Combination Guidance of Contrast-Enhanced US and Fusion Imaging in Radiofrequency Ablation for Hepatocellular Carcinoma with Poor Conspicuity on Contrast-Enhanced US/Fusion Imaging

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Key Words
Contrast-enhanced US · Fusion imaging · Hepatocellular carcinoma · Poor conspicuity · Radiofrequency ablation · Sonazoid

Abstract
Purpose: The purpose of this study was to evaluate the usefulness of the combination guidance of contrast-enhanced US (CEUS) and fusion imaging in radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) with poor conspicuity on B-mode US and CEUS/fusion imaging. Materials and Methods: We conducted a retrospective cohort study, which included 356 patients with 556 HCCs that were inconspicuous on B-mode US. A total of 192 patients with 344 HCCs, 123 patients with 155 HCCs, and 37 patients with 57 HCCs underwent RFA under CEUS guidance, fusion imaging guidance, and the combination of CEUS and fusion imaging guidance. Results: The average number of treatment sessions was 1.1 (range: 1–2) in the CEUS guidance group, 1.1 (range: 1–2) in the fusion imaging guidance group, and 1.1 (range: 1–3) in the combination of CEUS and fusion imaging guidance group. Treatment analysis did not reveal significantly more RFA treatment sessions in the combination guidance group than in the other groups (p = 0.97, Student’s t test). During the follow-up period (1.1–85.3 months, mean ± SD, 43.2 ± 59.5), the 3-year local tumor progression rates were 4.9, 7.2, and 5.9% in the CEUS guidance group, the fusion imaging guidance group, and the combination guidance group, respectively (p = 0.84, log-rank test). Conclusion: In spite of selection bias, session frequency and local tumor progression were not different under the combination guidance with CEUS and fusion imaging in RFA. The combination of fusion imaging and CEUS guidance in RFA therapy is an effective treatment for HCC with poor conspicuity on B-mode US and CEUS/fusion imaging.

Introduction
Radiofrequency ablation (RFA) is widely performed as a percutaneous local treatment for unresectable hepatocellular carcinoma (HCC). Extensive worldwide experience has supported the use of RFA as an excellent treatment option for small HCC (<3 cm), with 3-year disease control rates of up to 80–90% [1–3]. Some centers adopt RFA as first-line treatment for single HCC nodules <3.0 cm in diameter [4–7]. Percutaneous RFA is performed by advancing a specially designed electrode into the tumor under re-
al-time sonographic guidance. The technical effectiveness of RFA depends on correct targeting on US and adequate placement of the RFA needle. However, difficult situations are sometimes encountered in which B-mode US cannot adequately visualize HCCs. For example, viable HCC could not be differentiated from dysplastic nodules in cirrhotic liver or ablated liver tissue due to previous RFA [8, 9].

Contrast-enhanced US (CEUS) or fusion imaging of US with CT/MRI has been increasingly used for the detection, characterization and planning of therapeutic interventions for liver tumors [10, 11]. Especially, CEUS or fusion imaging has been reported to be useful for RFA guidance in difficult cases. CEUS is able to detect tumor vascularity sensitively and accurately [12–16]. In particular, when using only perfluorocarbon microbubbles (sonazoid), HCCs have been shown as defects during the Kupffer phase [10, 17–21]. These defect lesions could be used as targets for the insertion of a RFA needle [22–28]. Moreover, a definitive diagnosis of HCC can be made by tumor staining in defect lesions after injecting an additional new dose of sonazoid [21, 24]. On the contrary, a fusion imaging system enables the synchronized display of real-time US images and multiplanar reconstruction images of CT/MRI corresponding to the cross section of real-time US. The multiplanar reconstruction images are reconstructed based on CT/MR images and displayed as a reference with real-time US images side-by-side on the same monitor. Therefore, fusion imaging is also useful for the detection of HCC and safe RFA therapy of HCC [29–36]. Occasionally, however, there are HCC cases which are more difficult to be detected even when using CEUS or fusion imaging [37].

Incorrect targeting on imaging could cause inadequate placement of the RFA needle. This could lead to more treatment sessions or more frequent local recurrence after RFA. For those more difficult cases, we have attempted to conduct RFA under the combination of CEUS and fusion imaging guidance. The purpose of this study was to assess the value of the combination guidance of CEUS and fusion imaging in RFA for HCC with poor conspicuity on B-mode US and CEUS/fusion imaging.

Materials and Methods

Written informed consent to perform RFA was obtained from all patients before treatment. This cohort study was conducted as a retrospective analysis of a prospective database in a single institution in which RFAs are routinely performed.

The records of HCC patients with poor conspicuity on B-mode US, who received RFA guided by CEUS, fusion imaging, or the combination of CEUS and fusion imaging, were reviewed. Between January 2007 and October 2013, 352 patients with 556 HCCs were enrolled in this study. The first objective was to compare the numbers of treatment sessions for technical effectiveness of ablation between the three guidance groups in RFA. The second objective was to compare the incidences of local tumor progression after RFA. The third objective was to investigate the occurrences of postprocedural complications.

HCC was diagnosed based on three-phase contrast-enhanced CT findings such as positive enhancement in the arterial phase and washout in the equilibrium phase in patients with chronic liver disease. All patients met the following criteria for treatment with RFA: percutaneous accessibility of the tumors, absence of portal tumor thrombus and extrahepatic metastasis, prothrombin time ratio >50%, total bilirubin <4.0 mg/dl, and platelet count >30,000/μl.

Equipment

B-mode sonographic scans were obtained using a LOGIQ 7 or E9 (GE Healthcare, Chalfont St. Giles, UK) with a 1–5-MHz convex probe (4C). The acoustic power of contrast harmonic sonography was set at the default setting with a mechanical index of 0.2. A single focus point was set at the deepest point of the monitor. The sonographic contrast agent was perfluorocarbon microbubbles of NC100100 (Sonazoid; Daiichi-Sankyo, Tokyo, Japan; GE Healthcare) with a median diameter of 2–3 μm. This contrast agent was reconstituted for injection with 2 ml sterile water for injection. The anticipated clinical dose for imaging of liver lesions was 0.010 ml of encapsulated gas per kilogram of body weight.

Fusion imaging using the fusion system by GE Healthcare was composed of a main unit in the US machine, a corresponding probe sensor, and a magnetic field generator. Additionally, dedicated software must be installed on the US system. The probe sensor is detected by a magnetic positioning system, which calculates the exact position of the sensor in the room. Standard Digital Imaging and Communications in Medicine (DICOM) data sets of all cross-sectional modalities (CT or MRI) are used for image fusion. The DICOM data are loaded in the US system, after which registration of the datasets takes place. This registration can be performed based on a number of fixed reference points or by plane. After successful image fusion, the registered CT or MR images move simultaneously with the examined US imaging plane.

Patients were treated by RFA (Cool-Tip RF Ablation System; Covidien, Boulder, Colo., USA). 20-cm long, 17-gauge monopolar internally cooled electrodes with 3- or 2-cm long exposed metallic tips were used to deliver radiofrequency energy. A 200-Watt, 480-kHz monopolar radiofrequency generator regulated by impedance was used as the energy source.

RFA Procedure for HCC with Poor Conspicuity

We have used LOGIQ E9 for RFA treatment since September 2011 (before then LOGIQ 7 was used). Percutaneous RFA is mainly performed for clearly visualized HCC under B-mode US guidance in our hospital. If necessary, it can also be used under the guidance of CEUS or fusion imaging for HCC with poor conspicuity. The guidance selection in RFA is a complex decision involving many factors (fig. 1). Sonazoid-enhanced US guidance could be an option because of visualization or qualitative diagnosis of HCC (n = 196). On the contrary, the fusion imaging guidance in RFA could be an option because of the detection of HCC (n = 123). Moreover, in patients having poorly inconspicuous HCC on fusion imaging, additional CEUS using sonazoid was performed in order to accurately localize the tumor at the time of the RFA procedure.
The patients with poorly conspicuous HCC on CEUS underwent additional fusion imaging during the RFA procedure (n = 13).

In patients with the combination imaging guidance in RFA, HCCs were targeted on the Kupffer phase of the CEUS image, when the tumor was seen as a perfusion defect on CEUS at the corresponding site of the fused CT/MR image (Fig. 2). After the RF electrode penetrated the HCC using a fixed-angle guide attachment, each ablation was performed for >8 min with >40 W at the beginning. Thereafter, the hyperechoic zone appeared and gradually increased at the ablated site. The ablation was continually monitored and was stopped when the HCC (including the safety margin) was completely covered by the zone of hyperechogenicity.

Assessment of Technical Effectiveness and Follow-Up
A few days after treatment, the technical effectiveness of ablation was assessed based on contrast-enhanced CT scan findings. A tumor was considered to have been successfully ablated when there were no longer any enhanced regions either within the entire tumor during the arterial phase or a >0.5-cm margin of apparently normal hepatic tissue surrounding the tumor during the portal phase [38]. Part of the tumor was diagnosed as remaining viable when images of the ablated area showed nodular peripheral enhancement. The residual portion was treated with additional RFA the next week. Any complications were recorded. If the follow-up CT images showed successful RFA and the absence of new tumors, three-phase dynamic CT scans were repeated at 3-month intervals.

Statistical Analysis
All values were expressed as means ± standard deviation (SD). Comparisons between the three groups were analyzed using the Student t test or Mann-Whitney U test. Local tumor progression rate curves of the three groups were compared by using a log-rank test. The χ² test was used to compare the rate of complications. p < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 12.0 (SPSS, Chicago, Ill., USA).

Results

Patient Characteristics
During the study period, we detected 556 HCCs that were inconspicuous on B-mode US. The patient population included 252 men and 100 women (age range, 49–88 years; 65.8 ± 27.6 years). The maximal diameter of the tumors ranged from 0.5 to 6.0 cm (1.5 ± 0.9) on dynamic CT. Table 1 shows the characteristics of the three groups. The distributions of sex, age, viral etiology, platelet count and tumor location were not different between these groups. A total of 29 (78.4%), 6 (16.2%) and 2 (5.4%) patients in the combination guidance group were classified as Child-Pugh classes A, B and C liver function, respectively. The proportions of patients with each Child-Pugh score and classification did not differ significantly. The mean tumor diameter was 1.5 ± 1.1 cm (range, 0.5–6.0) in the CEUS guidance group, 1.4 ± 0.6 cm (range, 0.5–4.0) in the fusion imaging guidance group and 1.3 ± 0.4 cm (range, 0.5–2.5) in the combination of CEUS and fusion imaging guidance group (p = 0.143).
Table 1. Patients’ characteristics of the CEUS guidance group, the fusion imaging guidance group and the combination of fusion imaging and CEUS guidance group

<table>
<thead>
<tr>
<th></th>
<th>CEUS guidance (n = 192 with 344 HCCs)</th>
<th>Fusion imaging guidance (n = 123 with 155 HCCs)</th>
<th>Fusion imaging + CEUS guidance (n = 37 with 57 HCCs)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69.6 ± 8.8</td>
<td>70.9 ± 7.9</td>
<td>65.8 ± 8.5</td>
<td>0.088</td>
</tr>
<tr>
<td>Sex (male/female), n</td>
<td>138/54</td>
<td>91/32</td>
<td>23/14</td>
<td>0.441</td>
</tr>
<tr>
<td>HBV/HCV/no HBV/no HCV, n</td>
<td>25/150/21</td>
<td>20/86/17</td>
<td>7/28/2</td>
<td>0.475</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td>5.7 ± 0.9</td>
<td>5.8 ± 1.0</td>
<td>5.6 ± 1.1</td>
<td>0.423</td>
</tr>
<tr>
<td>Platelet, x10^5/μl</td>
<td>11.3 ± 5.6</td>
<td>11.4 ± 5.7</td>
<td>12.2 ± 5.5</td>
<td>0.475</td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td>1.5 ± 1.1</td>
<td>1.4 ± 0.6</td>
<td>1.3 ± 0.4</td>
<td>0.143</td>
</tr>
<tr>
<td>Location S1/lat/med/ant/post</td>
<td>3/54/46/144/97</td>
<td>2/15/25/64/49</td>
<td>0/4/7/22/24</td>
<td>0.110</td>
</tr>
</tbody>
</table>

HBV = Hepatic B virus; HCV = hepatic C virus; S1 = segment I; lat = lateral segment of the liver; med = medial segment of the liver; ant = anterior segment of the liver; post = posterior segment of the liver.

Fig. 2. Images of a 61-year-old man with a 1.2-cm local tumor progression of HCC after transcatheter arterial chemoembolization. a Local tumor progression of HCC as a defect lesion (arrow) in segment V of the liver is shown on a hepatobiliary phase image of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced MRI. b B-mode US showing an area of segment V of the liver, but the HCC nodule cannot be clearly detected. c The right panel shows an oblique MR image with a HCC focus defect (arrow). The left panel shows a hypoechoic area (arrowhead) by CEUS using sonazoid. d A RFA needle (arrowhead) was inserted in the defect. e The hyperechoic area (arrow) covers the treated HCC after RFA. f An early-phase dynamic CT scan obtained 1 day after RFA therapy shows that the tumor and the surrounding area (arrow) are not enhanced.
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Technical Success of RFA Treatment
The technical success rates after a single session were 92.2% (177/199), 91.1% (112/123) and 89.2% (33/37) for the CEUS guidance group, the fusion imaging guidance group and the combination guidance group, respectively. The average number of treatment sessions was 1.1 ± 0.2 (range: 1–2) in the CEUS guidance group, 1.1 ± 0.3 (range: 1–2) in the fusion imaging guidance group, and 1.1 ± 0.4 (range: 1–3) in the combination of CEUS and fusion imaging guidance group. Treatment analysis revealed that the number of RFA treatment sessions in the combination guidance group was not significantly higher than in the other groups (p = 0.97, Student’s t test).

Local Tumor Progression
Follow-up time ranged from 1.1 to 85.3 months (43.2 ± 59.5). During the follow-up period, the 3-year local tumor progression rates were 4.9, 7.2, and 5.9% in the CEUS guidance group, the fusion imaging guidance group, and the combination guidance group, respectively (p = 0.84, log-rank test)(fig. 3).

Complications
No major complications were encountered in any of the guidance groups, and the overall rates of minor complications were 15.1% (29/192) in the CEUS guidance group, 10.6% (13/123) in the fusion imaging guidance group, and 5.4% (2/37) in the combination of CEUS and fusion imaging guidance group (table 2). There were no significant differences in incidence between the imaging guidance groups (p = 0.31, χ² test).

Discussion
Small HCCs with poor sonographic conspicuity are difficult to localize for RFA therapy in patients with liver cirrhosis. These inconspicuous HCCs could be blindly ablated by placing an electrode into the expected area of the liver, but more frequent mistargeting or incomplete ablation would be induced. Patients with poor conspicuity on B-mode US and CEUS/fusion imaging receive RFA treatment under the most difficult conditions, and we expected that more frequent sessions of RFA and/or local tumor progression would occur. However, there were no significant differences in the technical success rates of RFA therapy and the incidence of local tumor progression between the imaging guidance groups.

By the combination guidance of CEUS and fusion imaging, we could place the RFA electrode close to incon-

Table 2. Complications of RFA guided by CEUS, fusion imaging and the combination of CEUS and fusion imaging

<table>
<thead>
<tr>
<th></th>
<th>CEUS guidance, % (n = 192)</th>
<th>Fusion imaging guidance, % (n = 123)</th>
<th>Fusion imaging + CEUS guidance, % (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusion</td>
<td>6.8 (13/192)</td>
<td>7.3 (9/123)</td>
<td>0</td>
</tr>
<tr>
<td>Ascites</td>
<td>2.1 (4/192)</td>
<td>0.8 (1/123)</td>
<td>0</td>
</tr>
<tr>
<td>Hemothorax</td>
<td>1.6 (3/192)</td>
<td>1.6 (2/123)</td>
<td>0</td>
</tr>
<tr>
<td>Diaphragmatic injury</td>
<td>1.6 (3/192)</td>
<td>0.8 (1/123)</td>
<td>5.4 (2/37)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1.0 (2/192)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic infarction</td>
<td>0.5 (1/192)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemobilia</td>
<td>0.5 (1/192)</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>
spicous HCC under the most difficult conditions. In addition, a larger ablation zone would preclude incomplete ablation. These might explain the absence of differences in the technical success of the combination guidance group.

In a strict and fair assessment of treatment response, a sufficient ablation margin can reduce the risk of local tumor progression after RFA. Our database is prospectively managed under the same criteria of treatment response assessment. Accordingly, it is unsurprising that there was no significant difference in the incidence of local tumor progression between the three imaging guidance groups. However, local tumor progression was observed in 3 patients with the combination of fusion imaging and CEUS guidance in RFA. In those patients, partial volume effects could have caused an underestimation of the tumor ablation margin.

There were several limitations in this study including its retrospective and single-center design. We are fully aware that this study suffered from selection bias because the imaging guidance method for RFA was chosen according to the RFA operator’s subjectivity.

In summary, poor conspicuity on B-mode US and CEUS/fusion imaging represents the most difficult condition for percutaneous RFA. However, both increased frequency of RFA sessions and local tumor progression under the combination guidance with CEUS and fusion imaging in RFA did not occur in HCC patients with poor conspicuity on B-mode US and CEUS/fusion imaging. The combination of fusion imaging and CEUS guidance in RFA therapy is an effective treatment for poorly defined HCCs on B-mode US and CEUS/fusion imaging.

Disclosure Statement

The authors declare that no financial or other conflicts of interest exist in relation to the content of this article.

References


