Comparison of Contrast Enhanced Ultrasound With Contrast Enhanced Computed Tomography for the Diagnosis of Hepatocellular Carcinoma

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Background/Aims: **The most common primary malignant tumor of liver is hepatocellular carcinoma (HCC). The highest risk of developing HCC is seen in patients of cirrhosis. Ultrasound is used for surveillance in these patients. This study evaluates the role of contrast enhanced ultrasound (CEUS) in the diagnosis of HCC and compares CEUS to contrast enhanced computed tomography (CECT).** ***Materials and methods:*** **This prospective study included 22 patients with cirrhosis and suspected to have HCC on the basis of gray scale ultrasound or elevated Alpha-fetoprotein. Multiphasic CECT and CEUS were done. On both CECT and CEUS, arterial phase enhancement patterns of the lesions were classified as heterogeneously hyperenhancing, homogeneously hyperenhancing, isoenhancing or nonenhancing. The enhancement patterns of the lesions in portal venous phase were classified as hyperenhancing, isoenhancing, washout or nonenhancing. Presence or absence of neovascularity and peripheral capsule were also noted. The diagnosis of HCC was made as per American Association for the Study of Liver Diseases (AASLD) guidelines.** ***Results:*** **There was moderate degree of agreement between the two modalities in characterizing the enhancement pattern in arterial phase, as calculated by using kappa test (k = 0.59, P < 0.05). Substantial agreement between them, for demonstrating the neovascularity, was also seen (k = 0.772, P < 0.05). CEUS was found to be superior to CECT in demonstrating portal venous phase wash out and peripheral capsule. Only fair agreement was seen between them, with kappa value for portal venous washout being k = 0.38 (P < 0.05) and for peripheral capsule being k = 0.328 (P < 0.05).** ***Conclusion:*** **CEUS is comparable to CECT in demonstrating the arterial phase enhancement pattern of HCC and the neovascularity. CEUS was found to be better than CECT in demonstrating the portal venous phase washout and peripheral capsule. (J Clin Exp Hepatol 2017;7:222–229)**

The most common primary malignant tumor of liver is hepatocellular carcinoma (HCC). It is the leading cause of death among patients with cirrhosis.[1] During hepatocarcinogenesis, there is marked increase in neovascularity and arterial blood flow becomes dominant which produces the characteristic imaging features of HCC.[2] Arterial enhancement (hypervascularity) and neovascularity are considered as the essential characteristics of HCC and are used as the radiologic features on contrast enhanced ultrasound (CEUS), contrast enhanced computed tomography (CECT) or contrast enhanced magnetic resonance (CEMR) images for the non-invasive diagnosis of HCC.

The assessment of intratumoral vascularity and dynamic enhancement pattern of HCC has now become possible with the help of second generation ultrasound (US) microbubble contrast agents like SonoVue (sulfur hexafluoride gas encapsulated by a flexible shell of phospholipids) and with appropriate scanner technology (low-mechanical index (MI) real-time contrast imaging). Diagnostic performance of SonoVue has been found to be comparable to multiphasic CT and dynamic CEMR.[3] The ultrasound contrast agents (UCA) being blood-pool agents do not leave the intravascular space; hence demonstrate the washout phenomenon consistently and clearly. On the other hand, CT or MRI, due to contrast leakage into the tumor interstitium, may show prolonged enhancement. A white suspension of microbubbles is obtained by adding physiologic saline to the lyophilisate powder. This suspension of microbubbles is stable in the vial for a few hours. This offers a strong nonlinear harmonic response on low transmit power insonation.[4] Malignant tumors, which have increased

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Abbreviations: AASLD: American Association for the Study of Liver Diseases; CECT: contrast enhanced computed tomography; CEMR: contrast enhanced magnetic resonance; CEUS: contrast enhanced ultrasound; CT: computed tomography; HCC: hepatocellular carcinoma; *k*: kappa value; MI: mechanical index; MRI: magnetic resonance imaging; OPD: outpatient department; RFA: radiofrequency ablation; UCA: ultrasound contrast agents; US: ultrasound
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vascular permeability and large interstitial space, are better characterized with ultrasound contrast agents, due to the unique intravascular properties of these microbubbles.

CEUS is not limited to fixed pre-defined time points as is dynamic CT or MR imaging. This imaging method operates in real-time, that is, continuous imaging with high temporal resolution over the whole enhancement period. This helps in determining the very early or late enhancement pattern of tumors that may not be possible at the predetermined timing of CT or MRI scans. CEUS also offers better contrast and spatial resolution along with better temporal resolution, than the other modalities. The use of perfluorocarbon based contrast agent and low-mechanical index imaging has further improved the diagnostic utility of US for liver imaging.[3,5]

The lipid layer confers the elasticity to the microbubbles used in CEUS, hence allowing them to withstand the pressure of ultrasound waves and pass through the microvasculature.[6] During the passage of microbubbles through the pulmonary circulation, gas diffuses in alveolar air and is eliminated from the blood circulation in about 20 min.[7,8] UCAs are rapidly cleared from lungs and remain in the circulation for a short span of time only. Thus examination can be repeated within a short period of time.[7,9,10] This allows repeated visualization of tumor enhancement pattern during the same sitting.

The contrast agents are easy to use, are well tolerated by patients and are not nephrotoxic. CEUS is the only dynamic imaging modality available for evaluating the subset of cirrhotic patients with compromised renal functions. CEUS evaluation can also be done at the bedside in an intensive care unit, when shifting the patient to CT/MRI unit is not possible. It is a radiation free tool and can also be used in patients with claustrophobia and cardiac pacemakers.

The highest risk of developing HCC is seen in patients of cirrhosis. US surveillance for HCC is recommended every 6 months for these patients. Ultrasound is used for surveillance, because it is widely available and well tolerated. It has sensitivity of approximately 59%.[11] US is also the primary modality used in the imaging of the whole abdomen. Patients with other vague abdominal symptoms also undergo US, which frequently shows incidental liver abnormalities. 5-Year-survival rate of more than 50% can be achieved if HCC is diagnosed at an early stage, when it can be treated with ablation, embolization, resection or liver transplantation.[12] Thus it is important to evaluate the potential of CEUS to become the initial diagnostic radiological tool in evaluation of HCC. Only very few studies have been undertaken in the Indian subcontinent, which have evaluated the role of CEUS in the primary diagnosis of HCC.[13]

MATERIALS AND METHODS

This prospective study included a total of 22 patients of either sex, presenting to the OPD of our tertiary level care hospital, with cirrhosis and suspected to have hepatocellular carcinoma (HCC) on the basis of gray scale US or elevated AFP. Informed consent was taken from the patients. Their clinical data was also recorded.

The exclusion criteria for the study was patients with recent myocardial infarction, renal failure, angina pectoris, cardiac insufficiency, right to left cardiac shunt, severe cardiac arrhythmia, severe pulmonary hypertension, acute respiratory distress syndrome, uncontrolled systemic hypertension or history of severe contrast allergy.

Multiphasic CT scans were done on 16- or 64-slice CT scanner (120 kVp; 200 mAs; reconstruction interval 5 mm; pitch 1) using 100 mL of intravenous low osmolarity iodine based nonionic contrast material using a pressure injector (rate of injection 3.5 mL/s). 1.5–2 L of oral contrast material (1.5% iodinated ionic contrast media) was given 30–40 min before the CT. After acquiring the non-contrast images of the liver, the upper abdomen was scanned in arterial phase using automated bolus tracking technique. At 70 s after initiation of the injection, portal venous phase images were acquired from the domes of the diaphragm to the symphysis pubis. The data was later transferred to the workstation for reconstruction and reformation.

Baseline gray scale ultrasound with contrast-enhanced imaging was done using the iU 22 system (Philips Medical Systems, Bothell, WA). Broadband convex probe (1–5 mHz) and dedicated low-MI (<0.2) contrast-imaging software was used. Settings were adjusted according to the individual patient. Second-generation US contrast agent (SonoVue, Bracco, Italy) was injected as a bolus of 2.4 mL followed by a flush of 5 mL normal saline solution intravenously, through 18 or 20 gauge cannula placed in the antecubital vein. Digital cine clips representing the dynamic contrast enhancement pattern of the lesion and the surrounding liver tissue were recorded, starting at the time of contrast injection and covering the arterial (at 10–45 s), portal (at 60–90 s) and late phases (at 120–150 s) after the injection. Recordings were made up to 6 min after the contrast injection. Any complications arising during or after the procedure were recorded. The raw data was later transferred to the workstation for evaluation and perfusion studies.

On both CECT and CEUS, arterial phase enhancement patterns of the lesions were classified as heterogeneously hyperenhancing, homogeneously hyperenhancing, isoenhancing or nonenhancing (absent enhancement or hypoenhancing), as compared to the surrounding hepatic parenchyma. The enhancement patterns of the lesions in portal venous phase were classified as hyperenhancing, isoenhancing, washout or nonenhancing, as compared to