CLINICAL STUDY

Contrast-enhanced US-guided Radiofrequency Ablation of Hepatocellular Carcinoma

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ABSTRACT

Purpose: Contrast-enhanced ultrasound (US) has been shown to be an efficient imaging modality in guiding radiofrequency (RF) ablation of hepatocellular carcinomas (HCC). The purpose of the present study was to assess the usefulness of contrast-enhanced US in guiding RF ablation in patients with early-stage HCC that was not clearly visible on grayscale US or noncontrast computed tomography (CT).

Materials and Methods: During a 17-month period, contrast-enhanced US–guided RF ablation was performed in 14 patients with 19 early-stage lesions that were poorly defined on grayscale US and noncontrast CT. Contrast-enhanced US was repeated after 30 minutes, and complete ablation was defined as absence of any arterial-phase enhancement within the ablated lesion. Patients were followed periodically with clinical evaluation, liver function tests, α-fetoprotein measurement, and multiphasic CT or magnetic resonance (MR) imaging for a minimum of 1 year after ablation to look for local recurrence or disease progression. Survival probability was estimated with the Kaplan–Meier method.

Results: Complete tumor ablation was achieved in all 19 lesions, with no evidence of residual or recurrent tumor in the ablated areas after a mean follow-up of 16 months. No major complications were observed in any patient. However, new lesions developed in other parts of the liver on follow-up scans in three patients, and were accordingly treated with RF ablation. Two patients died of disease progression or liver failure within the 1-year follow-up.

Conclusions: For early-stage HCCs not well visualized on unenhanced US or CT, contrast-enhanced US provides an additional tool to guide RF ablation.

ABBREVIATIONS

HCC = hepatocellular carcinoma, RF = radiofrequency

Radiofrequency (RF) ablation can provide potentially curative results in early stages of hepatocellular carcinoma (HCC), but the procedure is intrinsically dependent on imaging for its planning and for assessment of the final outcome (1–7). Traditionally, grayscale ultrasound (US) has been employed in the performance of RF ablation. For lesions not visualized on grayscale US and noncontrast computed tomography (CT), contrast-enhanced CT and magnetic resonance (MR) imaging are thought to be useful. However, they are not real-time imaging modalities, and the early washout of contrast agent from lesions gives a very short time frame to the interventionist for proper localization and subsequent ablation. In addition, CT is associated with use of potentially nephrotoxic intravenous contrast agents and ionizing radiation, and MR imaging requires compatible instruments.

Contrast-enhanced US, on the contrary, provides a relatively longer time window to the operator to perform RF ablation, allows real-time visualization, can be used in patients with compromised renal function, and has been shown to have sensitivity comparable to those of contrast-enhanced CT and MR imaging (1–8). Moreover, it can be repeated after completion of the procedure in the same session to assess the adequacy of ablation (1–5,8). The present study aimed to assess the usefulness of contrast-enhanced US in guiding RF ablation.
ablation in patients with early-stage HCC in whom the tumor was not well discernible on grayscale US or noncontrast CT.

MATERIALS AND METHODS

Departmental review board approval was obtained for this retrospective analysis of all patients who underwent RF ablation for HCC in a single institution from April 2010 to September 2011. RF ablation was performed for 49 lesions in 37 patients. All patients had cirrhosis, and clinical and biochemical data and multiphasic CT findings (Fig 1) suggested the lesions within the liver to be HCC. All patients had Barcelona Clinic Liver Cancer stage A disease and Child class A or B cirrhosis. They were evaluated for possible liver transplantation or curative surgical resection but were unsuitable or unwilling to undergo surgery. Of the 37 patients, 14 patients had 19 lesions suboptimally visualized by grayscale US or noncontrast CT and received contrast-enhanced US–guided RF ablation.

Inclusion criteria for this study were (i) fewer than three lesions per patient, (ii) maximum tumor diameter less than 4 cm, and (iii) lesion located at least 3 mm away from main, right, or left portal vein and gallbladder. Lesions with a large exophytic component, adjacent

![Image](83x386 to 502x549)

Figure 1. Axial contrast-enhanced CT image acquired during arterial phase (a) shows a nodular enhancing HCC (arrow) in the right lobe of the liver, which was not optimally visualized on noncontrast CT (b), demonstrating how CT guidance without contrast enhancement would have been difficult in this patient.

### Table 1. Demographic Data, Disease Characteristics, and Follow-up Details

<table>
<thead>
<tr>
<th>Pt. No./Age (y)/Sex</th>
<th>Etiology of Cirrhosis</th>
<th>No. of Lesions</th>
<th>Largest Lesion Size (mm)</th>
<th>AFP/PIVKA-II (ng/mL)</th>
<th>CTP Score/Child Class</th>
<th>Follow-up (mo)</th>
<th>Residual/Recurrent Lesion on Follow-up</th>
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<td>1/47/M</td>
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<td>35</td>
<td>241/8</td>
<td>6/A</td>
<td>26</td>
<td>None</td>
</tr>
<tr>
<td>2/48/M</td>
<td>HBV, alcohol</td>
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<td>17</td>
<td>15/22</td>
<td>6/A</td>
<td>12</td>
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</tr>
<tr>
<td>3/69/M</td>
<td>HBV</td>
<td>1</td>
<td>25</td>
<td>296/NA</td>
<td>8/B</td>
<td>24</td>
<td>New lesion (12 mo)</td>
</tr>
<tr>
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<td>HBV</td>
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<td>10</td>
<td>7/NA</td>
<td>6/B</td>
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</tr>
<tr>
<td>5/75/M</td>
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<td>23</td>
<td>334/12</td>
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<td>22</td>
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</tr>
<tr>
<td>6/58/F</td>
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<td>35</td>
<td>12/NA</td>
<td>6/A</td>
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<td>HBV</td>
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<td>15</td>
<td>889/28</td>
<td>9/B</td>
<td>Died of liver failure (11 mo) (6 mo)</td>
<td>New lesion (6 mo)</td>
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<td>10/53/M</td>
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<td>32</td>
<td>1,598/9</td>
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<td>11/57/M</td>
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<td>12/41/M</td>
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<td>18</td>
<td>250/32</td>
<td>9/B</td>
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<td>New lesion (8 mo)</td>
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<td>988/82</td>
<td>6/A</td>
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</tr>
</tbody>
</table>

AFP = α-fetoprotein, CTP = Child–Turcotte–Pugh, GI = gastrointestinal, HBV = Hepatitis-B virus infection, NA = not available, NASH = nonalcoholic steatohepatitis, PIVKA = protein induced by vitamin K antagonism.
organ or bowel invasion, or associated tumor thrombosis of the portal vein or extrahepatic metastases were excluded. Baseline clinical profiles of patients and lesion characteristics are provided in Table 1. The group consisted of 11 men and three women, with a mean age of 56 years (range, 41–75 y).

Procedure Technique
RF ablation was performed under conscious sedation with use of a RITA 1500X RF generator (AngioDynamics, Manchester, Georgia) and RITA Starburst XL electrode (AngioDynamics) with seven to nine curved deployable tines and an active trocar tip for uniform ablation of lesions ranging from 2 to 5 cm. The US contrast agent used was sulfur hexafluoride (SonoVue; Bracco, Milan, Italy), which was supplied as a lyophilized powder and reconstituted with 5 mL of saline solution to form a homogeneous microbubble suspension, which contained 8 μL/mL sulfur hexafluoride (equivalent to 45 μg) stabilized by a phospholipid shell. Each patient was given 1.5 mL of contrast agent through the antecubital vein over a period of 2–3 seconds, followed by a 5-mL bolus of normal saline solution. US was performed with an iU22 US system (Philips, Bothell, Washington) with contrast pulse sequence technology. Low acoustic output power levels as determined by the low mechanical index (0.15) were used to limit bubble destruction and allow tumor detection over a relatively long time period. Precontrast grayscale, postcontrast real-time grayscale, and dynamic contrast-enhanced images were acquired and stored in a cine loop.

When the lesions had been identified, the RF ablation probe was introduced under US guidance (Fig 2), the electrode tines were deployed according to the size of the lesion, and ablation was performed. Needle tract ablation was also performed while withdrawing the probe. All RF ablation procedures were performed percutaneously by a single interventional radiologist (A.M.) with more than 7 years of experience in US-guided interventional procedures. Thirty minutes after ablation, contrast-enhanced US was repeated to look for any residual arterial-phase enhancement and to assess for adequacy of ablation. Complete ablation was defined as (i) complete devascularization of the ablated lesion with no arterial-phase enhancing area within or surrounding the ablated zone on contrast-enhanced US and (ii) ablation zone extending at least 1 cm beyond the tumor borders. After the procedure, the patients were observed overnight and discharged the following day.

Follow-up Protocol and Statistical Analysis
Follow-up imaging was performed within 1 month after tumor ablation to assess the therapeutic response and every 3 months thereafter to look for tumor progression. Imaging consisted of multiphasic contrast-enhanced CT or MR imaging depending on the baseline imaging modality used to diagnose the disease before ablation. Therapeutic response was evaluated per modified

![Figure 2](https://www.jvir.org)

**Figure 2.** Side-by-side venous-phase contrast-enhanced and grayscale US images show RF electrode (arrowheads) with the electrode tines (arrow, b) fully opened within the lesion (arrow, a). (Available in color online at www.jvir.org.)

![Figure 3](https://www.jvir.org)

**Figure 3.** Kaplan–Meier survival curve for patients with HCC treated with RF ablation. Numbers of patients at risk at different time points are displayed above the graph.
Response Evaluation Criteria In Solid Tumors (9). Complete response was defined as the disappearance of any intratumoral arterial enhancement in all target lesions. Residual tumor or local tumor progression was defined as an arterial-phase enhancing lesion within or surrounding the RF ablation–treated site showing wash-out on subsequent portal venous and equilibrium-phase images. New HCC was defined as an intrahepatic tumor showing the characteristic enhancement pattern of HCC outside the RF ablation–treated site. Clinical follow-up included physical examination, liver function tests, and α-fetoprotein measurement. The endpoint was local tumor progression–free interval, defined as the minimum time between RF ablation and progression of the treated tumor or last follow-up contact for patients who did not experience tumor progression before the last contact. Survival probability was estimated by Kaplan–Meier method (Fig 3). Data analysis was performed with commercially available software (MedCalc version 12.3; MedCalc, Mariakerke, Belgium).

RESULTS
A total of 19 lesions ranging in diameter from 10 to 40 mm (mean, 21 mm) were ablated under contrast-enhanced US guidance in 14 patients. Contrast-enhanced US was repeated 30 minutes after completion of the ablation. None of the lesions showed any residual arterial-phase enhancement. No major postprocedural complications were seen in any of the patients. Minor complications, in the form of postprocedural pain, were seen in eight of the 14 patients (57%). This was self-limiting or relieved by analgesic agents in all cases. All patients were asymptomatic the following morning and were discharged.

Follow-up
After a mean follow-up of 16 months (range, 9–26 mo), imaging revealed complete response (Fig 4) in all 19 lesions, with no evidence of residual or recurrent tumor in the ablated areas. However, three patients were found to have new lesions in other parts of the liver on follow-up scans; these were accordingly treated with RF ablation. All these patients had Child class B cirrhosis, and the lesions were recognized at 6 months, 8 months, and 1 year of follow-up, respectively. One of these patients presented with increasing α-fetoprotein levels, whereas the other two presented with signs of liver decompensation (abnormal liver function test results and ascites).

DISCUSSION
RF ablation is a simple and effective treatment option that can be offered to patients with early-stage HCC. The success rate of RF ablation depends on precise targeting of the lesion under imaging guidance. However, visualization of a lesion on grayscale US is difficult at times as a result of surface nodularity and coarse parenchymal echotexture of a cirrhotic liver (3). In a study of 898 patients (10), it was reported that only 74.7% of HCCs smaller than 3 cm in diameter were visible on preablation planning grayscale US performed with known CT or MR imaging results. Although contrast-enhanced CT– and MR imaging–guided RF ablation are potentially useful for such nodules, real-time visualization is inferior to US guidance, and the early washout of contrast agent from lesions coupled with the interruptions required during the procedure for imaging gives a very short time window to the operator for precise needle placement (3). Lately, virtual sonographic images reconstructed from multi-detector-row CT images have been shown to be of use in the detection of HCC nodules that are not visualized by grayscale US (11). However, virtual sonographic images do not always accurately correspond to the actual US images because of the discrepancies caused by respiratory movements, changes in posture, and bowel peristalsis.
Recent studies have demonstrated the use of contrast-enhanced US in such patients (1,3,4,12–21). One of the earlier reports on the utility of contrast-enhanced US in guiding ablation of HCC (22) demonstrated in a rabbit model that RF needle insertion and deployment was easier and more accurate with contrast-enhanced US than with grayscale sonographic guidance, particularly for small tumors. Also, the use of contrast-enhanced US permitted the detection of residual tumor vascularity, if any, after RF ablation (22). Subsequently, a number of studies have evaluated the role of contrast-enhanced US as a guiding tool in ablating HCCs with the use of different contrast agents (Table 2) (1,3,4,9–18). A suspension of galactose (99.9%) stabilized with 0.1% palmitic acid (Levovist; Bayer Schering, Berlin, Germany) was one of the first such agents to be used. In a randomized controlled study (15) that used this agent, it was reported that the complete ablation rate after a single treatment session was significantly higher in the contrast-enhanced US group than in the grayscale US group (94.7% vs 65.0%; \( P = .043 \)) and that the number of treatment sessions was significantly lower in the contrast-enhanced US group (mean, 1.1 ± 0.2 vs 1.4 ± 0.6; \( P = .037 \)). However, galactose–palmitic acid microbubbles are rapidly destroyed during exposure to high acoustic power insonation, resulting in an enhancement effect with a short duration, limiting its utility as a guiding tool during RF ablation (23).

On the contrary, shelled perfluorobutane-based US contrast agent (Sonazoid; GE Healthcare, Oslo, Norway) is more resistant to sonographic exposure and provides sufficient signals at low mechanical index transmission power to allow for continuous real-time imaging (23). The major advantage of perfluorobutane is that it is phagocytosed by the reticuloendothelial cells, providing enhancement of liver parenchyma lasting for approximately 10–120 minutes (16). Because malignant hepatic lesions lack reticuloendothelial cells, they appear hypoechoic in the background of enhanced liver (16). Therefore, compared with sulfur hexafluoride, it provides more time for the interventionist for the detection, localization, and ablation of the lesion. In a large case-control study evaluating the role of perfluorobutane in guiding RF ablation of HCC (3), it was reported that the number of RF ablation sessions required with contrast-enhanced US was significantly less than seen in historical controls (1.33 vs 1.49; \( P = .0019 \)). Another study (4) showed that there was a tendency for a reduced number of treatment sessions required with contrast-enhanced US–guided RF ablation with perfluorobutane (1.19 vs 1.33), although the difference was not found to be significant. However, limited availability of perfluorobutane has prompted investigators to look at other avenues for a possible solution.

Sulfur hexafluoride, a more widely available second-generation US contrast agent, is similar to perfluorobutane

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Contrast Agent</th>
<th>Type</th>
<th>No. of Pts.</th>
<th>Mean Tumor Size (mm)</th>
<th>Procedure</th>
<th>Success of First Treatment Session (%)</th>
<th>Mean Treatment Sessions</th>
<th>Mean Follow-up (Mo)</th>
<th>Mean Progression (%)</th>
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<tr>
<td>Numata et al (9), 2003</td>
<td>Levovist</td>
<td>Case series</td>
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<td>14</td>
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<td>1.0</td>
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<td>Case series</td>
<td>13</td>
<td>17</td>
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<td>1.07</td>
<td>13</td>
<td>7.7</td>
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<td>Levovist</td>
<td>Case-control study</td>
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<td>17/17</td>
<td>RF</td>
<td>95.2/32</td>
<td>1.05/2.0</td>
<td>16/15</td>
<td>10/15</td>
</tr>
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<td>Solbiati et al (1), 2004</td>
<td>Sonovue</td>
<td>Case series</td>
<td>51</td>
<td>ND</td>
<td>RF</td>
<td>94.7</td>
<td>1.21</td>
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<tr>
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<td>Levovist</td>
<td>RCT</td>
<td>19/20</td>
<td>12/13</td>
<td>RF</td>
<td>94.7/65</td>
<td>1.1/1.4</td>
<td>21.5/19.4</td>
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HCC = hepatocellular carcinoma, ND = not described, NR = not reported, PEI = percutaneous ethanol injection, RCT = randomized controlled trial, RF = radiofrequency, TAI = transcatheter arterial infusion chemotherapy with Lipiodol.
even though it does not undergo phagocytosis by Kupffer cells (23). It acts as a blood pool agent that is dispersed into the extracellular space and can be seen for only 5–6 minutes during the contrast-enhanced imaging process (1,21). There have been scattered reports of the use of sulfur hexafluoride as a modality in guiding ablation of HCC. A recent study (21) described contrast-enhanced US-guided RF ablation with the use of sulfur hexafluoride in 12 patients with metastatic HCC after liver transplantation and reported a success rate of 91.7% for the first treatment session.

The results of the present study are in agreement with most of the previous reports in this subject. Complete response was achieved in a single session in all patients, with no major procedure-related complications. During the follow-up period (mean, 16 mo; range, 9–26 mo), no residual or recurrent tumor was detected in the ablated area. All patients with Child class A cirrhosis had progression-free disease as of the last follow-up contact. In contrast, distant tumor progression was seen in three of 14 patients (21.4%), all of whom had Child class B cirrhosis. During the follow-up period, two of these three patients with new lesions died of progression of disease.

The limitations of the present study include the lack of randomization, combined with its retrospective nature, small sample size, and limited follow-up. Moreover, because US is operator-dependent, visualization of nodules in certain locations of the liver, such as those immediately below the diaphragm, may be difficult for safe and effective RF ablation even with the use of contrast agent, and it remains to be seen whether the results of the present study can be replicated in a different setting.

In conclusion, the present study suggests that contrast-enhanced US can be an efficient tool for guiding RF ablation of early-stage HCC lesions that are not optimally visualized on grayscale US or noncontrast CT, with encouraging results in terms of tumor-free survival and minimal complication rate. Also, the results achieved with sulfur hexafluoride were comparable to those reported with the use of perfluorobutane. In addition, contrast-enhanced US does not involve radiation exposure and uses non-nephrotoxic contrast medium. Because a sizeable proportion of patients with advanced chronic liver disease and HCC can have marginal to substantial renal dysfunction, contrast-enhanced US can be a safer alternative to contrast-enhanced CT and MR imaging for guiding RF ablation in such patients.

REFERENCES