Application of volume navigation image fusion assisted contrast-enhanced ultrasound in detection and characterization of hepatocellular carcinoma invisible on conventional ultrasound

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Aims and objectives

During the radiofrequency (RF) ablation guided with ultrasound, we quite frequently encounter hepatocellular carcinomas (HCCs) that have poor sonographic conspicuity. Thus, it is difficult to accurately localize and target the index lesion, including isoechoic lesions in patients with advanced cirrhosis, lesions located near the diaphragm or deep within the liver, and post-RFA tumor residues [1-2]. In recent years, new developments of real time image fusion of dynamic contrast-enhanced ultrasound (CEUS) with contrast-enhanced MRI (ce-MRI) have been used in both diagnosis and image-guided interventions [3-4]. This is particularly helpful for detection and characterization of tumors which were only displayed on ce-MRI [5]. The purpose of the present study was to explore the value of volume navigation (Vnav) image fusion assisted CEUS in detection and characterization of HCCs which were invisible on conventional ultrasound.
Methods and materials

This prospective study was approved by the institutional ethics review board. Before the procedures were conducted, fusion imaging procedure combining CEUS and ce-MRI were used, and written informed consent was obtained from each patient.

From January 2011 to October 2014, 43 patients with a total of 43 single HCC lesions underwent CEUS/ce-MRI fusion in our hospital. All lesions were detected by contrast-enhanced MRI but were invisible on conventional ultrasound. For each lesion, the examination protocols comprised a three-step examination, including conventional ultrasound, CEUS and CEUS/ce-MRI imaging fusion. One experienced ultrasonographic physician (more than 5000 examinations per year) who was aware of the patients’ clinical histories and prior ce-MRI results, performed ultrasound scanning and imaging fusions. LOGIQ E9 ultrasound system (GE Healthcare, Milwaukee, WI, USA) equipped with Volume Navigation system (version R1.0.5, GE Healthcare) was used for CEUS/ce-MRI image fusion. A 1-5MHz broad-spectrum convex transducer volumetric probe (C1-5-D) was used. Once synchronized, after a bolus injection of 2.4ml SonoVue® (Bracco, Italy), real-time CEUS and the corresponding ce-MRI fusions were performed. The fusion time, fusion success rate, lesion enhancement pattern and detection rate were analyzed. The final diagnoses of HCCs were based on the biopsy results or radiologic findings. The pathologic diagnoses of HCCs were made by a pathologist who had 10 years experiences in liver specializes.

The overall detection rate of conventional CEUS and CEUS/ce-MRI fusion imaging was calculated and compared using the McNemar test. A $P$ value of less than 0.05 was considered to indicate a statistically significant difference. The statistical analyses were performed using SPSS 11.0 for windows (SPSS Inc, Chicago, IL, USA) and the continuous data were expressed as means±standard deviations (SD).
Results

Image fusions were conducted successfully in all 43 HCCs, the technical success rate was 100%. Average fusion time was (6.1±0.5) min (3-17 min). The mean maximum diameter of HCCs was 25.2±5.3mm (mean ± SD), mean depth was 41.8±17.2mm. The detection rate of HCCs using Vnav (95.3%, 41/43) was significantly higher than CEUS (48.8%, 21/43) (P < 0.05). For small HCCs (maximum diameter, 1-2 cm), the detection rate using Vnav (93.9%, 31/33) was also significantly higher than CEUS (33.3%, 11/33) (P < 0.01). Artificial pleural effusion was performed in 2 cases, resulting in additional detections of 2 lesions. All HCCs displayed a rapid wash-in pattern in the arterial phase of CEUS.
Conclusion

During RFA procedures, when HCC lesions can be precisely detected using US, they can be ablated safely and easily [6]. Nowadays, CEUS is widely used for the diagnosis of HCCs. However, CEUS dependents on the conventional ultrasound images to target the lesion. When the HCC lesion did not show obvious arterial enhancement or venous washout on CEUS, it will be hard for CEUS to detect and localize the HCC lesion [7-8]. Ce-MRI may improve the perceptibility and visualization of most HCC lesions after intravenous injection of contrast agents. However, it is difficult to perform the ablation using ce-MRI because lacking of real-time imaging guidance [9-10]. To increase the sensitivity and specificity of diagnosis of those invisible HCC lesions, a navigation system and dynamic positioning system was used to combine CEUS images with patients' previously acquired ce-MRI image data [11-13].

In our study, CEUS and ce-MRI imaging fusions were performed to accurately localize and characterize HCCs invisible on conventional ultrasound (Fig. 1). Our results showed that the detection rate of HCCs using Vnav was significantly higher than CEUS.

Recently, Lee et al reported that 13 (13.1%) out of 99 HCCs (1-2 cm) were invisible even after image fusion [14]. Not all small HCCs can be identified on fusion imaging. When fusion imaging is available, CEUS can be displayed combined with fusion imaging: a CEUS image on the left side and a fused CT/MR image on the right side [15]. Our study showed the fusion imaging of CEUS and ce-MRI were performed successfully in small HCCs (Fig. 2). Vnav had several advantages over CEUS alone for localizing small HCCs with poor sonographic conspicuity.

Also, there existed some limitations in our current study. Technically, CEUS /ce-MRI image fusion was affected by patient breathing, which may change the anatomical positions of the lungs, ribs and liver [16-17]. Moreover, a very deeply located lesion (more than 10cm deep to the body surface) could be associated with serious signal attenuation of the CEUS, leading to poor image quality [18].

The use of image fusion Vnav combined real-time CEUS with reconstructed ce-MRI images, which can dramatically increase detectability and conspicuity of HCCs and allow more precise targeting and monitoring [16-17]. Image fusion Vnav assisted CEUS is a promising technique for improving the detection and diagnosis of HCCs, especially the small and invisible HCCs on conventional ultrasound.
Fig. 1: Hepatocellular carcinoma invisible on conventional ultrasound in a 57-year-old woman, with elevated AFP. A. Conventional grayscale ultrasound did not detect the hepatocellular carcinoma lesion in the right lobe of liver. However, it was obviously on ce-MRI. B. After CEUS and ce-MRI imaging fusion was performed, the hepatocellular carcinoma was accurately localized and characterized on real-time CEUS. The lesion displayed a rapid wash-in pattern in the arterial phase of CEUS. One month after RFA, originally elevated AFP had dropped to normal level in this patient. References: Department of Ultrasound, Zhongshan Hospital, Fudan University- Wen-Ping Wang / China
**Fig. 2:** Small hepatocellular carcinoma invisible on conventional ultrasound in a 63-year-old man. Conventional grayscale ultrasound did not detect the hepatocellular carcinoma lesion in the left lobe of liver. After a bolus injection of 2.4ml SonoVue® (Bracco, Italy), real-time CEUS and the corresponding ce-MRI fusion was successfully performed. A small lesion displayed a rapid wash-in pattern in the arterial phase of CEUS, its diameter was about 9mm. References: Department of Ultrasound, Zhongshan Hospital, Fudan University- Wen-Ping Wang /China
Fig. 3: Atypical hepatocellular carcinoma invisible on conventional ultrasound in a 63-year-old man. Conventional grayscale ultrasound did not detect the hepatocellular carcinoma lesion in the left lobe of liver. In the late phase of CEUS, the lesion's enhancement did not wash-out. We considered it was a small and atypical hepatocellular carcinoma lesion. References: Department of Ultrasound, Zhongshan Hospital, Fudan University- Wen-Ping Wang /China

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