Evaluation of Local Recurrence After Treatment for Hepatocellular Carcinoma by Contrast-Enhanced Ultrasonography Using Sonazoid: Comparison with Dynamic Computed Tomography

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ABSTRACT: Purpose. To evaluate the effectiveness of contrast-enhanced ultrasonography (CEUS) using Sonazoid for the diagnosis of the local recurrence after treatment for hepatocellular carcinoma (HCC) by comparing it with dynamic CT.

Methods. Seventy-one patients with 87 HCC lesions (mean ± SD; 19.5 ± 9.6 mm) underwent CEUS using Sonazoid and dynamic CT after radiofrequency ablation (n = 55), transcatheter arterial chemoembolization (n = 22), or radiofrequency ablation combined with transcatheter arterial chemoembolization (n = 10). Two hepatologists (observer 1; 10 years of experience, and 2; 20 years of experience) reviewed the CEUS and dynamic CT images independently and evaluated presence or absence of the local recurrence. Diagnostic performance for the local recurrence was assessed using receiver operating characteristic curve analysis.

Results. The Az value for dynamic CT was significantly lower in observer 1 than 2 (p < 0.05). The sensitivity of CEUS was 79% in observer 1 and 83.9% in observer 2, and that of dynamic CT was 83.9% and 90.3%, respectively. The specificity of CEUS was 96%, and that of dynamic CT was 92%, in both observers.

Conclusion. This study suggests that CEUS using Sonazoid is less affected by the observer’s experience and is more accurate in the diagnosis of local recurrence after treatment for HCC than dynamic CT. © 2010 Wiley Periodicals, Inc. J Clin Ultrasound 38:182–189, 2010; Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jcu.20685

Keywords: contrast-enhanced ultrasonography; Sonazoid; hepatocellular carcinoma; local recurrence

Hepatocellular carcinoma (HCC) is one of the most common primary malignancy tumors throughout the world and occurs in almost all patients with liver cirrhosis. Surgical resection has been found to be a very effective treatment for the prevention of the local recurrence of HCC.1 However, in most patients with HCC, surgical resection is limited by liver dysfunction caused by liver cirrhosis. Recently, radiofrequency ablation (RFA) has begun to be more widely used for the treatment of HCC because of a higher rate of complete necrosis and because fewer treatment sessions are required than with percutaneous ethanol injection therapy (PEIT).2 On the other hand, transcatheter arterial chemoembolization (TACE) and RFA combined with TACE are recommended for unresectable HCC with a size of more than 3 cm or 4 or more lesions.3–5 For the therapeutic response in HCC treated with these therapies, dynamic CT6,7 and MRI8 are mainly performed. Recently, the usefulness of contrast-enhanced ultrasonography (CEUS) using Levovist (Schering, Berlin, Germany) for the assessment of HCC immediately after treatment or its recurrence has been reported, but several problems concerning the limitation...
for imaging in real-time scans and technical aspects of the procedure itself have also been suggested.9–14 Sonazoid (Daiichi-Sankyo, Tokyo, Japan), a new second-generation contrast agent, has been licensed for clinical use in Japan. Sonazoid is more stable and resistant to sonographic exposure; it produces sufficient harmonic signals at a low mechanical index (MI) transmission power to allow continuous real-time imaging. Under low acoustic pressure, CEUS using Sonazoid can show the vessel images in the vascular phase and liver parenchymal images in the postvascular phase in real-time.15–21 Because of these characteristics, Sonazoid is expected to be useful for the detection, characterization, and hemodynamic evaluation of hepatic lesions and assessment of function of Kupffer cells.

There have been reports on the assessment of residual HCC after TACE by CEUS using Sonazoid,22 but no study comparing the diagnostic efficacy of CEUS using Sonazoid and dynamic CT for residual HCC or local recurrence after RFA. In this study, we evaluated the accuracy of CEUS using Sonazoid for the diagnosis of the local recurrence of HCC after treatment and compared it with dynamic CT.

MATERIALS AND METHODS

This study was approved by the Ethical Review Board of Toho University Medical Center, Omori Hospital.

Patient Sample

Seventy-one patients (51 men, 20 women, with a mean ± SD age of 70 ± 8 years (range, 46–86)) with a background of chronic hepatitis and liver cirrhosis had a total of 87 lesions which were treated by RFA (n = 55), TACE (n = 22), and RFA combined with TACE (n = 10), between May 2002 and October 2008. The patients either had no surgical indication according to the Milan criteria (20 patients) or did not wish to undergo surgical treatment (51 patients). The mean ± SD maximal diameter of the HCC lesions was 20 ± 10 mm (range, 8–65 mm). The final diagnosis of HCC was based on sonography (US)-guided percutaneous fine-needle biopsy using a fine cutting needle, dynamic CT, gadolinium-MRI, and/or clinical laboratory data, including an elevated serum α-fetoprotein level, lens culinaris agglutinin-reactive α-fetoprotein level, and des-gamma-carboxyprothrombin (PIVKA2) level.

All patients underwent CEUS with Sonazoid and dynamic CT during posttreatment follow-up. CEUS and dynamic CT examinations were performed within a time period of 3.1 ± 2.5 days. The median time period from each treatment to the CEUS or dynamic CT examination was 267 days (range, 34–1882 days).

In this study, two experienced radiologists read the dynamic CT scans of the lesions and diagnosed the presence or absence of local recurrence for each treated lesion. In case of disagreement or in case of atypical findings or difficulty in the diagnosis of local recurrence, fine-needle biopsy, gadolinium-MRI, and gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid-enhanced MRI (Gd-EOB-DTPA-MRI) were performed, and the presence or absence of local recurrence was definitively determined concerning all lesions. Consequently, 62 lesions diagnosed with and 25 diagnosed without local recurrence were evaluated.

RFA Method

RFA techniques were previously described.23 RFA systems used in this study were the RTC 2000 and 3000 Systems (Boston Scientific Inc., Natick, MA) and the Cool-tip RFA System (Covidien, Boulder, CO). All patients underwent US-guided RFA.

TACE Methods

TACE was performed using the right femoral arterial approach with the Seldinger method. Prior to chemoembolization, the patency of the portal vein was confirmed by celiac trunk and superior mesenteric artery arteriography. After the tumor vessels and their feeding artery had been revealed, an emulsion of epirubicin (20–40 mg/person; Farmorbicin; Kyowa Hakko, Tokyo, Japan) and iodized oil (2–4 ml; Lipiodol; Guerbet, Aulnay-sous-Bois, France) was administered into the feeding artery under fluoroscopic guidance and followed by gelatin sponge (Gelpart; Astellas Pharma, Tokyo, Japan) via a catheter. The gelatin sponge was administered until feeding arteries were completely obliterated.

RFA Combined with TACE Methods

For large HCC with a maximal diameter of 25 mm or greater, TACE was performed first by
the method described above, and RFA was conducted after about 1 month later. In patients who underwent RFA or RFA combined with TACE, dynamic CT was performed 2–4 days after RFA, and if unablated regions were observed in the treated area, additional RFA was carried out on the day after dynamic CT.

CEUS with Sonazoid
All CEUS were performed by one of two sonographers (with more than 10 years of experience). Examination of US was performed using an Aplio XG (Toshiba, Tokyo, Japan) and a microconvex probe (PVT-375BT, 3.75 MHz; Toshiba). The acoustic power of CEUS was set at MI of 0.2; the dynamic range was fixed at 60–65 dB. A single focus point was set at the lower margin of the lesion, and a bolus intravenous injection of Sonazoid (0.015 ml/kg body weight) was performed via the left elbow venous line followed by 10 ml normal saline flush. After injection of Sonazoid, the patients were requested to hold their breath. The images of the ideal scanning plane were displayed in real-time mode for all phases. The vascular findings on pulse subtraction harmonic imaging US were shown as lesion vessel flow in the early vascular phase (about 15–40 seconds after the injection of Sonazoid). Parenchymal findings were obtained as Kupffer imaging in the postvascular phase at least 15 minutes after the intravenous injection of Sonazoid. Images were recorded in cine loop memory and stored digitally on hard disc. The observers reviewed the images frame by frame from the stored video-clips.

Dynamic CT
All dynamic CT examinations were performed by 16-multidetector CT scanner (Aquilion 16; Toshiba), and images were obtained cephalocaudal with sections thickness of 5 mm and pitch of 0.94, with intravenous bolus injection of nonionic contrast material (90 ml of 300 mgI/dl; Iopamiron, Bayer Schering Pharma, Osaka, Japan) at 3 ml/s via an antecubital vein. The scanning delay set for arterial phase and equilibrium phase was 30–40 seconds and 120–150 seconds, respectively.

Imaging Analysis
All CEUS and dynamic CT images were reviewed by two clinicians specialized in liver diseases, one with 10 years of experience (observer 1) and the other with 20 years of experience (observer 2). The two observers were not involved in the treatment of the HCC. They also evaluated CEUS and dynamic CT images without the knowledge of the clinical characteristics or therapeutic regimen of each patient. CEUS and dynamic CT images were evaluated with an interval of about 1 week by the two observers.

When a lesion was identified within or in contact with the treated area during the follow-up period, it was considered to be a local recurrence. On CEUS, based on previous descriptions of HCC on CEUS with Sonazoid,22,24 we considered an enhancing lesion that was either nodular or crescent-shaped at the margins of the treated area in the early vascular phase associated with a defect in the postvascular phase to be a local recurrence (Figure 1A–D). On dynamic CT, we considered a lesion that was hypervascular in the arterial phase and hypovascular in the equilibrium phase to be a local recurrence (Figure 1E,F).6 The observers scored each examination for the presence or absence of local recurrence using the following scoring system: 1 = definitely absent; 2 = probably absent; 3 = possibly present; 4 = probably present; 5 = definitely present.

Statistical Analysis
For each imaging method, a binomial receiver operating characteristic curve was fitted to each clinician’s confidence rating using maximum likelihood estimation. The diagnostic accuracy of each imaging set for each observer and the composite data were calculated by measuring the area under the alternative free response receiver operating characteristic curve. The differences between imaging sets in terms of the mean Az value were statistically analyzed using the two-tail Student’s t test for paired data. The sensitivity and specificity in the diagnosis of recurrence for each image set were then calculated. The sensitivity of each observer was determined by detecting the number of lesions assigned a score of 4 or 5 out of the 87 lesions. The degree of interobserver agreement was calculated with a kappa statistics. In general, a kappa value greater than 0.75 is considered excellent agreement; 0.4–0.75 is good agreement, and less than 0.4 is poor agreement.25 Statistical analysis was performed using SPSS version 11.0 (Statistical Package for the Social Sciences) for Windows (Microsoft). A p value of less than 0.05 was considered to indicate a statistically significant difference.

Mean ± SD and median values are given with ranges.
RESULTS

Local recurrence was confirmed in 62 of the 87 lesions. The kappa values were excellent between observer 1 and 2 for CEUS (κ value = 0.89) and they were good between observer 1 and 2 for dynamic CT (κ value = 0.66).

The Az values calculated by each observer with CEUS and dynamic CT for 87 lesions are shown in Table 1. While the Az values for CEUS (observer 1 = 0.99, observer 2 = 0.99) and dynamic CT (observer 1 = 0.94, observer 2 = 0.99) were high and showed no significant difference between observer 1 and 2, the Az value for dynamic CT (Az = 0.94) was slightly lower in observer 1 with 10 years experience. In both observers, although the mean Az value for CEUS (Az = 0.99) was higher than that for dynamic CT (Az = 0.96), they showed no significant difference. When the Az value of each imaging modality was compared between the two observers, the value for dynamic CT was significantly lower in observer 1 (Az = 0.94) than in observer 2 (Az = 0.99) (p < 0.05). The sensitivity of CEUS was 79% in observer 1 and 83.9% in observer 2, and that of dynamic CT was 83.9 and 90.3%, respectively. The specificity of CEUS was 96%, and that of dynamic CT was 92%, in both observers.

The additional treatment of the 62 lesions that showed a local recurrence was RFA in 49, and TACE in 13. Among the 25 lesions that showed no local recurrence, local recurrence was detected in 2 after 8 months and in 1 after 20 months by

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Area Under the ROC Curve and p Value for CEUS Using Sonazoid and Dynamic CT in Detecting Local Recurrence of HCC</th>
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<tbody>
<tr>
<td></td>
<td>Observer 1</td>
</tr>
<tr>
<td>CT</td>
<td>0.939</td>
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<tr>
<td>CEUS</td>
<td>0.985</td>
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<td>p</td>
<td>NS</td>
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* Statistical significance.

Abbreviations: CEUS, contrast-enhanced ultrasonography; HCC, hepatocellular carcinoma; ROC, receiver operating characteristic.
CEUS and dynamic CT during a median follow-up period of 288 days (range, 70–674 days).

DISCUSSION

Recently, RFA for HCC has been increasingly used in clinical applications because it is a simple minimally invasive and highly effective treatment modality. Also, TACE or RFA combined with TACE have been performed for unresectable HCC such as those 3 cm or greater and in patients with 4 or more lesions. HCC is known to be multicentric with intrahepatic metastasis, and a poor prognosis due to rapid enlargement of the residual tumor or local recurrence after treatment, although rare, has been reported. Therefore, to achieve a satisfactory survival rate, it is very important to accurately evaluate the therapeutic efficacy and ensure the early detection of local recurrence on follow-up examinations.

Although US has generally been used to guide the RFA electrode placement, the treatment response has been mostly evaluated by dynamic CT or MRI. Fully treated lesions show no contrast enhancement by dynamic CT or MRI, which indicates the disappearance of blood flow in the tumor, ie, necrosis. If treatment is incomplete, the residual tumor is detected by contrast enhancement in the treated area.

Dynamic CT is considered the standard imaging technique in the evaluation of residual lesions, recurrence, and complications such as abscess, infarction, hemorrhage, or needle tract seeding in patients who have undergone RFA. However, some hypervascular lesions may be imaged as hypovascular by dynamic CT due to various factors including the timing of imaging, cardiac output, and portal hemodynamics. Disadvantages of dynamic CT include radiation exposure and the risk of allergy to iodine.

Choi et al compared helical CT and CEUS using Levovist in the evaluation of the therapeutic efficacy of RFA for HCC at a mean time of 18 hours post-RFA. They noted a peripheral rim enhancement of uniform thickness around the ablated area, which was considered reactive hyperemia in 75% of the 73 lesions by helical CT and 34% of the lesions by CEUS using Levovist, and reported that helical CT was more sensitive than CEUS in the diagnosis of reactive hyperemia. Because an unablated region usually appears as a contrast-enhancing nodule on helical CT, it can usually be distinguished from reactive hyperemia. However, small residual tumors may not be distinguished from reactive hyperemia on helical CT performed immediately after treatment or during a short-term follow-up. Based on these observations, they reported that CEUS using Levovist was more useful for evaluation of the lesions shortly after treatment.

When evaluating response of HCC to TACE, both necrotic and viable areas exhibit high attenuation on contrast-enhanced CT after TACE owing to accumulation of iodized oil in tumor. Therefore, such evaluation should be delayed by at least 1 month because iodized oil in viable areas is washed out gradually, even if it filled the tumor immediately after treatment. CEUS using Levovist was reportedly useful for assessing the therapeutic response to TACE because Levovist is not affected by iodized oil accumulation. However, Levovist consists of microbubbles that collapse easily when exposed to high acoustic power. Therefore, CEUS using Levovist has major limitations for imaging the enhancing lesions in real-time.

Sonazoid consists of microbubbles of perfluorobutane gas stabilized by phospholipid monolayer shells with a median volume diameter of 2–3 μm. It is more stable and resistant to US than Levovist and generates sufficient harmonic signals at low MI transmission power to allow continuous real-time imaging. Also, it is taken up by Kupffer cells immediately after intravenous injection where it stays for 3 hours. The hepatic parenchyma-specific contrast phase is due to the distribution of the Sonazoid microbubbles in Kupffer cells.

When CEUS using Sonazoid and dynamic CT were compared regarding the evaluation of residual HCC 1 week after TACE, Sonazoid, like Levovist, was not affected by iodized oil accumulation and was reported to be effective for assessment of the early therapeutic response. However, there has as yet been no study that compared the diagnostic ability of CEUS using Sonazoid and dynamic CT for residual HCC or local recurrence after the treatment.

In our study, the \( \kappa \) coefficient between the two observers for CEUS was higher, at 0.89, than that for dynamic CT. Also, the Az value for dynamic CT was significantly higher in observer 2 with a 20-year experience than in observer 1 with a 10-year experience, but no significant difference was noted in the Az value for CEUS between the observers. This suggests that CEUS using Sonazoid is less affected by experience and allows a more accurate diagnosis of the local recurrence of HCC after treatment than dynamic CT. Without extensive experience in image read-
ing, it is considered difficult to distinguish a high-
attenuation area around the treated area due to
local recurrence from one due to reactive hypere-
mia or arterio-portal shunt in an early phase of
dynamic CT. The difference in the evaluation with
experience is considered to have been smaller by
CEUS using Sonazoid, because the assessment of
viable lesions around the treated area was easier
using this modality than dynamic CT.

For both observers, the sensitivity was higher
using dynamic CT, but the specificity was 96% by
CEUS and 92% by dynamic CT. In the study con-
ducted by Youk et al,32 the sensitivity of CEUS
using Levovist for residual tumor detection was
94.7% after TACE and 72.7% after RFA or PEIT.
The specificity of CEUS using Levovist for resid-
ual tumor detection was 80% after TACE and
79.2% after RFA or PEIT. In our study, the mean
sensitivity of CEUS was 81.5%, within the range
reported by Youk et al. The specificity of CEUS
(96%), however, was higher than the value
reported by Youk et al using CEUS by Levovist.
Choi et al11 suggested technical difficulties of US
as problems with the evaluation of the therapeu-
tic efficacy of RFA by CEUS using Levovist. In
CEUS using Levovist, images are basically
obtained intermittently while microbubbles are
destroyed at a high acoustic power, so that scan-
ing at intervals of the exact same area is not
easy for unskilled examiners. By employing
CEUS using Sonazoid, in contrast, the status of
contrast enhancement in the region of interest
can be observed in real-time continuously after
injection of the contrast agent. Moreover, unlike
CEUS using Levovist, CEUS using Sonazoid also
enhances the contrast of the tumor and paren-
chyma in real-time in the postvascular phase.

Generally, when grayscale US is performed to
screen for chronic liver disease, lesions are diffi-
cult to detect because the images are likely to be
affected by the echogenicity of the background
liver, and experience is required for their detect-
ion. Also, local recurrences after treatment are
small with a low amount of internal blood flow,
and their detection by grayscale US or dynamic
CT is difficult. In this study, the specificity was
higher by CEUS using Sonazoid than by dynamic
CT, suggesting that CEUS using Sonazoid is very
useful for the evaluation of the presence or ab-
sence of local recurrence.

In our study, 5 of the 8 lesions confirmed as
recurrences by dynamic CT alone were difficult to
detect, because they were deep-seated, the
patient was obese, or they were present in the
subcapsular region in S7 or S8 and were prone to
being obscured by artifacts from the lung. Con-
cerning disadvantages of CEUS using Levovist,
Choi et al11 also observed that harmonic signals
from a deep-seated lesion are often insufficient
for acceptable imaging. They could not perform
CEUS after RFA in 5 ablation zones that were
located deeper than 10 cm in the liver. Moreover,
CEUS is dependent on the patient’s ability to con-
trol breathing between scan phases. Thus, patient
training may be essential for achieving
acceptable image sets. Certainly, there are
patients that may not be suitable for CEUS
because of the site of their lesions or their inability
to control breathing. In this study, no local re-
currence was found at the initial examination
but about 10% of the lesions (3/25) were found to
have recurred on follow-up examinations. Whether
they were new lesions that arose from
treated areas or satellite lesions that had been
present around the tumor before treatment is
unknown.

This study had several limitations. First, the
study is a retrospective review of HCCs examined
by CEUS using Sonazoid and dynamic CT nearly
simultaneously after treatment, and the selection
of the lesions was biased. Second, the number of
evaluated lesions was small. Third, histopatho-
logic findings were not obtained from all patients
for the diagnosis of local recurrence. Finally, the
time elapsed from treatment of HCC to the exam-
ination was not uniform. For further evaluation of
the usefulness of CEUS using Sonazoid for the
detection of local recurrence after treatment for
HCC, a larger number of cases undergoing each
treatment including RFA, TACE, and RFA com-
bined with TACE must be accrued with follow-up
examinations done at fixed intervals.

CONCLUSION
To our knowledge, this is the first report compar-
ing the diagnostic ability of CEUS using Sonazoid
and dynamic CT for local recurrence after treat-
ment for HCC between observers with different
levels of experience. As indicated by the high
specificity, CEUS using Sonazoid improves the
accuracy of the diagnosis of local recurrence after
treatment for HCC. The modality seems to be
less affected by the observer’s experience than
dynamic CT.

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