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Liver

Contrast-enhanced ultrasound-guided radiofrequency ablation in inconspicuous hepatocellular carcinoma on B-mode ultrasound

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ABSTRACT

Background/Aims: B-mode ultrasound (US) has difficulty targeting small hepatocellular carcinomas (HCCs) with poor conspicuity during radiofrequency ablation (RFA). Contrast-enhanced ultrasound (CEUS) can improve visualization of small or inconspicuous HCCs. This study was conducted to evaluate the effectiveness of CEUS-guided RFA electrode insertion during the arterial phase in inconspicuous HCCs.

Materials and Methods: Ninety-three treatment-naïve HCCs from 80 patients treated with RFA from August 2012 to December 2014 were retrospectively reviewed. Seventy-five HCCs from 65 patients underwent B-mode US-guided RFA, and 15 HCCs from 14 patients that were inconspicuous on B-mode US underwent CEUS-guided RFA during the arterial phase after injection of sulfur hexafluoride microbubbles (SonoVue®). Technical success was assessed by contrast-enhanced computed tomography within 1 week and 3 months after the procedure.

Results: The mean size of HCCs treated with CEUS-guided RFA was smaller than that of HCCs treated with B-mode US-guided RFA (1.17±0.36 vs. 1.63±0.55 cm, p=0.003). Technical success rates of CEUS-guided RFA within 1 week and 3 months were 100% (15/15) and 93.3% (14/15), respectively. Technical success rates of B-mode US-guided RFA were 97.3% (73/75) and 94.5% (69/73), respectively.

Conclusion: CEUS-guided RFA is highly efficacious for ablation of very small and inconspicuous HCCs.

Keywords: Contrast-enhanced ultrasound, guiding technique, hepatocellular carcinoma, radiofrequency ablation

Original Article

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of cancer mortality worldwide (1). It is often associated with cirrhosis and is the most important cause of death in patients with liver cirrhosis. Liver transplantation, surgery, or local ablation therapy are curative options for HCC (2). However, the majority of HCCs are not suitable for curative resection at the time of diagnosis. Therefore, local ablative techniques including radiofrequency ablation (RFA), microwave coagulation therapy, and percutaneous ethanol injection have emerged in clinical practice to treat small HCCs (3). In particular, RFA has been widely performed for the management of small HCCs, showing a more than 50% 5-year survival rate (4,5).

For successful and complete treatment of HCC with RFA, confident visualization of a target lesion is essential (3). Generally, RFA procedures are implemented under real-time guidance of unenhanced B-mode ultrasound (US). However, because the detection of HCC by B-mode US is considered to be related to tumor size and conspicuity, it might be difficult to identify and target very small or ill-defined HCCs on conventional US, even if they are visible with other imaging modalities such as dynamic liver computed tomography (CT) or magnetic resonance imaging (MRI) (6-9).

Recently, novel contrast agents for ultrasound have been developed to improve the diagnostic yield. SonoVue (Bracco, Milan, Italy) and Sonazoid (Daiichi-San-

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kyo, Tokyo, Japan) are second-generation contrast agents. SonoVue consists of sulfur hexafluoride microbubbles. It is a gas contrast agent with low solubility that enables imaging at low mechanical index, effectively suppressing tissue signals. It enhances the blood and consequently improves the signal-to-noise ratio in US. Contrast-enhanced ultrasound (CEUS) with SonoVue showed improved diagnostic sensitivity and detectability for small and inconspicuous HCCs, compared with conventional B-mode US (10,11). Moreover, detection of hypervascularity in early HCC was significantly improved with CEUS compared with dynamic studies such as CT or MRI (12). To our knowledge, few studies have assessed the usefulness of CEUS-guided RFA electrode insertion into inconspicuous HCCs during the arterial phase of SonoVue (3,13-16).

Therefore, this study was conducted to determine the effectiveness of real-time CEUS-guided RFA using SonoVue in the treatment of invisible or poorly visible HCCs on B-mode US.

MATERIALS AND METHODS

Patients

Ninety-three treatment-naïve HCCs in 80 consecutive patients treated with percutaneous RFA from August 2012 to December 2014 were included.

The diagnosis of HCC was based on the pathologic findings in patients who underwent biopsy or the typical enhancement pattern (arterial enhancement followed by portal or delayed washout) in dynamic contrast-enhanced CT and/or MRI of the liver in cases without biopsy, according to the American Association for the Study of Liver Diseases guidelines (17).

The enrollment criteria for percutaneous RFA in the institution were as follows: a single tumor less than 3 cm in the largest diameter, multiple nodules (≤3) with each tumor less than 3 cm, Child-Pugh class A or B, no evidence of portal vein thrombosis or distant metastasis, a prothrombin time/international normalized ratio <1.5, and a platelet count > 50,000/mm^3.

This study was approved by the Institutional Review Board/Ethics Committee, and formal consent is not required for this type of study.

Ultrasonography

To confirm the feasibility of RFA, B-mode US and/or CEUS for HCCs was performed by one hepatologist before performing a percutaneous RFA. The hepatologist was certified and had more than 10 years of experience of B-mode US-guided percutaneous RFA procedures. The LOGIQ E9 premium ultrasound (GE Healthcare, Milwaukee, WI, USA) equipped with C1-5-D (1-6 MHz) probe was used for B-mode and planning CEUS.

Planning CEUS was performed for poorly conspicuous HCCs (probably identifiable, but not with confidence) or invisible HCCs on B-mode US that were visible with dynamic CT or MRI. We used SonoVue as a contrast agent. For the enhancement of the target lesion, 2.4 mL of SonoVue was administered via a 21-guage peripheral intravenous cannula in bolus and then 5 mL of saline was flushed. CEUS imaging was performed on a single monitor in split-screen mode, displaying the CEUS image on the right side of the screen and the B-mode US image on the left side. The mechanical index was 0.21 and focused to the lowest position on the screen to minimize microbubble destruction. The visual field and gain were optimized to clearly describe the target lesion.

Immediately after the injection of SonoVue, the liver where it was considered to contain the target lesion was scanned with a transducer to detect the arterial enhancement.

RFA Procedure Technique

Radiofrequency ablation procedure was performed using a guiding device with an internally cooled single electrode (Cool Tip™ RF ablation system, Covidien, Boulder, CO, USA) and 200-Watt generator (Covidien). Each ablation was performed for more than 9 minutes.

For HCCs that were identifiable with conventional US, B-mode US-guided RFA was performed. On the other hand, HCCs with poor conspicuity or invisible HCCs due to isoechogenecity compared with normal parenchyma on B-mode US underwent planning CEUS. HCCs which showed arterial enhancement on planning CEUS were treated with CEUS-guided RFA. Immediate insertion of RFA electrode was performed upon HCC enhancement due to the short duration of the arterial phase (about 30s); an electrode was not inserted during the venous phase or delayed phase in our study (Figure 1).

Technical Success and Effectiveness

Post-RFA evaluation was obtained with contrast-enhanced liver dynamic CT within 1 week after RFA, 3 months later, and then every 3 months. Technical success was assessed by post-RFA CT images that were taken within a week and 3 months later.

Statistical Analysis

Continuous data are expressed as means±standard deviations, and the categorical data are expressed as numbers and proportions in parenthesis. Data analysis was performed with the χ^2 test or Fisher's exact test and independent Student's t-test for categorical and continuous variables, respectively, to compare results for groups of patients who underwent B-mode US-guided RFA and CEUS-guided RFA. The cumulative recurrence rates of HCCs were estimated with the Kaplan-Meier method using Statistical Package for Social Sciences version 23.0 software (IBM Corp.; Armonk, NY, USA).

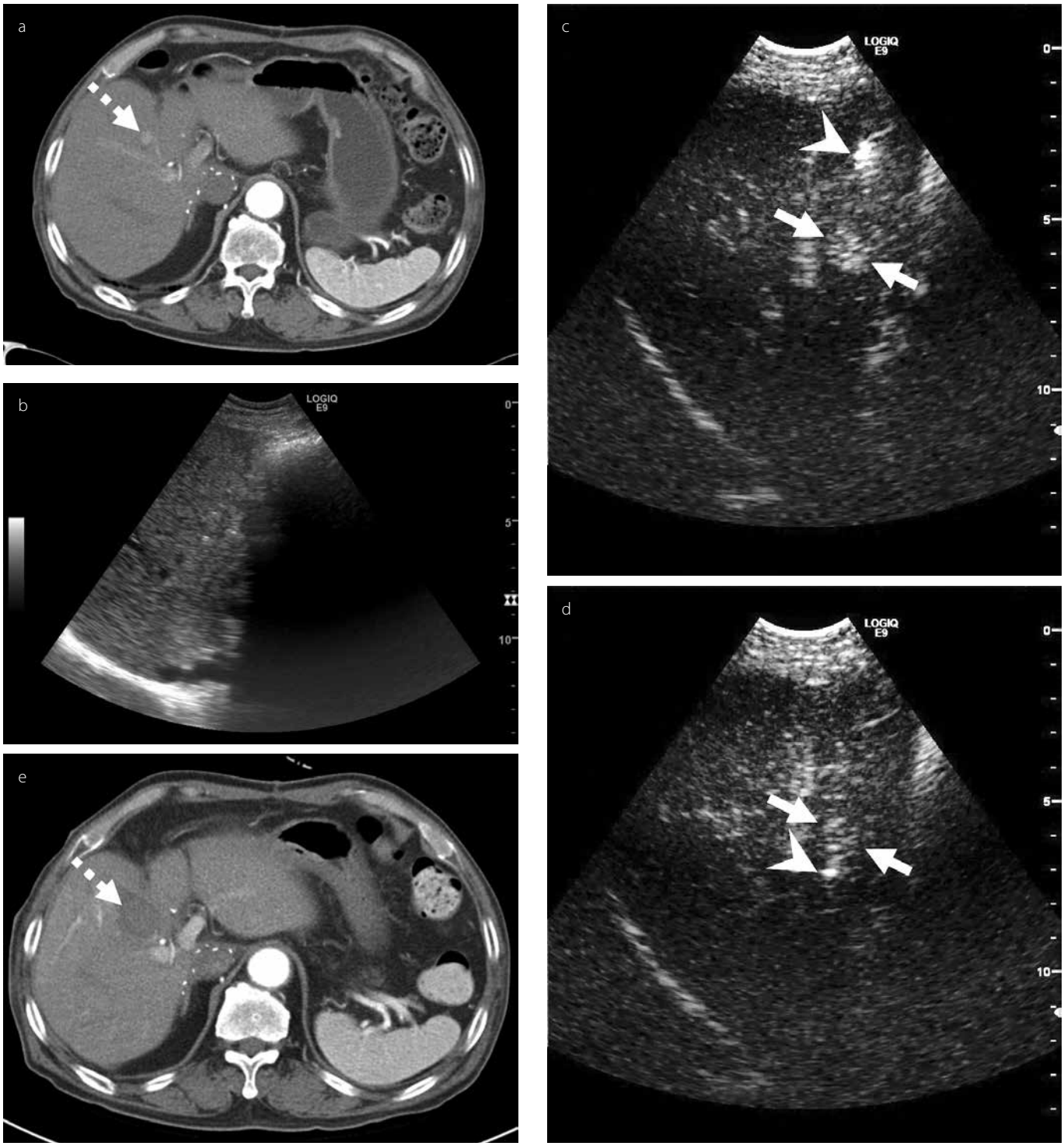

Figure 1. a-e. A case of small HCC treated with CEUS-guided RFA. (a) The arterial phase on enhanced CT showing a 1.2-cm-sized tumor with enhancement in liver segment IV (dotted arrow), (b) the tumor was poorly visualized on B-mode US, (c) the arterial phase in CEUS showed definite enhancement of the lesion (arrows), and the RFA electrode is being inserted (arrowhead), (d) CEUS image showing inserted single electrode through the tumor (arrowhead) during the arterial phase, (e) enhanced CT scan within a week after RFA treatment showing no enhancement of the target lesion, indicating complete ablation (dotted arrow)

HCC: hepatocellular carcinoma; CEUS: contrast-enhanced ultrasound; RFA: radiofrequency ablation; CT: computed tomography

RESULTS

Baseline Characteristics

Eighty patients with 93 treatment-naïve HCCs underwent planning sonography for RFA and 18 (19%) HCCs were not confidently identified; seven HCCs were invisible and 11 HCCs were inconspicuous. Among those 18 HCCs, 15 lesions were visualized on planning CEUS and the remaining three HCCs were still vague or invisible on planning CEUS. Detectability of inconspicuous HCCs with CEUS was 83% (15/18). Remain-

Table 1. Baseline characteristics of the patients

	CEUS-guided (n=15)	B-mode US-guided (n=75)	p
Sex (male)	14 (93.3%)	66 (88.0%)	1.000
Age	58.20±11.04	59.84±10.11	0.574
HBV	11 (73.3%)	50 (66.7%)	0.770
HCV	1 (6.7%)	11 (14.7%)	0.818
Child-Pugh Classification(A)	15 (100%)	72 (96.0%)	1.000
ALT(U/L)	26.67±6.24	36.99±23.74	0.004
Total bilirubin(mg/dL)	0.82±0.33	0.87±0.33	0.643
Albumin(g/dL)	4.26±0.39	3.84±0.51	0.004
PT (INR)	1.03±0.10	1.12±0.15	0.040
Size (cm)*	1.17±0.36	1.63±0.55	0.003
αFP(ng/mL)	30.29±0.29	78.39±233.93	0.450

CEUS: contrast-enhanced ultrasound; US: ultrasound; HBV: hepatitis B virus; HCV: hepatitis C virus; ALT: alanine transaminase; PT: prothrombin time; INR: international normalized ratio; αFP: α-fetoprotein

*Tumor size was measured by computed tomography scan

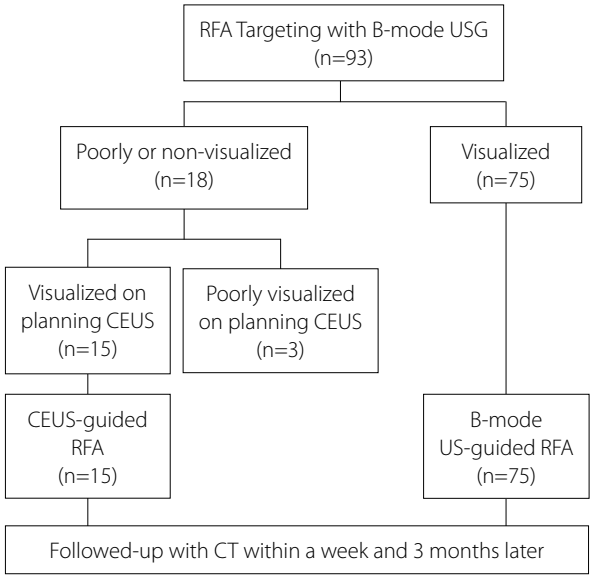

Figure 2. Flowchart of this study

RFA: radiofrequency ablation; CEUS: contrast-enhanced ultrasound; CT: computed tomography

ing 75 HCCs in 65 patients that were visible with B-mode US underwent RFA under unenhanced B-mode US guidance (Table 1, Figure 2).

The 15 HCCs that were treated with CEUS-guided RFA included four CEUS-guided biopsy-proven HCCs (two with Edmondson-Steiner grade 1 and two with Edmondson-Steiner grade 3); 11 lesions were diagnosed with dynamic imaging modalities. Eleven cases were positive for hepatitis B virus surface antigen and one case was positive for hepatitis C virus antibody. The mean size of the HCCs that were treated with CEUS-guided RFA was 1.17±0.36 cm, and the size of HCCs that were treated with B-mode US-guided RFA was 1.63±0.55 cm (p=0.003; Table 1).

Table 2. Technical success rate according to the mode of RFA

	CEUS-guided (n=15)	B-mode US-guided (n=75)
Technical success, 1wk*	15/15 (100%)	73/75 (97.3%)
Technical success, 3 mo	14/15 (93.3%)	69/73 (94.5%)
Minor complication	0 (0%)	10/75 (13.3%)
Hospital day	3.60±0.60	3.81±2.78

RFA: radiofrequency ablation; CEUS: contrast-enhanced ultrasound; US: ultrasound; wk: week; mo: month

*Technical success was assessed by contrast-enhanced computed tomography after RFA

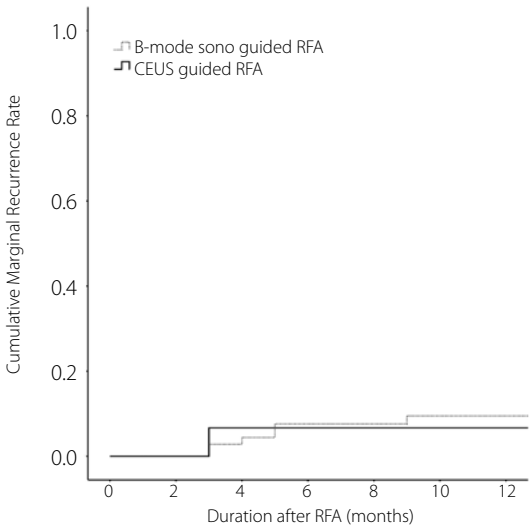

Figure 3. Cumulative marginal recurrence rates estimated by the Kaplan-Meier method

RFA: radiofrequency ablation; CEUS: contrast-enhanced ultrasound

Treatment Outcome of CEUS-Guided RFA

The mean duration of energy application for each tumor was 10.9±0.9 min for the CEUS-guided RFA group and 11.2±1.7 min for the B-mode US-guided RFA group (p=0.434).

All the cases that completed CEUS-guided RFA achieved complete ablation, confirmed by liver dynamic CT scan within 1 week after ablation. The technical success rate within a week was 100% (15/15), and the success rate at 3 months was 93.3% (14/15); there was one case with marginal recurrence on CT imaging at 3 months (Table 2). The technical success rate of B-mode US-guided RFA was 97.3% (73/75) within 1 week and 94.5% (69/73) at 3 months. Cumulative marginal recurrence rates of the CEUS-guided RFA group and the B-mode US-guided RFA group at 12 months, as estimated by the Kaplan-Meier method, were 6.7% and 9.5%, respectively (p=0.657; Figure 3).

There were no major complications and no deaths or thrombosis of major vessels in any patients in either group. There were

only minor complications in both groups, including abdominal pain and fever.

DISCUSSION

Radiofrequency ablation is a curative treatment for small HCCs, and the outcome is comparable to other curative treatment modalities, including surgery (18-20). However, because of the limitation of B-mode US in detecting very early and small HCCs with poor conspicuity, B-mode US-guided RFA might result in missed targeting or incomplete ablation (6). The detection rate of small HCCs not greater than 3 cm in diameter was only about 70% with sonography (6,8). Although advanced imaging techniques including liver dynamic CT and MRI made it possible to overcome this limitation of sonography and to detect very early HCCs, the treatment for these very small HCCs using US guidance is still challenging. Several techniques have been devised to overcome the limitations of B-mode US, and CEUS can serve as a good rescue method. In one report, sensitivity and overall accuracy of detection of HCCs smaller than 2 cm improved with CEUS from 29% to 80% and 64% to 87%, respectively (21).

There are some new techniques to overcome the limitation of B-mode US-guided RFA (22-29). One of the new techniques is fusion imaging-guided RFA. In one retrospective study, the proportion of HCCs with poor conspicuity was higher in fusion imaging-guided RFA (15.4% vs. 1.7%), indicating that inconspicuous HCCs could be treated with fusion imaging-guided RFA (28). In another study that included 46 HCCs treated with US fusion imaging-guided RFA, the technical success rate was 100% and the tumor progression rate was 8.7%, with a mean follow-up period of 18.2 months (29). On the basis of these results, US fusion imaging-guided RFA might be another possible rescue method for RFA in inconspicuous HCCs.

Although there are discrepancies in protocols between studies, CEUS-guided RFA is very useful because it is easily interchangeable with conventional B-mode US mode without additional specialized instruments. Levovist (Schering SA, Berlin, Germany) consists of microbubbles with a weak encapsulating shell; it is easily disrupted with sonographic energy, and is not suitable for CEUS-guided RFA. As second-generation contrast agents including SonoVue and Sonazoid have been developed, CEUS has emerged as a rescue method for RFA for inconspicuous small HCC on B-mode US. Several studies reported that CEUS using Sonazoid was very useful in RFA for small HCCs (15,25). In one study, the initial success rate was 94%, and there was no case with local tumor progression during follow-up (15). However, with Sonazoid, some well-differentiated HCCs do not show a hypoechoic appearance in Kupffer phase, and HCCs distant from the body surface are difficult to detect because of signal attenuation, which is a limitation of CEUS with Sonazoid (21,30).

Few studies have evaluated the usefulness of CEUS with SonoVue during the arterial phase because of the short duration of the arterial phase with SonoVue. In one study that consisted of 109 patients with HCCs and 53 with metastatic liver cancers, the rate of partial ablation decreased from 16.1% to 5.9% with CEUS-guided RFA in which study CEUS was performed before, during, and after RFA (16). In another study, CEUS using SonoVue was performed instead of real-time targeting prior to B-mode US-guided RFA for pretreatment localization of the index tumor (11). In this study, CEUS was performed prior to B-mode US-guided RFA, and the complete tumor necrosis rate in the group with screening CEUS was higher than that in the group without CEUS (92.2% vs. 83.0%; p=0.036).

Our study is unique in performing electrode insertion during the arterial phase using SonoVue despite the short duration of arterial phase. On visualization of tumor enhancement, immediate insertion of the RFA electrode is essential before hypervascularity becomes diminished. We used the arterial phase rather than the venous phase on the basis of the results of Shin et al. (12) study, which demonstrated CEUS finding of small atypical HCCs in cirrhotic liver; 20.8% of small HCCs with atypical enhancement pattern on CT and MRI did not show hypoenhancement during the venous phase on CEUS.

In this study, among the 15 HCCs treated with CEUS-guided RFA, nine HCCs were poorly conspicuous, preventing accurate insertion of electrodes without CEUS, and six lesions were not visualized at all with B-mode US. The mean size of HCCs treated with CEUS-guided RFA was significantly smaller than lesions treated with B-mode US-guided RFA (12 vs. 16 mm, p=0.003). The technical success rate within 1 week was 100% (15/15), and the success rate at 3 months was 93.3% (14/15). Considering the success rate of B-mode US-guided RFA for HCCs (97.3% within a week, 94.5% at 3 months), the success rate of CEUS-guided RFA showed comparable results, despite poor visualization with B-mode US.

Because this is not a comparison study, the superiority or inferiority of CEUS-guided RFA over B-mode US cannot be determined. An evaluation of the superiority of CEUS-guided RFA over B-mode US-guided RFA with a randomized controlled study will be impossible because B-mode US-guided RFA for invisible HCCs on sonography would be unethical.

A limitation in this study is that 11 of the 15 HCCs treated with CEUS-guided RFA were not confirmed histologically. The HCCs treated with CEUS-guided RFA in this study were very small lesions that were inconspicuous or invisible with conventional B-mode US, pathologic confirmation was therefore difficult. Because of this difficulty in pathological diagnosis, the only way to diagnose HCCs was with imaging findings of CT and/or MRI. Another limitation is selection bias. Because the decision of whether to use CEUS-guided RFA or B-mode US-guided RFA

was made by a single experienced hepatologist, there could be selection bias. However, because US-guided RFA requires very subjective skills and is dependent on the operator's experience, this type of bias is not avoidable. And also, there can be a technical limitation. Because the arterial phase is short and delayed insertion frequently causes failure of adequate insertion, skillful electrode manipulation is mandatory. However, since repeated injections of contrast agents are applicable without any major side effects, if the probe cannot be placed within a reasonable time, the target lesion can be repeatedly enhanced as needed in a single CEUS session.

Although CEUS or fusion imaging is useful for ablation of inconspicuous HCCs, there is no definitive guiding modality for such HCCs because the superiority of a specific method has not been determined with a randomized controlled study. In the future, a randomized controlled trial including a variety of guiding techniques for inconspicuous HCCs is needed.

In conclusion, real-time CEUS-guided RFA using SonoVue is a useful rescue technique that improves visualization of small and inconspicuous HCCs on B-mode US and makes RFA possible with a high technical success rate.

Ethics Committee Approval: Ethics committee approval was received for this study from Institutional Review Board of Gachon University Gil Medical Center (Decision Date: 04.02.2014/Decision No: GCIRB2014-34).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

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