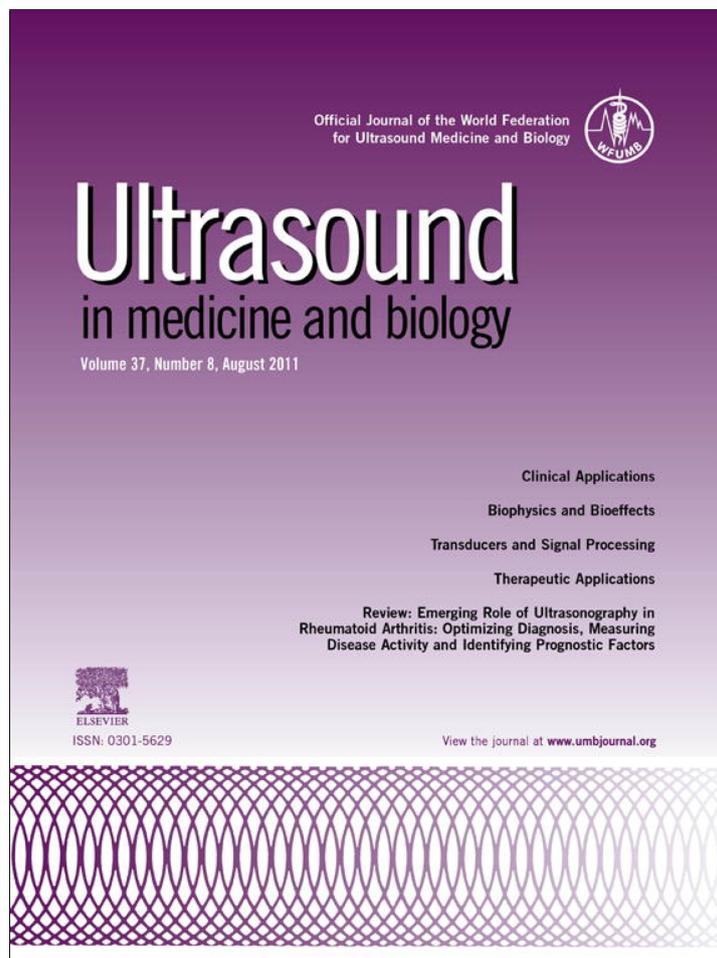


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● *Original Contribution*

TREATMENT OF SMALL HEPATOCELLULAR CARCINOMAS WITH US-GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND

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Abstract—High-intensity focused ultrasound (HIFU) is a noninvasive method that can cause complete coagulation necrosis without requiring the insertion of any instruments. The purpose of this study was to evaluate the safety and efficacy of HIFU treatment for small liver cancers without performing transcatheter arterial chemoembolization (TACE) or rib resection. HIFU ablation was performed without rib resection or the aid of TACE or percutaneous ethanol injection (PEI) in 12 patients with hepatocellular carcinoma. The HIFU system (Chongqing Haifu Tech, Chongqing, China) was used under ultrasound guidance. All 12 patients completed the treatment without experiencing any adverse events. Complete coagulation was achieved by applying the sonications from the intercostal space when the tumor was located in the right lobe. After treatment, serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) levels were significantly higher than the baseline values; these levels recovered within 1 week. C-reactive protein (CRP) levels increased 1 week after treatment but decreased within 1 month. An epidural anesthetic provided sufficient pain suppression during the procedure. Edema of the subcutaneous tissue was detected in five cases, but the edema disappeared within 1 month. None of the patients developed acute hepatic failure, liver abscess or renal dysfunction. In conclusion, HIFU is effective for the treatment of patients with small liver cancer. (E-mail: fukuhiro1962@hotmail.com) © 2011 World Federation for Ultrasound in Medicine & Biology.

Key Words: High-intensity focused ultrasound, Hepatocellular carcinoma, Ultrasound.

INTRODUCTION

A variety of nonsurgical procedures, such as percutaneous ethanol injection (PEI) (Bartolozzi et al. 1996; Lencioni et al. 1995), microwave therapy (Matsukawa et al. 1997; Sato et al. 1998), cryotherapy (Dale et al. 1998; Lezoche et al. 1998) and radiofrequency ablation (RFA) (Gazelle et al. 2000; McGahan et al. 2001), have been used for the treatment of small hepatocellular carcinoma (HCC) in patients with liver dysfunction arising from infection with chronic hepatitis virus (B or C) (Lin et al. 1997,1987; Zibari et al. 1998). High-intensity focused ultrasound (HIFU), a noninvasive method that can cause complete coagulation necrosis without requiring the insertion of any instruments

(ter Haar 2001; Wu et al. 2001; Hynynen et al. 2001; Jolesz et al. 2004; Zhu et al. 2009; Numata et al. 2010), has been applied for the treatment of several human neoplasms (Gianfelice et al. 2003; Tempany et al. 2003). However, in patients with large liver tumors, rib resection or transcatheter arterial chemoembolization (TACE) are performed to shorten the HIFU treatment time. The main motivations for performing TACE before HIFU are that TACE can decrease the tumor blood supply and thereby reduce the thermal conductive loss in the target tumor (Rossi et al. 2000; Goldberg et al. 1998) and that depositing of iodized oil in a lesion results in increased absorption of ultrasonic energy in the targeted region (Cheng et al. 1997). In addition, rib resection is performed to help achieve complete tumor ablation by enabling a wide acoustic window (Wu et al. 2004).

Conversely, TACE and rib resection may not be necessary for the HIFU ablation of small HCCs. The purpose of this study was to evaluate HIFU ablation

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without rib resection or the aid of TACE in patients with small liver carcinoma. This report details our preliminary experiences using HIFU to treat patients with liver tumors.

MATERIALS AND METHODS

Patients

Between July 2007 and October 2008, 12 patients with HCC were enrolled in this clinical study. The patients included six men and six women, ranging in age from 65 to 80 years old (mean, 73.8 years). The maximum diameter of the tumors measured on sonography ranged from 10 to 20 mm (mean, 15.7 mm; SD, 6.0 mm). The patients had liver cirrhosis with Child-Pugh classification A or B, a prothrombin time ratio greater than 50% and a platelet count greater than 50,000/mm³. In two patients, the diagnosis of hepatocellular carcinoma was confirmed using a percutaneous needle biopsy. The remaining 10 patients were diagnosed as having hepatocellular carcinoma based on imaging findings (*e.g.*, newly presenting tumor on follow-up ultrasonography [US] in patients with chronic liver disease or characteristic enhancement pattern on contrast-enhanced multiphase helical computed tomography [CT] or contrast-enhanced magnetic resonance imaging [MRI]). The 12 patients had liver cirrhosis as a result of hepatitis C ($n = 10$) or alcoholism ($n = 2$). At the time of HIFU, the patients exhibited cirrhosis classified as Child-Pugh classification A ($n = 8$) or B ($n = 4$). TACE, PEI and rib resection were not performed prior to HIFU treatment. Prior to treatment, the patient's skin was shaved and degassed using a suction pump. An epidural anesthesia was performed during the procedure. This study was approved by our hospital ethics committee and patients gave informed consent at the time of enrollment.

Ultrasound therapy system

Sonications were performed using a clinical ultrasound (US) guided surgery system. The Tumor Therapy System (Model AC 0501; Chongqing Haifu Tech Co., Ltd, Chongqing, China) used in this study was guided using real-time US imaging (Wu *et al.* 2001, 2003). A HIFU 6150S US imaging unit was installed on the HIFU system to enable real-time US imaging during HIFU ablation. A 2–5 MHz imaging probe was located at the center of the HIFU transducer and was mounted in a reservoir of degassed water (Wu *et al.* 2004, 2005). Therapeutic US energy was produced using a piezoelectric ceramic transducer with a diameter of 20 cm, focus length of 15 cm and an operating frequency of 1.0 MHz. The focal lesion was ellipsoid, with dimensions of 9.8 mm along the beam axis and 1.3 mm in the transverse direction. The targeted tissue was exposed to acoustic focal peak

intensities of 5000 and 15000 W cm⁻². A calibrated polyvinylidene difluoride membrane hydrophone with spot diameter 0.5 mm (Shanghai Jiao Tong University, Shanghai, China) was used to map the acoustic pressure field of the focused transducer at peak intensities from 200 to 300 W cm⁻². Before every treatment, the acoustic outputs from the transducer were used to create lesions on acrylic boards. These were then compared with lesions on acrylic board that had been created when the device was last calibrated. This served as a rapid check on the consistency of the output of the device. After the induction of suitable anesthesia, the patient was carefully positioned (either prone or on his or her right side) such that the skin overlying the target lesion could be easily placed in contact with the degassed water. The US power was increased in a stepwise manner until a power of 300–450 W was reached. During the focused ultrasound ablation of each section, the real-time US images obtained before and after each exposure were immediately compared to determine whether the echogenic changes, which are indicative of the extent of coagulation necrosis, had covered the desired treatment area (Kum *et al.* 2005; Rabkin *et al.* 2005; Vaezy *et al.* 2001; Kennedy *et al.* 2004). Patients were trained to hold their breath at the point at which their entire tumor became visible between the ribs or just behind the diaphragm.

Assessment of treatment efficacy and follow-up

Dynamic CT scans (Aquilion TSX-101A; Toshiba Medical Systems Corp., Tokyo, Japan) with a section thickness of 5 mm were obtained to evaluate the ablation. In these data, complete ablation was defined as hypodensification of the lesion, including the surrounding liver parenchyma, at 1 week after the HIFU procedure (Ebara *et al.* 2005).

Dynamic MRI scans (Signa HDX 3.0 T system; GE Healthcare, Milwaukee, WI, USA) with gradient-echo (GRE) sequences and T1 fat saturation (TR/TE, 4.8/1.9 ms; flip angle, 12°; matrix size, 320 × 192; section thickness, 4 mm; intersection gap, 0–2 mm; one acquisition) were also performed. Scans were acquired at 22 s, 60 s and 30 min after the bolus injection of a 0.025 mmol dose of gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid (Gd-EOB-DTPA) (Primovist; Bayer Schering Pharma, Berlin, Germany) per kg body weight. Assessment was performed using MRI scans when the tumors were not detected by dynamic CT scans.

All patients were assessed using contrast-enhanced (0.2 mL of Sonazoid suspension; Daiichi Sankyo, Tokyo, Japan) ultrasonography (LOGIQ 7; GE Healthcare, Milwaukee, WI, USA) when the hyperechoic change covered the original tumor at 1 week following the HIFU procedure. A convex volume 4D3C-L probe (GE

Healthcare) was used. All patients received an intravenous bolus injection of 0.2 mL of Sonazoid *via* a 24-gauge cannula into a forearm vein, followed by 2 mL of a 5% glucose solution and a subsequent infusion of a 5% glucose solution at 10 mL/min. A coded harmonic angio (CHA) mode with a high mechanical index (0.5–0.9) at 8–13 frames per second was selected for the contrast-enhanced 3-dimensional (3-D) US procedure (Ohto *et al.* 2005). The focus point was set beneath the tumor (Numata *et al.* 2010). Complete ablation based on the contrast-enhanced US findings was defined as a perfusion defect with no enhancement and no tumor vessels during both the early vascular phase and the post vascular phase (Hotta *et al.* 2005).

Potential complications and adverse effects related to the HIFU procedure were recorded for each patient; such complications included pain, fever, skin burn, local infection, tumor bleeding or large vessel rupture, hepatic dysfunction and bowel perforation. During their hospital stay, the patients were assessed every second day using hematologic evaluations and routine serum chemistry examinations. Vital signs were monitored for 24 h after the patient recovered from the anesthesia. Any changes were recorded. All patients remained in the hospital for 7 days to enable follow-up blood tests, contrast-enhanced ultrasonography, and CT and MRI examinations. At the time of writing, follow-up time ranged from 11 to 25 months (mean, 18 months).

Statistical analysis

All data are reported as the mean \pm standard deviation. Differences in the sonication time associated with tumor location and tumor size were evaluated using a paired *t*-test. The statistical significance of changes in the serum alanine aminotransferase, serum aspartate aminotransferase and C-reactive protein (CRP) levels were evaluated using the Wilcoxon signed rank test. Statistical significance was defined as a *p* value of less than 0.05.

RESULTS

Treatment data

An overview of the 12 patients and their liver tumors is given in Table 1. HIFU treatment was successfully performed in all 12 patients. Complete coagulation was achieved by sonication from the right intercostal space when the tumor was located in the right lobe. Hyperechoic changes were detected after HIFU ablation in 11 patients (Fig. 1a and b; Fig. 2a and b).

The total sonication time ranged from 6.2 to 25.3 min (mean, 12.4 min). The sonication time for tumors located in the left lobe (mean, 11.5 min) was shorter than that for the tumors located in the right lobe (mean, 13.3 min); however, these times were not significantly different. The sonication time for tumors smaller than 15 mm in diameter (mean, 11.3 min) was also shorter than that for tumors larger than 16 mm in diameter (mean, 13.9 min); however, these times were not significantly different. The overall procedure time, defined as the time from the first sonication to the last sonication, ranged from 43 to 420 min (mean, 226 min).

The following data were obtained from a representative case (No. 6). An enhancement representing the tumor was detected before the treatment. Based on the results of contrast-enhanced US performed immediately after the HIFU procedure, the treated lesion showed discrete areas of decreased vascular flow, which implies a successful treatment (Fig. 1c and d). Figure 1e and f show the CT assessment of the coagulation of the HCC. A CT scan obtained before HIFU treatment shows a hyperattenuated lesion with an 18 mm diameter during the arterial phase (Fig. 1e) and low attenuation during the equilibrium phase. A CT scan obtained 7 days after HIFU treatment shows a 23 \times 22 mm necrotic area (Fig. 1f), which was large enough to encompass a safety margin of approximately 5 mm. The decreased vascular flow implied tissue devascularization and necrosis, suggesting that the lesion had been treated effectively.

Table 1. Focused ultrasound treatment of liver tumors: Patient data, results, and complications

Patient No.	Patient age (y)	Tumor diameter (mm)	Tumor location (segment)	Sonication time (min)	Procedure time (min)	Results	Complications
1	73	20	S5	8.4	420	Completed	No adverse event
2	80	15	S5	9.9	330	Completed	No adverse event
3	65	15	S4	12.1	407	Completed	No adverse event
4	80	19	S5	8.4	188	Completed	Subcutaneous edema
5	76	18	S5	15.5	169	Completed	Subcutaneous edema
6	75	18	S6	25.3	219	Completed	Subcutaneous edema
7	73	15	S3	15.6	257	Completed	Subcutaneous edema
8	65	19	S3	12.1	145	Completed	No adverse event
9	80	10	S3	13.9	153	Completed	No adverse event
10	79	13	S3	9.4	83	Completed	Subcutaneous edema
11	65	12	S3	12.0	303	Completed	No adverse event
12	75	13	S3	6.3	43	Completed	No adverse event

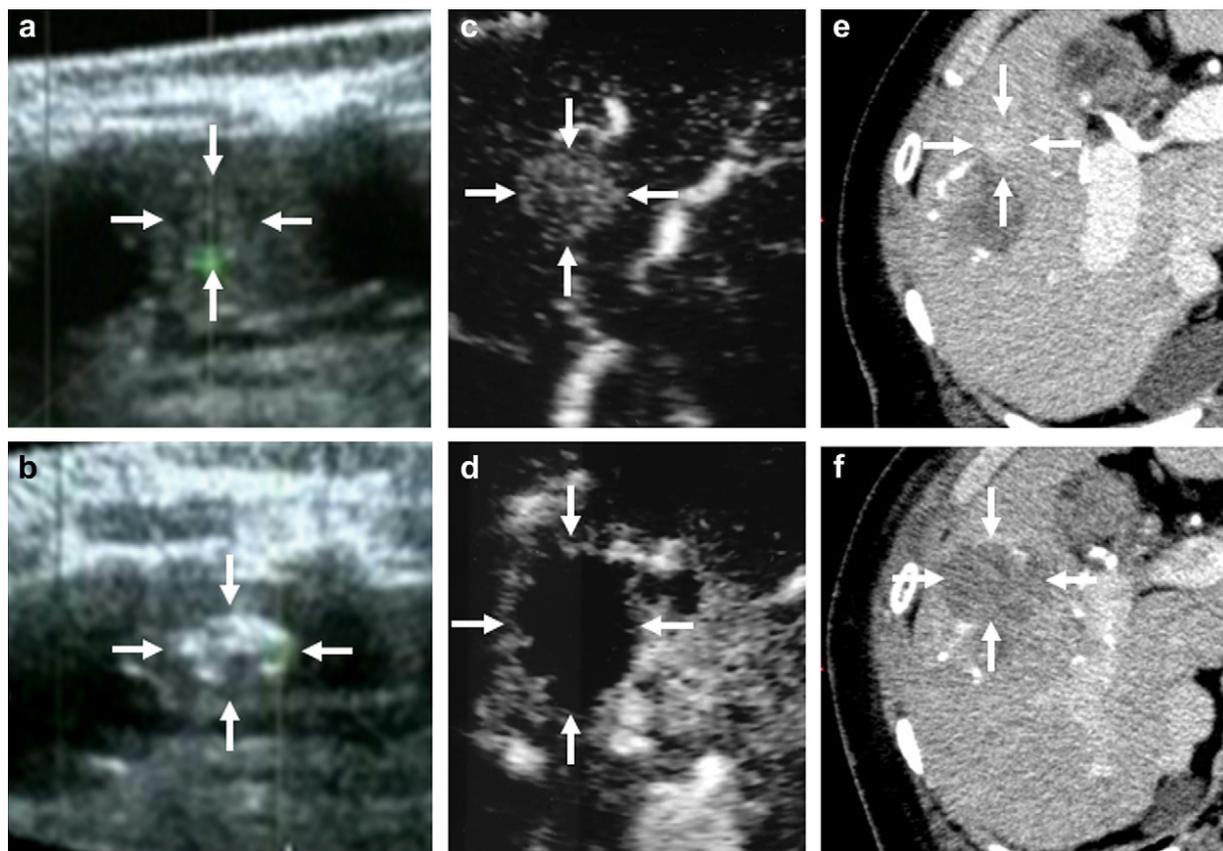


Fig. 1. Sonication monitoring using real-time ultrasonography (US) imaging obtained in patient No. 6. (a) Before high-intensity focused ultrasound (HIFU). Hyperechoic changes were detected in the treated lesion after HIFU (b). Contrast-enhanced US imaging before (c) and just after HIFU (d). The blood flow disappeared after HIFU. Assessment of coagulation using a computed tomography (CT) scan. Before HIFU, tumor enhancement was detected during the arterial phase (e) and the low-density area posterior to the tumor was a liver cyst. The arterial phase image at 1 week after HIFU treatment (f) shows the tumor enhancement has disappeared.

Figure 2c and d show a contrast-enhanced US assessment of coagulation in another representative case (No. 12). A perfusion defect was observed immediately following the HIFU procedure (Fig. 2d). Figure 2e and f show an MRI assessment of the coagulation. Hypointensity of the liver, including the liver parenchyma, was observed after the HIFU procedure (Fig. 2f).

Laboratory evaluation

One day after treatment, serum alanine aminotransferase (ALT, 73.9 ± 48.2 vs. 198.5 ± 94.0 U/L; $p < 0.01$, $n = 12$) and serum aspartate aminotransferase (AST, 52.8 ± 41.6 vs. 95.1 ± 54.0 U/L; $p < 0.01$, $n = 12$) levels were significantly higher, compared with baseline values. However, both levels had recovered within 1 week. CRP levels (0.29 ± 0.52 vs. 0.86 ± 0.91 mg/dL; $p < 0.01$) had increased significantly at 1 week after the treatment but normalized within 1 month. Serum amylase levels were elevated at one day following HIFU treatment in two cases (118.0 ± 9.0 vs. 371.5 ± 17.6 IU/L). In both of

these cases, the salivary amylase levels, not the pancreatic amylase levels, were elevated. The elastase-1 and trypsin levels were not increased and no pancreatic swelling was observed using the various imaging modalities, which suggests the absence of pancreatitis. In both cases, the elevated amylase levels returned to the normal range within 7 days after HIFU treatment.

Complications

Edema of the subcutaneous tissue at the entry point of the acoustic beam occurred in five cases; the edema disappeared within 1 month in all of these cases (Fig. 3). Epidural anesthesia was effective for pain control during the HIFU treatment and no patients complained of pain after the HIFU treatment. No other complications were noted in any of the patients. No signs of tumor hemorrhage, large blood vessel rupture, abscess, or gastrointestinal perforation were seen in any of the patients during their hospital stays. No evidence of post-interventional peritonitis or jaundice was noted in any

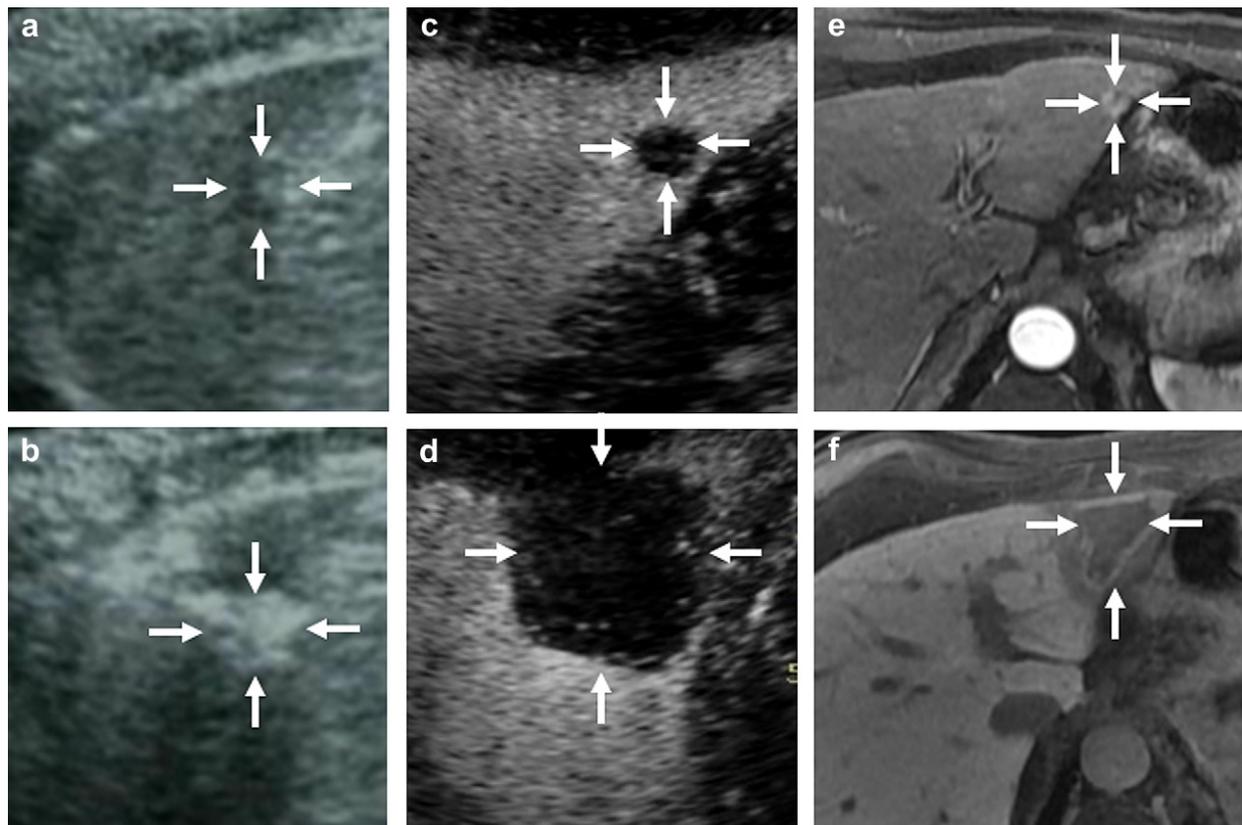


Fig. 2. Sonication monitoring using real-time US imaging in patient No. 12. (a) Before high-intensity focused ultrasound (HIFU). Hyperechoic changes were detected after HIFU (b). Contrast enhanced US imaging before (c) and just after HIFU (d). The ablated area was sufficiently broad with a wide safety margin. Assessment of coagulation using magnetic resonance imaging (MRI). Arterial-phase MRI obtained before HIFU (e) and late-phase MRI obtained 1 week after HIFU (f). A hypointense area including the surrounding liver is visible.

patients during the follow-up period. No patients developed acute hepatic failure, liver abscess, or renal dysfunction. No patients developed a fever. No death occurred during the follow-up period.

Follow-up and recurrence at treated site

During the follow-up period, there was one case of recurrence at the treated site (8.3%) (Fig. 4). In this case, the enhancement that represented the tumor had disappeared at 7 days after treatment. Despite the decreased size of the treated area at 1 month after treatment, enhancement and washout were noted at 10 months after treatment. No patient died during the follow-up period in this study.

DISCUSSION

Transcatheter arterial chemoembolization (TACE) is widely performed before PEI (Ebara et al. 2005) or RFA (Livraghi et al. 1999) when the size of the liver tumor is greater than 3 cm in diameter. Wu et al. (2005) also performed TACE before HIFU because they treated

large HCCs and needed to shorten the treatment time. Because of the large HCCs that were being treated (mean, 10.3 cm), a portion of the ribs was also resected to provide an adequate acoustic window (Wu et al. 2004). However, we suspected that TACE and rib resection were not necessary in the present series because the liver tumors were less than 2 cm in diameter in all cases. As a result, we applied this noninvasive HIFU procedure for the treatment of small tumors without performing TACE or rib resection and achieved complete coagulation in all cases. Although the average sonication time in this study was 12.4 min, which is comparable to the times of other ablation therapies, the average treatment time (226 min) was longer than that of other ablation therapies. This difference is mostly attributable to the extended time required to cool the skin to prevent skin damage. A time interval of 1 to 3 min between sonications was required to cool the skin using degassed cold water. As a result, the time required to perform HIFU was longer than that typically required to perform RFA because the skin does not need to be cooled during RFA. Other reasons for the lengthy treatment time are

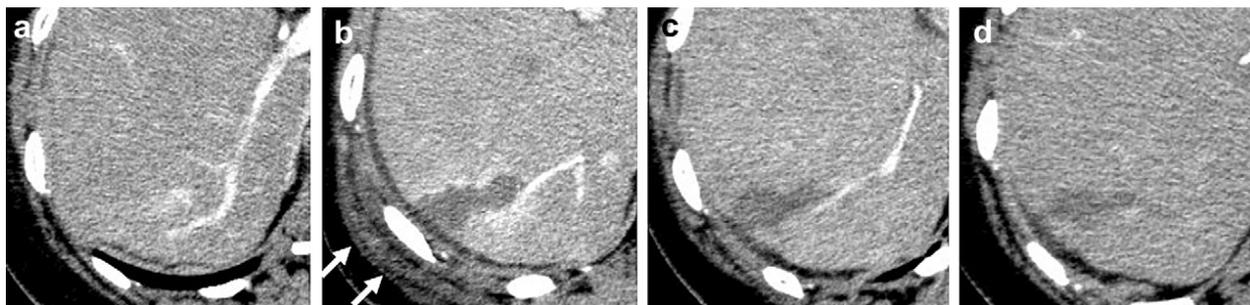


Fig. 3. Edema of the subcutaneous tissue in patient No. 6. (a) Before high-intensity focused ultrasound (HIFU) treatment. (b) Seven days after HIFU treatment, an edematous change in the subcutaneous tissue was detected (arrow). (c) One month after treatment, the edema had disappeared. (d) Four months after treatment, the findings had completely disappeared.

thought to be the additional time required for the patient to control his or her respiration, which was necessary for the targeting of the tumor, and the time required to obtain a sufficient level of anesthesia. The treatment of liver tumors greater than 2 cm in diameter using our methods would likely be rather long, as our average treatment time was already 226 minutes for tumors less than 2 cm in diameter. During RFA or microwave ablation, the treatment proceeds continuously once the tumor has been punctured and the patients' respiratory movements do not affect the treatment. Although the HIFU treatment is noninvasive, some health-compromised patients may have difficulty maintaining the same position for a long period of time. MR-guided HIFU is equipped with thermometry capabilities, whereas the US-guided HIFU therapy system used in the present study was unable to monitor the temperature in the ablated area. To compensate for this limitation, a hyperechoic change in the gray-scale level was used as a sign that the treated lesion had been completely coagulated (Wang *et al.* 2003). However, the temperature of the ablated area may have increased higher than was necessary to obtain coagula-

tion because microbubbles were generated to change the gray-scale image to hyperechoic. We think that these repeated sonications that were required to achieve a change in the hyperechoic gray-scale may have also contributed to the long procedure time. Additionally, contrast-enhanced ultrasonography was also performed to evaluate the ablated area immediately after sonication because a change in the hyperechoic gray-scale is not an absolute sign of complete coagulation. Consequently, the lengthy procedure time could possibly be shortened by improvements such as respiratory control, pain control, effective sonication and the efficient evaluation of complete coagulation.

In this study, no patients experienced severe complications and HIFU was largely demonstrated to be safe. The serum AST and ALT levels have been reported to increase above 1000 IU upon liver infarction after RFA treatment (Tateishi *et al.* 2005). In our study, although the serum AST and ALT levels increased significantly after the HIFU treatment, the elevated levels were not overly high and recovered within 1 week. HIFU has also been reported to not influence blood vessels larger

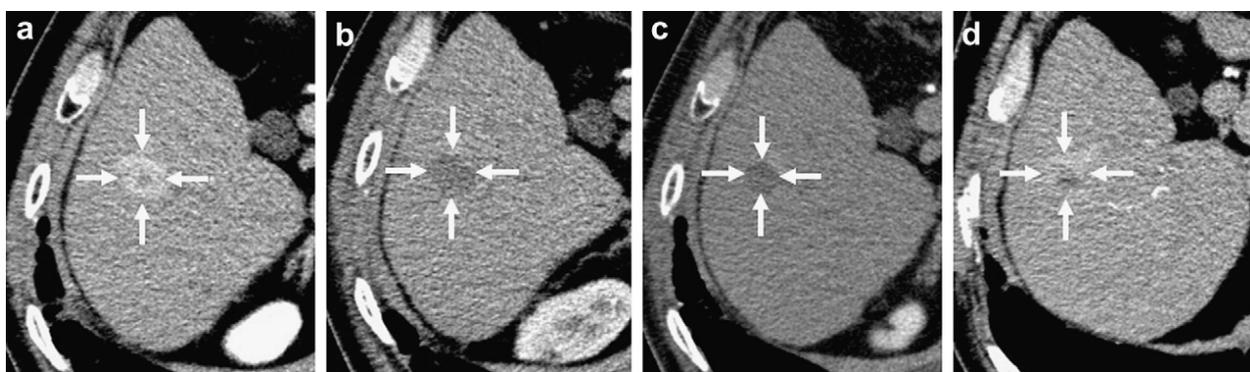


Fig. 4. Recurrence at the treated site (patient No.1). (a) Before high-intensity focused ultrasound (HIFU) treatment, a tumor 2 cm in diameter was located in segment 5. (b) Tumor enhancement disappeared 7 days after treatment. (c) The size of the ablated area decreased 1 month after HIFU. (d) Tumor enhancement and washout appeared 10 months after HIFU and the patient was diagnosed as having a recurrence at the treated site.

than 2 mm in diameter (Wu et al. 2001) and, thus, HIFU is unlikely to cause liver infarction. We observed subcutaneous edema in five cases in this series. Kovatcheva et al. (2010) reported that subcutaneous edema was seen after HIFU treatment for primary hyperthyroidism. Jansen et al. (1990) also reported that edema and neutrophilic inflammatory infiltration were seen histologically in skin and subcutaneous tissue after hyperthermia. In our study, the pain associated with the subcutaneous edema was controllable with oral analgesics. The condition of the subcutaneous tissue improved within 1 month after the HIFU treatment; thus, the edema was not regarded as a severe complication. No other severe adverse effects (e.g., skin burns, tumor hemorrhage, large blood vessel rupture, peritonitis, obstructive jaundice or gastrointestinal perforation) were observed in any of the patients during the follow-up period. Amylase levels were elevated in two of the 12 cases in this study and pancreatitis was initially suspected. However, the elevated amylase levels were salivary in nature and no symptoms or clinical findings of acute pancreatitis were found, nor was the pancreas located in the sonication zone. The amylase levels recovered within 1 week and no signs of impaired renal function were observed. The salivary amylase level has been reported to increase after surgery but the reason for this elevation remains unclear (Harada et al. 1974). Similarly, the mechanisms responsible for the acute increase in the serum amylase activity levels after HIFU in the present study are also unclear and further study is warranted.

In one of the 12 patients, a recurrence of the tumor at the treated site was detected 10 months after the treatment. This recurrence rate (8.3%) is somewhat low, compared with the rates for other ablations therapies reported elsewhere but further follow-up remains necessary for a definitive assessment (Ebara et al. 2005; Tateishi et al. 2003).

In conclusion, this study has shown HIFU to be a safe and effective method with a satisfactory curability. Nonetheless, the present study is limited in that it was a feasibility study involving a small number of patients. Further study will be necessary to ascertain conclusively whether HIFU treatment has an effect on survival.

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