Comparison of CEUS and CECT or CEMRI in Assessment of Tumor Vascularity and Response to Thermal Ablation in Patients with Hepatocellular Carcinoma: A Multi-centre Study in China

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Hepatocellular carcinoma (HCC) is one of the most common forms of cancer in China. There are more than 300,000 newly cases diagnosed per year which accounting for 45% of all yearly cases worldwide. HCC is the second leading cause of death from cancer with more than 300,000 people die per year which accounting for 53% of all liver cancer deaths globally. In clinically only about 30% of the patients with HCC are candidates for surgical resection or liver transplantation because the majority of the cases are advanced tumor stage at the time of diagnosis and underlying liver cirrhosis caused by hepatitis B. Percutaneous ablation of HCC is a widely used therapeutic modality with advantages of minimally invasive, easy repeatability, and cost-effective. As to assessment of local response to tumor ablation contrast enhanced CT (CECT) or contrast enhanced MRI (CEMRI) are currently accepted as standard imaging method since unenhanced ultrasound (US) is not able to evaluate the treatment results. In recent years contrast enhanced ultrasound (CEUS) has noteworthy developments along with the advent of the new ultrasound contrast agents and contrast specific imaging methods. In China the new technique of CEUS has been available since 2004 by using sulphur hexafluoride-filled microbubble and contrast dedicated imaging mode working at low mechanical index and in real-time. CEUS is applied at university hospitals or big city hospitals mainly for characterization of focal liver lesions and assessment of local response to liver tumor ablation.

This was a phase IV, multi-center, open label study conducted at eight hospitals in China. The aims of the study were to evaluate the diagnostic efficacy of CEUS in assessment of HCC vascularity and response to tumor thermal ablation by comparing with a reference standard, CECT or CEMRI. The inclusion criteria of the study were patients with HCC and scheduled for percutaneous thermal ablation in case of single nodule ≤6 cm or up to 3 nodules ≤ 3 cm. The study was designed as two individual sessions. At session I CEUS examination was performed within 14 days before ablation for detection of the tumor vascularity, and at session II CEUS was applied one month after treatment for assessment of the local response. For each CEUS examination 2.4 ml of SonoVue® (Bracco), which consists of an aqueous suspension of phospholipid-stabilized sulfur hexafluoride (SF6) gas microbubbles, was injected via antecubital vein in bolus fashion. Three kinds of low mechanical index mode including General Imaging Contrast (Philips), Contrast Tuned Imaging (CnTI®, Esaote) and Contrast Pulse Sequencing (CPS®, Siemens) were used for imaging. The daily examinations of CECT using dual/multi-slices helical CT with iodinated contrast media, and CEMRI using 1.5-3 T machines with...
gadolinium based contrast media were employed. The thermal ablation treatment was performed under local anesthesia with intravenous conscious sedation or general anesthesia. The applicator was inserted into the tumor percutaneously under US guidance and then radio-frequency or microwave energy was delivered with intention of achieving complete ablation of the tumor.

One hundred and thirty-nine patients were enrolled in the current study. At session I the tumor vascularity was detected in 104/139 (74.8%) patients with unenhanced US, 129/139 (92.8%) with CEUS and 133/139 (95.7%) with CECT/CEMRI. Compared with CECT/CEMRI, the sensitivity and accuracy of CEUS in detecting tumor vascularity were 97.0% and 94.2%, respectively, being significantly higher than those of unenhanced US (both p <0.001). At session II 118 patients were able to be evaluated the local response to treatment. CECT/CEMRI determined that 112 tumors achieved complete ablation and 6 residual tumors. Diagnostic test indicated that CEUS had true negative in 110, true positive in 4, false negative in 2 and false positive in 2. The specificity, accuracy and diagnostic agreement of CEUS were 98%, 97% and 96%, respectively.

In conclusion, the current study suggested that the both contrast enhanced imaging modalities, CEUS and CECT/CEMRI, have equal diagnostic efficacy in detection of HCC vascularity and assessment of the response to tumor thermal ablation. In addition CEUS has advantages of safe, easy to access, cost saving in the clinical practice.
OBJECTIVE: In this study we used contrast-enhanced 3D sonography with Sonazoid to scan hepatocellular carcinoma (HCC) lesions before and after radiofrequency ablation (RFA) therapy and evaluated the therapeutic efficacy of RFA therapy.

METHODS: We examined 30 patients with 30 nonresectable HCC lesions by both contrast-enhanced multi-detector row CT and contrast-enhanced 3D harmonic gray-scale sonography before and after RFA therapy. Before injecting Sonazoid we performed 3D sonography to choose an adequate sweep angle to acquire 3D volume data for the target HCC lesion by using a LOGIQ 7 ultrasound system (GE Healthcare, Milwaukee, WI, USA) and three-dimensional (4D3C-L) probe. A tilt movement of the sectorial mechanical transducer was used to perform the volume automatically. After injecting 0.2 mL of Sonazoid, contrast-enhanced 3D harmonic gray-scale sonography was performed by using a coded harmonic angio (CHA) mode imaging software at a high mechanical index (0.7-1.0) in the early phase (15 to 60 seconds after the injection of contrast medium), middle phase (at about 120 seconds), and late phase (after more than five minutes). Immediately after data acquisition, the 3D volume data were sliced in equally spaced planes at predetermined distances, in three orthogonal planes. We compared the contrast-enhanced 3D harmonic gray-scale sonography findings obtained before RFA with those obtained one day after RFA. When hypervascular areas were observed within the tumor after RFA, they were assumed to be residual HCC lesions. When hypervascular enhancement in the early or middle phase of contrast-enhanced 3D harmonic gray-scale sonography before treatment was not seen in the middle phase after treatment, adequate tumor necrosis of the lesion was concluded to have occurred. Multi-detector row CT was performed four weeks after RFA therapy to evaluate the efficacy of treatment.

RESULTS: Contrast-enhanced 3D harmonic gray-scale sonography one day after RFA therapy showed adequate tumor necrosis in 28 of the 30 HCC lesions treated. This modality made it possible to see that tumor vessels and tumor stain of the treated lesions had disappeared after treatment, but that the relatively large portal veins or hepatic veins adjacent to the treated lesions were remained. Faint tumor vessels and enhancement in the early and middle phase were observed in the remaining 2 lesions, and they were suspected of being residual viable lesions. The arterial phase of multi-detector row CT performed four weeks after treatment showed a low-attenuation area in all lesions. Thus, the contrast-enhanced 3D harmonic gray-scale sonography findings in 28 (93%) of the 30 HCC lesions corresponded with multi-detector row CT findings. Incomplete local treatment was diagnosed 3 to 4 months after RFA therapy of the other two lesions which were suspected of being residual viable lesions by the contrast-enhanced 3D harmonic gray-scale sonography.

CONCLUSION: Contrast-enhanced 3D harmonic gray-scale sonography precisely locates the tumor on three axes and allows measurement of the exact distances between the tumor and the main vascular structures of the liver. This modality is a useful tool for evaluating the efficacy of RFA therapy of HCC lesions.
**S3-3**  
Real-time Virtual Sonography with Sonazoid is Easy-to-Understand Evidence-Based Imaging for Everyone

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Abstract:
Because ultrasound is simple, noninvasive and real-time, percutaneous radiofrequency ablation of hepatocellular carcinomas is usually performed under ultrasound guidance. However, it is often difficult to detect residue or recurrence after ablation. To solve the problem without spoiling the advantages, we developed Real-time Virtual Sonography (RVS).

RVS was performed in 82 hepatocellular carcinoma patients before treatment. The MPR imaging of each target tumor was displayed under good synchronization with the ultrasound imaging in all the patients. Ablation was successfully performed in all the patients. RVS was useful for the identification of residual tumor or recurrent tumor after ablation and the selection of the target tumor among multiple nodular lesions.

What guarantees the radical cure of the patient after radiofrequency ablation (RFA), is precise evaluation of treatment effect. The comparison of dynamic CT imaging between pre- and post-RFA is generally believed to be most reliable. The precise evaluation, however, is not as easy as generally believed. Difference of examination date and time makes subtle difference of the posture and respiratory status. Edema of the treated site and change of the tumor volume cause local deformation. Therefore, superimposing the post-RFA imaging onto the pre-RFA imaging is rarely possible. To synchronize each imaging easily and as precisely as possible, we developed Multi-window Realtime Virtual Sonography (MRVS).

MRVS was performed in 21 hepatocellular carcinoma patients treated RFA. Each imaging synchronized well in all the patients. We could compare the pre- and post-RFA imaging from one end of the tumor to the other continuously. Subcostal and intercostal scanning, that is clinically familiar imaging, is easily demonstrated on the screen; the evaluation of treatment effect was achieved more precisely and accurately.

Sonazoid that is a continuous enhancer different from Levovist can obtain real-time contrast imaging. Sonazoid enabled true Real-time Virtual Contrast Sonography. Now, we applied Sonazoid to MRVS. We obtained well-synchronized imaging that can call Easy-to-Understand Evidence-Based Imaging for Everyone. We present it with movie.
Radiofrequency ablation (RFA) has been widely used for primary and metastatic liver tumors, since it is potentially curative, minimally invasive, and easily re-performed for recurrence. RFA is usually performed under B mode ultrasound-guidance.

Sonazoid, a new generation ultrasound contrast agent which has become commercially available in Japan in January 2007, is useful not only in the diagnosis of liver tumors and diffuse liver disease but also in ultrasound-guided procedures, such as percutaneous RFA for liver tumors. For example, vascular imaging, which lasts only for 1 minute after injection of the contrast agent, can detect some classical hepatocellular carcinoma lesions which are not clearly observed by B mode ultrasound and can identify some viable portions adjacent to ablated area. Kupffer imaging, which lasts from 8 minutes to 2 hours after the injection, can be used for the whole liver screening, and may considerably increase the detection of small lesions, such as 1 cm or less in diameter, especially in cases of metastatic liver tumors. When doctors with sufficient skills and experience perform Sonazoid-enhanced ultrasound, its detectability of the lesions may be superior to that of B mode ultrasound or enhanced CT.

We performed Sonazoid-enhanced ultrasound-guided RFA both in vascular imaging and Kupffer imaging. Under Sonazoid-enhanced ultrasound, some lesions were more clearly detected and thus, the electrode was more precisely inserted into it. Tip of the cooled-tip electrode was clearly detected during its insertion. There were no complications related to the contrast-enhanced ultrasound-guided procedure.

Although further investigations are necessary, Sonazoid-enhanced ultrasound may improve the outcome of percutaneous RFA for liver tumors.
S3-5  Radiofrequency ablation of liver tumors with contrast-enhanced real-time three-dimensional ultrasonography

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In three-dimensional ultrasonography (3D-US), three-dimensional images are constructed on the basis of two-dimensional images, and diagnosis is made after completion of the examination. Now it is possible to display 3D-images in real time, using real-time 3D-US (4D-US), but further research is needed on its applications in the field of gastroenterology is necessary research. We report on the current state of mechanical 4D-US.

We employed an Aplio (Toshiba, Japan), an ultrasonic diagnostic device, with a 3.5 MHz mechanical 4D probe to study the three-dimensional structures of liver tumors and surrounding organs using 4D-US multiplanar reconstruction (MPR) and maximum intensity projection (MIP), the diagnostic capability of low-mechanical-index contrast harmonic 4D-US, and 4D-US guided radiofrequency ablation (RFA) using a phantom.

Because 4D-US can display the B-mode MPR in real time, it enabled immediate understanding of the three-dimensional structure of the tumor and the liver. In addition, contrast-enhanced 4D-US showed the staining of the tumors and the blood flow of surrounding organs three-dimensionally. Moreover, a three-dimensional grasp of needle placement for RFA was obtained.