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Role of Sonazoid-enhanced three-dimensional ultrasonography in the evaluation of percutaneous radiofrequency ablation of hepatocellular carcinoma

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ABSTRACT

Objective: We investigated contrast-enhanced three-dimensional ultrasonography (CE 3D US) with contrast agent Sonazoid for evaluating the effect of percutaneous radiofrequency (RF) ablation of hepatocellular carcinomas (HCCs).
Methods: 63 HCCs were treated by US-guided percutaneous RF ablation. CE 3D US after bolus injection of 0.2 mL of Sonazoid was performed 5–7 days before and 1 day after RF ablation. CE 3D computed tomography (CT) was performed 5–7 days before and 1 month after the ablation, and during the follow-up period. Multiplanar images in three orthogonal planes and US/CT angiograms were reconstructed on both modalities. Two blinded observers reviewed the images on both modalities to evaluate the ablation effects.
Results: After RF ablation, the evaluation on CE 3D US and that on CE 3D CT achieved concordance in 61 lesions. Among them, 59 lesions were detected with the absence of tumor vessels and tumor enhancement and evaluated as adequate ablation, and the remaining two lesions were detected with residual tumors. The kappa value for agreement between the findings on the two modalities was 0.65. When 1-month CE 3D CT scans were used as reference standard, the sensitivity, specificity, and accuracy of 1-day CE 3D US for detecting adequate ablation were 97%, 100%, and 97%, respectively.
Conclusion: By demonstrating the ablated areas and residual tumors in three dimensions, CE 3D US with Sonazoid was shown to be useful for evaluating the effect of RF ablation of HCCs, and there was good concordance with the results obtained by CE 3D CT.

1. Introduction

Hepatocellular carcinoma (HCC), with the increasing diagnosis at an early stage as a result of the development of modern radiological imaging methods, is now one of the most commonly diagnosed carcinomas worldwide [1–3]. For some HCC patients with no possibility of resection or liver transplantation, image-guided radiofrequency (RF) ablation, has been demonstrated to be an effective, relatively safe, and technically feasible method of coagulating tumors by elevating the local temperature to above 60 °C [4–6]. Completely ablated tumors become necrotic, however, because of certain factors, such as tumor location, imaging resolution, and operators' experience, thermal ablation of the tumor may be incomplete, resulting in the persistence of residual tumor and the need for additional ablation session at a later time. Thus, accurate evaluation of the effects after RF ablation, whether the tumor has been ablated adequately, is critical for further treatment.

Contrast-enhanced three-dimensional ultrasonography (CE 3D US) is a newly developed imaging technique that allows demonstration of the dynamic feature of HCCs and vessel structure in three orthogonal planes, and it has shown potential for characterizing hepatic tumors in recent studies [7–9]. However, to our knowledge, CE 3D US, which is expected to provide unique spatial views of ablated areas and residual tumors, has never been clarified in the evaluation of the effectiveness of RF ablation.

A novel second-generation ultrasound contrast agent, Sonazoid (Daiichi Sankyo, Tokyo, Japan), which has been commercially available in Japan since January 2007, was used for CE 3D US imaging in our study. Sonazoid consists of microbubbles of perfluorobutane gas with phospholipid monolayer shells. The stable

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Sonazoid microbubbles have been reported to be phagocytosed by reticuloendothelial cells in the liver parenchyma 5 min after administration, and thus they support a protracted contrast imaging [10–13].

The purpose of our study was to investigate the potential benefit of CE 3D US with a perfluorobutane-based contrast agent 1 day after ablation for evaluating the local effects of RF ablation of HCCs, in comparison with the findings of CE 3D computed tomography (CT) performed 1 month after RF ablation.

2. Materials and methods

2.1. Subjects

This prospective study was performed with the approval of our institutional review board. Full informed consent was provided by all patients before the study. Between February 2007 and November 2007, 69 consecutive patients with HCCs less than 30 mm in diameter were admitted to our department for RF ablation treatment. Their HCCs were not eligible for surgery but were accessible for a percutaneous RF ablation and had not been treated previously. The final diagnosis of HCCs 2 cm or more in diameter was made on the basis of both typical CE CT and CE magnetic resonance imaging (MRI) findings, and the final diagnosis of those less than 2 cm in diameter was confirmed by percutaneous biopsy. Among these 69 patients, we included the subjects for the prospective study according to the following inclusion criteria: patients with a hypervascular tumor enhanced on dynamic radiological imaging; patients with a tumor located in a proper position for CE 3D US scanning free of interference caused by costal bones, abdominal gas or heart motion; patients with good compliableness for both CE 3D US and CE 3D CT examinations before and after ablation. After excluding three patients with HCCs in inappropriate locations for acquisition of satisfactory CE 3D US images, two patients who were allergic to the CT contrast agent, and one patient with a HCC that was hypovascular in three phases by both modalities, the remaining 63 patients were adopted as the subjects of this study. Multiple HCCs were detected in 23 subjects and a single tumor in the other 40 subjects. In the subjects with multiple HCCs, the largest HCC whose diagnosis had been confirmed and which was in a proper position for CE 3D US scanning was selected to evaluate before and after RFA ablation. The clinical characteristics of the subjects are shown in Table 1.

Table 1
Clinical characteristics of the subjects with HCC lesions enrolled in this study.

Characteristics	
No. of patients	$n = 63$
Age (mean, range, years)	70, 53–80
Gender	
Male	$n = 38$
Female	$n = 25$
Etiology of HCC	
Hepatitis C	$n = 56$
Hepatitis B	$n = 4$
Alcohol abuse	$n = 3$
Child-Pugh classification	
Class A	$n = 55$
Class B	$n = 8$
Diameter of lesions	
>2 cm	$n = 35$
≤2 cm	$n = 28$
Diameter of lesions (mean, range, mm)	22, 10–30
Diagnosis confirmed by	
Biopsy	$n = 29$
Radiological imaging	$n = 34$

2.2. CE 3D US imaging

Five to seven days before and 1 day after RF ablation, CE 3D US was performed by a sonographer with 10 years of experience in abdominal US. The LOGIQ 7 ultrasound imaging system (GE Healthcare, Milwaukee, WI) and a convex volume 4D3C-L probe with a 2.0–5.5-MHz frequency were used. With internal sectorial mechanical tilt movement, the probe held by the sonographer allowed automatic scanning of a volume of interest (VOI). The position and size of the VOI could be adjusted before scanning so that it would cover the desired region. The LOGIQ 7 ultrasound imaging system is equipped with Autosweep 3D and Static 3D functionalities, and they were used for image acquisition by CE 3D US.

Before the CE 3D US scanning, all subjects received an intravenous bolus injection of 0.2 mL of Sonazoid, followed by 2 mL of 5% glucose solution, and subsequent infusion of 5% glucose solution at 10 mL/min. The contrast harmonic angio (CHA) mode (mechanical index = 0.5–0.9) at 8–13 frames per second was used as the insonation technique for CE 3D US. When the CE 3D US was performed, the reference images for the location of the lesions were shown on the same screen by the harmonic ultrasonography. The CE 3D US images were acquired during three contrast phases, consisting of an early phase (10–60 s after contrast medium injection), a middle phase (80–120 s after contrast medium injection), and a late phase (more than 5 min after contrast medium injection). The data acquired were stored as cineloops in the hard disk of the ultrasound imaging system.

After CE 3D scanning, the 3D images were reconstructed using the functionalities of the ultrasound imaging system. In each contrast phase tomographic ultrasound images (TUI) in view of parallel slices were reconstructed in three orthogonal planes, i.e., plane A, which could be translated from front to back in the VOI, plane B, which could be translated from right to left, and plane C, which could be translated from up to down. The distance between two adjacent slices could be adjusted in order to show the desired regions. Sonographic angiograms were reconstructed in angio-like views during the early phase and middle phase by using various rendering modes. The maximum intensity mode for displaying the maximum intensity grey value of the VOI, mixed with the surface mode for displaying the grey value on the surface of the object, was used to visualize tumor vessels and early tumor enhancement before RF ablation and to detect residual viable portions of hypervascular tumors after RF ablation, while the average intensity mode for displaying the average intensity grey value of the VOI, mixed with the surface mode, was employed to describe the unenhanced areas, such as the coagulated areas with perfusion defect after treatment. TUI in three orthogonal planes and sonographic angiogram images with raw volume data were stored in the hard disk of the ultrasound imaging system.

2.3. CE 3D CT imaging

Five to seven days before the RF ablation, 1 month after the RF ablation, and during the follow-up period CT scanning was performed with a commercially available CT scanner (16-channel multi-detector-row CT scanner; Toshiba Medical Systems Co., Ltd., Tokyo, Japan) with the following protocol: tube voltage, 120 kV; tube current, auto mA exposure setting; reconstruction section and interval thickness, 5 mm; detector configuration, 16 mm × 1 mm; pitch, 15; and 0.5 s per rotation. The subjects were divided into a group weighing under 70 kg, who were injected with a 300-mgI/mL dose of the nonionic contrast medium iopamidol (Iopamiron 300; Bayer Healthcare, Osaka, Japan) and a group weighing 70 kg or more, who were injected with a 370-mgI/mL dose of iopamidol. A catheter placed in the peripheral vein of the antecubital fossa was used to administer 100 mL of contrast medium at a rate of