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Original Article

Clinical value of dynamic 3-dimensional contrast-enhanced ultrasound imaging for the assessment of hepatocellular carcinoma ablation☆

Yandong Wang, Xiang Jing *, Jianmin Ding

Department of Ultrasound, Tianjin Third Central Hospital, Tianjin Key Laboratory of Artificial Cell, Tianjin 300170, China

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ABSTRACT

Objective: The aim of the study was to investigate the performance of dynamic 3-dimensional contrast-enhanced ultrasound (3D-CEUS) on assessment of efficacy of local ablation therapy of hepatocellular carcinoma (HCC) with contrast-enhanced computed tomography (CT) as reference standard.
Methods: Eighty-nine HCC lesions from 75 patients undergoing ultrasound-guided percutaneous thermal ablation or chemical ablation were studied by both dynamic 3D-CEUS and contrast-enhanced CT 1 month after ablation. Imaging results from two imaging modalities were evaluated independently by experienced readers to determine whether the treated lesions were ablated incompletely (residual unablated tumor) or completely. Sensitivity, specificity, positive and negative predictive values, and accuracy to identify incomplete ablation were calculated for dynamic 3D-CEUS imaging with contrast-enhanced CT as reference standard.
Results: Contrast-enhanced CT reported that 80.9% (72/89) of all the treated lesions were completely ablated and 19.1% (17/89) were incompletely ablated. The dynamic 3D-CEUS identified 82.0% (73/89) and 18.0% (16/89) of lesions as completely and incompletely ablated, respectively. With contrast-enhanced CT as the reference standard, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of dynamic 3D-CEUS for identifying residual unablated tumor were 88.2% (15/17), 98.6% (71/72), 93.8% (15/16), 97.3% (71/73), and 96.6% (86/89), respectively. The Kappa value for identifying residual unablated tumor between contrast-enhanced CT and dynamic 3D-CEUS was 0.89.
Conclusions: Dynamic 3D-CEUS is highly consistent with contrast-enhanced CT in assessment of efficacy of HCC ablation and has potential to serve as an alternative to contrast-enhanced CT in the follow-up assessment after HCC ablation.

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1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It is the sixth most common cancer worldwide and the third most common cause of cancer mortality [1]. For various reasons, the majority of patients with primary or secondary hepatic malignancies are not candidates for surgery. Image-guided percutaneous ablation has been shown to be a viable option for the treatment in some of these patients and had been considered as a safe and effective treatment for early HCC and small liver metastases in surgically unresectable patients [2–5].

Clinical, laboratory, and imaging follow-up are usually performed 1 month after treatment to assess treatment response to monitor evolution of the ablated tissue over time. For incompletely ablated lesions, further treatments are necessary. Early detection of residual tumor and recurrence after ablation is therefore the key to prompt intervention [6,7].

There are various imaging modalities [e.g., ultrasonography (US), contrast-enhanced computed tomography (CT), contrast-enhanced magnetic resonance (MR) imaging, positron emission tomography, and contrast-enhanced ultrasound (CEUS)] being used in follow-up of HCC ablation. Contrast-enhanced CT or MR imaging was routinely regarded as the reference standard in the evaluation of tumor response [8,9]. However, their application in clinical scenarios of HCC ablation is limited by higher cost, complexity of procedure, radioactive side effects, risk of allergies, and contradictions of renal insufficiency and metal implants. The accessibility of CT and MR imaging equipment also limits their application in HCC ablation follow-up. US has been used widely in HCC ablation to provide real-time guidance during the treatment because of its advantages of precise positioning, bedside monitoring and free of ionizing radiation. However, US only shows the size, echo changes, and hemodynamic data of the lesions after ablation but cannot distinguish the degree of tumor necrosis. Above all, US has a limited value in evaluating the local efficacy of ablation [10].

The performance of US in detecting HCC can be improved greatly by introducing contrast agents, i.e., CEUS. It has been demonstrated that

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* Corresponding author. No. 83 Jintang Road, Hedong District, Tianjin 300170, China. Tel.: +86-22-84112323.
E-mail address: dr.jingxiang@aliyun.com (X. Jing).

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CEUS is able to display the characteristics of liver tumors clearly and accurately, as well as the perfusion differences between necrotic tissue and residual carcinoma after ablation [11]. CEUS can provide details of tumor necrosis following ultrasound-guided local ablation more sensitively, which facilitate prompt supplementary treatment and better efficacy [9,12]. However, most of the residual lesions insufficiently ablated locate in the outer layer of original tumor and have irregular shape. It is not very easy for CEUS to evaluate them because CEUS provides cross-sectional image of the lesions only. While reconstruction of the holistic view of different sections can be achieved via moving the probe continuously, it is prone to misdiagnosis due to loss of details of abnormal blood supply outside the cross-section and inappropriate manipulation of probe. The brief arterial phase makes it even harder to display whole ablated area and obtain spatial information of residual lesion in a short timeframe.

The 3-dimensional contrast-enhanced ultrasound (3D-CEUS) combining the immediacy of CEUS and stereoscopic vision of 3-dimensional (3D) ultrasound overcomes the above limitations. Unlike CEUS, in addition to visualization of the dynamic vascular features of lesions, 3D-CEUS provides unique spatial visualization in three orthogonal planes and angiogram-like images according to a specific algorithm [13–15]. 3D-CEUS has had high sensitivity in the depiction of detailed spatial information about tumors and vessels and is thus expected to contribute to visualization of the characteristic vascularity of tumors [15,16].

We applied the dynamic 3D-CEUS in the follow-up of 75 HCC patients undergoing radiofrequency (RF) ablation, microwave ablation, or ethanol ablation (EA). It demonstrates that dynamic 3D-CEUS has similar performance in assessment on efficacy of HCC local ablations comparing to contrast-enhanced CT.

2. Patients and methods

2.1. Patients

Eighty-one consecutive HCC patients undergoing dynamic 3D-CEUS and contrast-enhanced CT examination in 1 month following ultrasound-guided percutaneous local ablation therapy at one hospital from July 2011 to February 2013 were included in this study. Four of them were excluded due to iodine allergy, and 2 were excluded due to respiratory dysfunction. The 75 patients in the study consist of 48 men and 27 women with average age of 57.5±13.5 years (range 29–84 years). The diagnoses of HCC were confirmed with needle biopsy. All the patients had chronic hepatic diseases, including hepatitis B (51 patients), chronic hepatitis C (20 patients), and alcoholic liver disease (4 patients). There were 89 lesions being treated with ultrasound-guided percutaneous local ablation therapy among 75 patients. Forty-seven patients were classified as Child-Pugh class A, 25 were class B, and 3 were class C. The maximum diameter of lesions ranged from 1.2 to 5.0 cm, mean diameter 3.7±1.3 cm. Fifty-seven patients (68 lesions) underwent RF ablation or microwave ablation, while 18 patients (21 lesions) are treated with EA. Among them, 3 patients with Child-Pugh class C were given several sessions of EA. After considering the location, size, number, boundary of tumors, and concise communication with patients and their family members, clinicians make the final decision of ablation protocol.

The inclusion criteria included the following: HCC cases confirmed by needle biopsy; patients with single lesion of size no more than 5 cm or with up to 3 lesions of size no more than 3 cm; patients underwent RF ablation, microwave ablation, or EA within 1 month before the imaging examination; informed consent before ablation; and the quality of 3D-CEUS images meets the requirements of diagnosis.

The exclusion criteria included the following: refused by patients or family member; history of allergy and/or iodine allergy; moderate to severe renal insufficiency [17]; inability to tolerate contrast-enhanced CT or dynamic 3D-CEUS examination; and interval between CT and 3D-CEUS longer than 1 week or receiving other therapies on HCC-like surgery between two examinations.

This retrospective study was approved by the Ethics Committee of the hospital.

2.2. 3D-CEUS

All the dynamic 3D-CEUS imaging were conducted with Philips iU22 Ultrasound system equipped with X6-1 pureWave xMatrix transducer, at a frequency of 1.0–6.0 MHz and a mechanical index of 0.05–0.09. The contrast agent (SonoVue, Bracco, Italy) was used during dynamic 3D-CEUS examination.

First, the patient underwent routine 2-dimensional (2D) grayscale scanning on liver and lesions to decide the best acoustic window. Then, the system was switched to dynamic 3D-CEUS mode with the biggest sampling frame and angle of insonation at 90°. Imaging timing started immediately after bolus injection of 1.0–1.5 ml contrast agent via elbow vein. When liver artery was visualized, the patient was instructed to hold his/her breath for 3D-CEUS data collection. Imaging video clips were recorded every 30 s from bolus injection of contrast agent to obtain 8–12 clips in 4–6 min for full record of all the phases, including arterial phase (starting 10–20 s after contrast agent injection, ending at 30–45 s), portal venous phase (starting at 30–45 s, ending at 120 s), and delayed phase (starting at 120 s, ending when the microbubble disappeared) according to guideline of CEUS by European Federation of Societies for Ultrasound In Medicine and Biology (2012) [18]. All the imaging data were saved in DICOM format on portable medium for further evaluation.

2.3. Contrast-enhanced CT Examination

A 16-slice CT system (Lightspeed 16 pro CT scanner, GE) was used for contrast-enhanced CT examination with iohexol (300 mg I/ml; Ousu, Yangtze River Pharmaceutical, China). The three-phase dynamic-enhanced scanning was conducted after bolus injection of 90–100 ml iohexol via elbow vein at the rate of 2.5–3.0 ml/s with high-pressure injector. The time delay for arterial phase, portal venous phase, and equilibrium phase scanning was 27–32 s, 60–70 s, and 120 s, respectively. The cross-sectional images of all three phases were obtained at thickness of 7.5 mm. Data of portal venous phase were reconstructed into images of thickness at 1.25 mm and increment at 0.625 mm and then transmitted to AW4.2 workstation for 2D multiple planar reconstruction, 2D curved planar reformation, and 3D volume rendering.

2.4. Image assessment

The dynamic 3D-CEUS and contrast-enhanced CT results were evaluated by an ultrasound specialist and a radiologist who have 5-year plus experience in their field. Each reader conducted assessment independently without knowledge of the other's result.

The stored DICOM data of dynamic 3D-CEUS were analyzed with Philips Qlab Special Image Processing Software. The initial images, which consists of three mutually perpendicular sections (coronal, sagittal, and cross-section), were positioned to display the ablated lesion clearly. The 3D images of region of interest (ROI) can be displayed by selecting "volume" mode from the software and carefully adjusting the thickness of slab under "Trim mode" until the ablated lesion was completely accommodated. The volume render mode was applied for artery phase images with appropriate elevated threshold (10–25%) to allow clear visualization of artery vessel as well as maximal suppression of background noise. The 3D images were observed from various perspectives by automatically "swivelling" and manually "rotating", with the focus on distribution and perfusion of artery vessel around the ablated lesion and existence of nodular or crescent abnormal enhanced area. The abnormal enhanced area and necrosis can be outlined with "stacked