm (median, 9.4 cm for C5V and 11.3 cm for TACE plus HIFU). Multifocal tumors were present in nine patients, five of whom were treated with TACE plus HIFU (55.5%). Within this group, two patients showed diffuse liver involvement with no healthy hepatic parenchyma visible on CT. Vascular involvement (hepatic veins, vena cava, and/or both branches of the portal vein) was present in five cases (all C5V). A tumor biopsy was performed at diagnosis in 34 of 35 cases (open biopsy in 12 and closed biopsy in 23). The pathologic diagnosis was determined by examination of the tissue submitted to the pathologists. Most tumors were classified as mixed epithelial and mesenchymal histologic variants of HB (25 of 35; 71.4%). Six of the 35 tumors were classified as embryonal-type tumors, and the remaining tumors (n = 4) had mixed epithelial (fetal, embryonal) or small cell histology. Table 1 describes the clinical and demographic characteristics and disease staging of patients with HB based on their treatment assignment. There were no significant differences in the distributions of any of these characteristics between the two regimens.

Table 1. Clinical Baseline Characteristics of the Children with HB by Treatment Assignment

	C5V (n = 23)	TACE Plus HIFU (n = 12)	P
Stage (n)			
III	15	9	.71 *
IV	8	3	.71 *
Tumor diameter (cm)	9.4	11.3	.52 †
Multifocal tumors (n)	4	5	.20 *
Serum AFP (ng/ml)	11369	8917	.64 †
Lung metastases (n)	7	5	.71 *
Vascular involvement (n)	5	0	.14 *
Histology (n)			
Embryonal	4	2	1.00 *
Mixed epithelial (fetal/embryonal) and mesenchymal	17	8	.71 *
Small cell	2	2	.59 *

* Fisher exact test.

† Unpaired t test.

Table 2. Grade 3 or 4 Toxicity according to Treatment Regimen

Acute Toxic Effects	Cycles			Patients		
	C5V (87)	TACE Plus HIFU (12)	*P*	C5V (*n* = 23)	TACE Plus HIFU (*n* = 12)	*P**
Neutropenia	23	0	.03	11	0	.006
Infection	14	1	.70	5	1	.64
Mucositis	2	0	1.00	1	0	1.00
Thrombocytopenia	12	0	.35	6	0	.07
Anemia	19	0	.06	10	0	.007
Renal and cardiac toxicity	3	0	1.00	2	0	.54

* Fisher exact test.

Adverse Events

Compared with the conventional chemotherapy for HB, patients treated with TACE plus HIFU ablation exhibited a lower rate of major complications. The HIFU procedure was well tolerated. Table 2 describes the most common toxicities associated with these regimens. Twenty-eight (80%) of the 35 eligible patients experienced an event while in the hospital. The overall toxicities, including infection, neutropenia, thrombocytopenia, anemia, stomatitis, adverse cardiac effects, ototoxicity, and nephrotoxicity, were more frequent in patients who received chemotherapy than in patients treated with TACE plus HIFU (Table 2). The combination of TACE plus HIFU ablation caused a transient disturbance of physiological and biochemical values. Among the patients with available data, there were transient bilirubin increases in two patients after TACE plus HIFU ablation. The bilirubin stabilized in both patients at day 14. There was also a transient insignificant drop in hemoglobin and an increase in white blood cell count immediately after HIFU ablation. The aspartate transaminase (AST), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) increased transiently after treatment in some patients, which is consistent with a small volume of hepatic cellular destruction.

Tumor Response

According to the Response Evaluation Criteria in Solid Tumors, the 1-month post-treatment evaluation showed that the response rate was 91.7% in the TACE plus HIFU group and 82.6% in the chemotherapy group (Table 3). Of the 12 patients with the TACE plus HIFU treatments, a complete response was observed in 10 (83.3%) of the 12 patients, and the AFP level decreased to normal in these patients. Disease progression occurred in one (8.3%) patient 3 months after HIFU ablation. In the C5V group, 19 patients (82.6%) exhibited partial responses to the treatment, while 2 patients (8.7%) had stable disease and 2 patients (8.7%) had progressive disease. Seven patients had initial lung metastases following C5V chemotherapy. Four patients had a complete response of the lung lesions, and three patients had partial responses. Three patients exhibited progressive disease. One patient had local tumor progression without distant metastasis, and one patient had bone metastasis without local progression (C5V). The remaining patient had lung metastasis without local progression (TACE plus HIFU). For one patient who was lost to follow-up, data on tumor response were missing.

The tumor sizes were gradually reduced by 1 month after TACE plus HIFU ablation. The tumor sizes at 1, 3, 6, and 12 months after the initial treatment in both groups are shown in Figure 2*A*. The tumor size reductions in the TACE plus HIFU group were significantly greater than those in the C5V group at each follow-up interval ($P < .01$).

Table 3. Immediate Efficacy Measures according to Treatment Regimen

	C5V (*n* = 23)	TACE Plus HIFU (*n* = 12)	*P*	Odds Ratio (95% CI)
Complete response (*n*)	0	10	.0001*	0.003 (0.0001-0.08)
Partial response (*n*)	19	1	.0001*	52.25 (5.164-528.6)
Stable disease (*n*)	2	0	.54*	
Progressive disease (*n*)	2	1	1.00*	
Operability (*n*, %)	9	10	.02	0.129 (0.023-0.728)
Tumor excision (*n*)	7	4	1.00	
TPN (*n*)	12	0	.002*	27.17 (1.438-513.3)
Duration of hospitalization (days)	14.3 ± 5.4	9.3 ± 3.3	.01†	

* Fisher exact test.

† Unpaired *t* test.

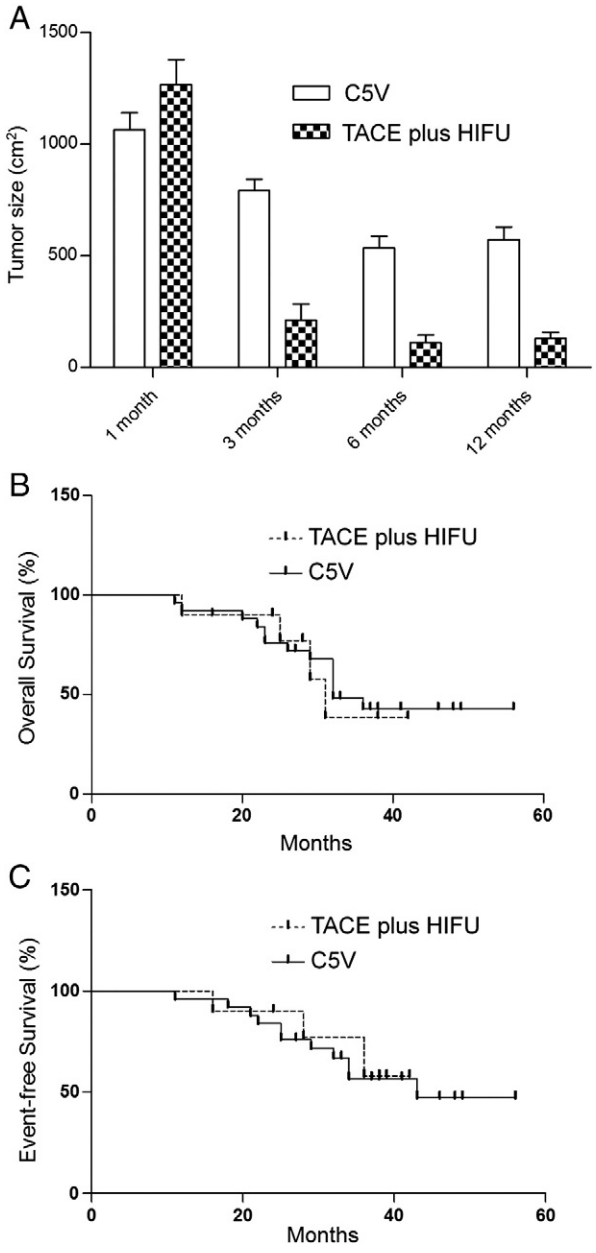

Figure 2. (A) The reduction in tumor volumes in patients treated with C5V or HIFU plus TACE was measured with Doppler US at the indicated follow-up day (*$P < .001$, unpaired Student's *t* test). (B) Kaplan-Meier curves for EFS [C5V *vs* TACE plus HIFU, $P = .85$, log-rank (Mantel-Cox) test]. (C) Kaplan-Meier curves for overall survival [C5V *vs* TACE plus HIFU, $P = .86$, log rank (Mantel-Cox) test].

None of the 12 HIFU patients required total parenteral alimentation (TPN), whereas the C5V patients required 25 to 87 TPN cycles (12 of 23 patients, $P < .01$). Similarly, the duration of hospitalization was significantly longer for patients treated with C5V compared with patients treated with TACE plus HIFU ($P < .01$).

Survival

The median follow-up time for EFS was 3.7 years (range, 1.1-6.4 years). The 3-year EFS was similar between the two regimens. The 3-year EFS was 51% (90% Confidence Interval [CI], 27 to 49%) in the TACE plus HIFU patient group and 49% (90% CI, 51 to 68%) in the C5V chemotherapy group ($P = .855$; Figure 2*B*). The risk of death in patients initially enrolled in the TACE plus HIFU group was similar to that in patients receiving C5V. The estimated 3-year overall survival was 68% for patients initially treated with HIFU and 63% for patients treated with C5V ($P = .865$; Figure 2*C*).

Surgical Features

The post-treatment assessment of the operability of the primary tumor by our surgical group showed that following HIFU ablation, 83% (10 of 12) of patients were eventually eligible for tumor resection, which is statistically superior to the eligibility rate (9 of 23) in the C5V chemotherapy group ($P = .02$). In 16 cases of HB (45.7%), primary tumors were not operable because of extensive liver involvement. Complete resection of all tumor lesions was eventually achieved in 11 patients (including four TACE plus HIFU patients and seven C5V chemotherapy patients). The following types of liver resection were performed: 1) seven right and left hemihepatectomies and (2) three extended hemihepatectomies. For one patient, he suffered from HB metastasis to the lung and received the right hemihepatectomy and lateral lobectomy. In one patient of extensive liver involvement, primary tumor never became operable. One patient died of postoperative bleeding complications. All 10 children with complete tumor resection experienced complete remission.

Disease Progression, Relapse, and Death

Eighteen patients exhibited recurrence or progressive disease during the follow-up, namely 6 patients in the TACE plus HIFU group (6 of 12, 50%) and 12 patients in the chemotherapy group (12 of 23, 52.2%; Table 4). The relapses occurred 6 to 46 months after treatment conclusion. The distribution of initial recurrence sites was similar between the treatment groups. Neither the risk of relapse nor the risk of death differed between the two groups. Of the six patients with relapse or disease progression in the TACE plus HIFU group, four patients had local progression and two had metastases. Twelve patients treated with C5V chemotherapy had a relapse, nine had local and distant progression, and three had metastases. At the last observation, two of these patients were alive without evidence of disease.

Table 4. Comparison of Disease Progression, Relapse, and Death between Treatment Regimens

	C5V	TACE Plus HIFU	*P**
Disease progression and relapse (*n*)	13 (*n* = 23)	5 (*n* = 12)	.49
Death (*n*)	11 (*n* = 23)	4 (*n* = 12)	.49
Death (*n*) without surgery	9 (*n* = 16)	4 (*n* = 8)	1.00
Post-surgery death	2 (*n* = 7)	0 (*n* = 4)	.49
Postoperative complications	1 (*n* = 7)	0 (*n* = 4)	1.00
Disease progression	1 (*n* = 7)	0 (*n* = 4)	1.00
Post-surgery relapse	3 (*n* = 7)	0 (*n* = 4)	.24

* Fisher exact test.

Eighteen patients experienced disease progression or recurrence. There were three deaths in the TACE plus HIFU group and nine deaths in the chemotherapy group. Two patients treated with TACE plus HIFU regimens were alive at the time of last contact after receiving additional C5V chemotherapy, and 3 of the 12 patients initially treated with chemotherapy were alive. Of the three deaths that occurred in the TACE plus HIFU group, two patients died of cancer progression. One death was attributed to complications from infection. There were nine deaths in the C5V group.

Among the 11 patients treated with surgical resection, 5 (2 in the C5V group and 3 in the TACE plus HIFU group) were alive with no evidence of disease. Three patients experienced relapses (all from the C5V group). Two of these patients had local progression, and one patient had metastases. At the last observation, two of these three patients were alive without evidence of disease, and one died of disease progression. One child died of postoperative complications (in the C5V group), and the data for two patients were missing (in the C5V group).

Discussion

The current study was designed to compare the outcomes in children treated with either the standard therapy for HB or a regimen consisting of TACE plus HIFU. Our goal was to improve overall surgical resection and decrease the long-term sequelae in children with unresectable and metastatic HB. To our knowledge, this study is the first report of such a large series of uniformly treated pediatric HB patients.

Currently, advanced-stage disease requires more intensive chemotherapy treatments and increases the risk of an adverse outcome [21–23]. On the basis of the goal of decreasing total chemotherapy exposure, we have favored HIFU in some patients for precise HB ablation. HIFU can completely ablate target animal liver carcinomas and improve the survival of animals with implanted liver tumors [14–18]. TACE is routinely performed in cases of large HB as repeated courses over a period of several months before HIFU ablation [18]. Due to the variation between populations, there is a large discrepancy between survival rates in different studies [24–26]. It is preferential to assess the survival benefits of a new treatment method within the same population. In this study, we prospectively compared different treatment regimens in our institute.

Complete tumor resection remains the only realistic option for obtaining a cure in childhood HB [27]. Thus, we chose the rate of complete resection as the primary study end point. Our results suggest that HIFU can improve the surgical resection rate. The disease burden is greatly reduced following HIFU ablation, so the surgical procedures were also easier to perform in these patients compared with the C5V patients. Although there were no significant differences between the two groups, 61% of patients in the HIFU group had lesions larger than 10 cm in diameter (mean diameter 11.3 cm), and the main branch of the portal vein was invaded in 50% of patients. The lesion diameters in the chemotherapy group were less than 10 cm (9.4 cm). Because parents of patients with larger tumors preferred to select HIFU treatment, some patients did not comply with the prescribed regimens, and some patients refused further surgical treatment. There was a trend toward improved survival in patients who received HIFU ablation, although no clinically acceptable marginal difference was statistically proven due to the limited number of patients. The 3-year survival rate for the 12 patients treated with TACE plus HIFU was 57.8%, which is similar to that associated with other regimens used to treat patients

with advanced-stage disease [28,29]. Previous studies suggested that relapses usually occur within the first 2 years after the end of HB treatment. The current study used a 3-year follow-up and enabled sufficient evaluation of the long-term efficacy of HIFU ablation and comparison with other studies.

Although HIFU reduced tumor size, the relapse rate was similar to that in patients treated with C5V during the follow-up period when tumor resections were not performed. Therefore, HIFU provides advantages of tumor excision but is not superior with respect to overall survival compared with the C5V regimen. Therapeutic strategies consisting of HIFU, surgery if operable, and four to six cycles of adjuvant chemotherapy are recommended in patients with HB. Importantly, the patients who did receive HIFU treatment had positive responses to chemotherapy, which suggested that drug resistance was not increased by HIFU administration. These results also emphasize that the presence of lung metastases at diagnosis is not a contraindication for HIFU. If effective chemotherapy is administered, the lung lesions are completely cleared by chemotherapy and metastasectomy (if needed).

Although the treatment regimens compared in the current study were not significantly different with respect to survival outcome, there were significant differences in the types of events and toxicities associated with the two regimens. The main treatment toxicity was hematological and included a profound neutropenia in most children treated with C5V. Conversely, an extremely low rate of major complications was observed in patients treated with HIFU ablation. No toxic deaths or other events occurred more than 3 years after study entry in patients treated with the HIFU regimen. This result suggests a very small risk of toxicities in late follow-up in patients treated with HIFU.

In summary, the results of this study suggest that the noninvasive HIFU technique can be combined with TACE as a promising approach for treating HB. The combination is effective, safe, and feasible and may play an important role in the treatment of patients with unresectable HB. We feel that this regimen should be included in combination with front-line therapy in this patient population. We acknowledge that these results were based on a small number of patients. Thus, it will be necessary to perform large-scale multicenter clinical trials in the future to determine the role of this modality in unresectable and metastatic HB.

New Findings

1. Until now, TACE plus HIFU was first successfully attempted in unresectable and metastatic hepatoblastoma in our institute.
2. Substantially significant improvement of the surgical resection rate was observed in patients treated with TACE plus HIFU ablation, concomitant with a low rate of major complications.
3. It exhibits rapid tumor size reduction within 6 months after TACE plus HIFU ablation compared with C5V chemotherapy.

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