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, iso-enhancing or nonenhancing (absent enhancement or hypo-enhancing), as compared to the surrounding hepatic parenchyma. The enhancement patterns of the lesions in portal venous phase were classified as hyperenhancing, iso-enhancing, washout or nonenhancing, as compared to

the surrounding hepatic parenchyma. The lesions classified as showing washout in portal venous phase were lesions which were hypoenhancing to surrounding liver parenchyma on venous phase, but which were hyper or isoenhancing on arterial phase. The lesions classified as nonenhancing lesions on portal venous phase were lesions which were hypoenhancing to surrounding liver parenchyma on both venous and arterial phase.

Presence or absence of neovascularity (in the form of intratumoral vessels, irregular feeding vessels, straight feeding vessels, radial intratumoral vessels/spoke and wheel sign or basket-like vessels around the lesion) and peripheral capsule (in the form of peripheral enhancing rim) were also noted.

The diagnosis of HCC was made as per American Association for the Study of Liver Diseases (AASLD) guidelines. The findings and characterization of the lesion on multiphasic CECT were taken as gold standard.

RESULTS

A total of 25 patients underwent CEUS. Three patients were excluded from the study (1 was post radiofrequency ablation (RFA), 2 patients CECT could not be done as one was lost to follow-up and the other had deranged renal functions). Out of 22 patients (20 males and 2 females with age range from 41 to 71 years), 18 patients had single lesion, two patients had two lesions and two patients had more than two lesions which were seen on multiphasic CECT. In patients who had 2 or more lesions, the largest lesion was considered for evaluation, characterization and statistical analysis. The lesion size ranged from 2 to 14 cm. The maximum number of lesions were in the range of 2–6 cm ($n = 14$) and the mean lesion size was 5.2 cm on ultrasound.

Hypervascularity

On CECT in arterial phase, 12 (54.5%) lesions out of 22 were heterogeneously hyperenhancing, 9 (40.9%) lesions were homogeneously hyperenhancing, none were isoenhancing and 1 (4.5%) was nonenhancing. While on CEUS in arterial phase, 11 (50%) lesions out of 22 were heterogeneously hyperenhancing, 8 (36.4%) lesions were homogeneously hyperenhancing, 1 (4.5%) was isoenhancing and 2 (9.1%) were nonenhancing (Figures 1 and 2).

Total of 21 lesions were hyperenhancing in arterial phase on CECT. 19 out of these were hyperenhancing on CEUS too. 2 out of these (one enhancing homogeneously and the other enhancing heterogeneously on CECT), revealed no contrast enhancement in arterial phase on CEUS. 1 lesion which was nonenhancing on CECT, was isoenhancing on CEUS in arterial phase.

11 out of 12 of the heterogeneously enhancing and 8 out of 9 of the homogeneously enhancing lesions on CECT, showed similar enhancement on CEUS as well.

For a given lesion, the enhancement was better seen in real-time, which was an asset for CEUS. There was moderate degree of agreement between the two modalities in characterizing the enhancement pattern in arterial phase, as calculated by using kappa test ($k = 0.59$, $P < 0.05$).

Neovascularity

The neovascularity was seen in 17 out of 22 (77.3%) lesions on CEUS and 15 out of 22 (68.2%) lesions on multiphasic CECT. Substantial agreement, for demonstrating the neovascularity, between these two modalities was found (kappa value of 0.772, $P < 0.05$). CEUS was better in demonstrating the various neovascular channels (Figure 3).

Washout

On CECT in portal venous phase, 2 (9.1%) lesions out of 22 were hyperenhancing, 10 (45.5%) were isoenhancing and 10 (45.5%) were showing washout. While on CEUS in portal venous phase, no lesion was hyperenhancing, 5 (22.73%) were isoenhancing, 15 (68.2%) were showing washout and 2 (9.1%) were classified as nonenhancing (Figures 4 and 5).

9 out of 22 lesions showed washout in portal venous phase on both modalities. 4 lesions and 2 lesions, which on multiphasic CECT in portal venous phase were isoenhancing and hyperenhancing respectively, showed washout on CEUS in portal venous phase.

Out of 2 lesions, which were classified as non-enhancing on CEUS, 1 of these non-enhancing lesions on CEUS, showed washout on multiphasic CECT in portal venous phase, while the other showed isoenhancement on CECT in portal venous phase.

Only fair agreement (kappa value of 0.38, $P < 0.05$) was seen between multiphasic CECT and CEUS indicating that CEUS is superior to CECT, in detecting portal venous phase washout than CECT.

3 lesions, which were isoenhancing on CEUS in portal venous phase, showed washout in delayed phase. 2 lesions, which were isoenhancing on CEUS in portal venous phase, remained isoenhancing even on delayed phase and no washout was seen. Washout was better seen in delayed phase on CEUS in 4 lesions though these already had shown washout on CEUS in portal venous phase.

Peripheral Capsule

CEUS was found to be better in demonstrating the peripheral enhancing rim which was seen in 7 out of 22 (31.81%) lesions on CEUS and in 5 out of 22 (22.73%) lesions on multiphasic CECT (Figure 6). The kappa test between the two modalities for demonstrating peripheral rim showed only fair agreement ($k = 0.328$, $P < 0.05$).

Multiple additional abdominal and chest findings were seen on multiphasic CECT which was its advantage over CEUS. The various additional findings seen in our study

Figure 1 (A: CECT arterial phase; B: CEUS arterial phase): 67-year-old male who had alcoholic cirrhosis was diagnosed with large mass in segment V and VI of liver (arrows). This large mass, which had enhancement characteristics of HCC, showed arterial heterogeneous hyperenhancement with necrotic areas on both CECT and CEUS. (C: CECT arterial phase; D: CEUS arterial phase): 50-year-old male who was HCV positive was diagnosed with HCC involving segment V of liver (arrows), which showed heterogeneous arterial hyperenhancement on both CEUS and CECT. Arterial hyperenhancement in both the above described lesions was better appreciated on CEUS, as compared to CECT.

were the degenerative disease of the vertebral column, pulmonary thromboembolism, aortic aneurysm, prostatomegaly, prostatic abscess, inferior vena cava thrombus, lung and pleural pathologies.

CECT had the advantage of screening the whole liver in a single scan and characterizing multiple HCCs simultaneously. This was not possible with CEUS.

DISCUSSION

HCC is one of the common causes of cancer related death. Early stage HCC patients have a good prognosis, as they are eligible for the potentially curative therapies, including surgical treatment (resection, liver transplantation) and locoregional treatment (transarterial chemoembolization, radiofrequency ablation or ethanol injection). Advanced HCC patients have poor prognosis. Therefore, diagnosing HCC at early stage is essential.

Ultrasound is usually the first-line examination to detect and evaluate the focal lesions of liver. CEUS in addition to providing morphological features of hepatocellular carcinoma also aids in evaluation of intratumoral vascularity and dynamic contrast enhancement pattern. This information is analogous to the information obtained by CECT and dynamic CEMR, except that CEUS provides the information in real-time.

In this study, 90.5% of HCCs that were hyperenhancing in arterial phase on multiphasic CECT, showed hyperenhancement in the arterial phase of CEUS with SonoVue.^{3,14-16} This finding was consistent with the earlier studies. Two lesions remained hypoechoic on CEUS in arterial phase. Both of these lesions showed arterial phase enhancement on multiphasic CECT. In one of these lesions the reason for its non-visualization may be attributed to the depth of imaging vis-à-vis the probe. One lesion that remained non enhancing in arterial phase could be the

Figure 2 Comparative bar diagram showing lesion characterization in arterial phase on CEUS and CECT. (Nonenhancing lesions are lesions, which were hypoenhancing on arterial phase as compared to rest of liver parenchyma.)

uncommon hypovascular form of HCC, which exhibits isoperfusion or hypoperfusion relative to the surrounding hepatic parenchyma. CEUS was able to demonstrate enhancement in a lesion that was hypoenhancing on multiphasic CECT in arterial phase. CEUS showed enhancement in this lesion probably due to the real-time scanning of CEUS, that is, continuous evaluation of the lesion rather than scanning it at a specific time. The arterial phase image of CECT, acquired with the help of bolus tracking technique, likely missed the peak enhancement time of the lesion. For a given lesion, the arterial enhancement was better seen on CEUS, which can again be due to real-time nature of imaging.

CEUS demonstrated neovascularity in 9.1% more lesions than multiphasic CECT. Substantial agreement was seen between CEUS as compared to multiphasic

CECT, which is the accepted gold standard in demonstrating the neovascularity of the lesions. Majority of the neovascular channels were seen in very early (10–15 s) arterial phase on CEUS before the whole lesion attained hyperenhancing character. This highlights the advantage of the dynamic real-time scanning nature of CEUS, which allows continuous assessment of enhancement of the lesion as soon as the contrast reaches the vessels with high spatial and temporal resolution. Multiphasic CECT, however, lacks this advantage as the scan is acquired at a specific single point of time during the arterial phase. In addition, more slice thickness may also reduce the CECT resolution.

In the portal venous phase, CEUS showed washout in 68.2% of the lesions. This observation was in concordance with previous studies in which they reported washout in portal venous phase in 54–80% of the HCC.^{3,14,16} CEUS

Figure 3 (A: CECT arterial phase; B: CEUS early arterial phase; C: CEUS late arterial phase): 50-year-old male diagnosed with alcoholic cirrhosis, had small lesion in segment VI of liver (arrows). This lesion showed minimal arterial hyperenhancement in the periphery of the lesion on CECT. CEUS showed neovascularity in the early arterial phase with a prominent arterial vessel seen supplying the lesion (hollow arrow). There was uniform arterial hyperenhancement in late arterial phase.

Figure 4 (A: CECT arterial phase; B: CECT portal venous phase; C: CEUS arterial phase; D: CEUS portal venous phase): 60-year-old male who was HCV positive diagnosed with HCC in segment V and VIII of liver (arrows). This lesion showed arterial hyperenhancement, persistent on portal venous phase on CECT. However, on CEUS there was arterial hyperenhancement with washout on portal venous phase.

was found to be better in demonstrating washout than the multiphasic CECT. CEUS showed washout in 68.2% of the lesions as compared to 45.5% of the lesions showing washout on multiphasic CECT, in portal venous phase.

Jang et al.¹⁷ concluded in their study that extending the portal phase observation by up to 5 min is imperative to make a confident diagnosis of HCC, as it allows appreciation of final washout, which occurred in the majority (91%) of HCCs in their study. Similar observation was made in present study. On observing the lesions up to 6 min, washout was better appreciated in 13.6% of the lesions. 60% of the lesions (3 out of 5), which were isoenhancing in portal venous phase, demonstrated the washout in delayed phase on CEUS. 2 of these isoenhancing

lesions on CEUS in portal venous phase, remained isoechoic even in delayed phase and did not show any washout. Thus a total of 81.8% of the lesions showed the washout on CEUS, if extended portal venous phase was taken into account. The reason for this wide variation in time to washout may be the different tumor cellular differentiation, which is seen in the pathogenesis of HCC. Worse differentiated HCCs show washout more quickly than better differentiated ones.^{18,19}

Another important feature of HCC is the presence of a peripheral pseudocapsule. On multiphasic CECT, it is seen as a complete or partial peripheral enhancing rim. Peripheral enhancing rim was well appreciated and seen in more number of the lesions on CEUS than CECT. Peripheral

Figure 5 Comparative bar diagram showing lesion characterization in portal venous phase on CEUS and CECT. (Nonenhancing lesions are lesions, which were not enhancing on arterial as well as portal venous phases.)

Figure 6 (A: CECT arterial phase; B: CECT portal venous phase; C: CEUS arterial phase; D: CEUS portal venous phase): 56-year-old male, who was diagnosed with HBV related cirrhosis, had a small lesion in segment V and VI of liver (arrows). Lesion showed arterial hyperenhancement on CECT, with iso-enhancement on portal venous phase and no evidence of peripheral ring in any phase on CECT. However, CEUS showed presence of hyperenhancement with peripheral ring on arterial phase and iso-enhancement on portal venous phase.

enhancing rim was found in 31.8% of the lesions on CEUS. Peripheral rim was shown in 22.7% of the lesions on CECT. CEUS and CECT had only fair agreement in demonstrating the peripheral enhancing rim. CECT demonstrated the peripheral enhancing rim in one lesion that showed no peripheral enhancing rim on CEUS, which may be attributed to the deep location of the lesion from the insonating probe.

Multiphasic CECT is a better modality when multiple hepatic lesions are to be evaluated and it also provides additional valuable information about the comorbidities. Presence of gas or obesity makes the evaluation of the lesion by CEUS difficult. A good window is desirable for an adequate study which is sometimes not possible, for lesions located high up near the dome of diaphragm or lesions obscured by the rib shadows. Deep-seated lesions are another area of concern as was seen in one of the lesions in the present study. This particular lesion showed typical HCC imaging pattern on multiphasic CECT but could not be evaluated on CEUS due to its deep location. This was consistent with the conclusion drawn in a previous study¹⁹ in which they found that the lesions in subdiaphragmatic liver segments were difficult to visualize and assess. Arterial phase lasts for about 30 s on CEUS. Hence it is difficult to scan the whole liver for characterization of multiple lesions with a single injection of contrast.

There are several advantages of CEUS over CECT or CEMR in the evaluation of hepatic tumors.²⁰ CEUS allows visualization of early enhancement pattern of the lesion and allows better characterization of the neovascularity, because it is a real time scanning technique. Its real-time dynamic aspect is also helpful in continuous evaluation of the enhancement pattern and washout of the HCC in all phases. This may not be possible on CECT or CEMR as a predetermined timing of scans or acquiring scans at a fixed point of time as calculated with bolus tracking is used and

thus the possibility of missing early or late enhancing lesions is greater. CEUS has the advantage of saving radiation exposure, no risk due to usage of iodinated contrast agents and a likely reduction of the time to achieve a final diagnosis. Ultrasound contrast agents have excellent tolerance, safety and unique pharmacokinetics and thus can be administered to the patients with compromised renal status or patients who are allergic to iodinated contrast agents. The incidence of serious adverse effects in abdominal applications has been reported to be 0.0086%.²¹

CEUS also has the advantage of being an easy to perform and widely available modality. As US can be performed on the bedside itself, CEUS may be used in an intensive care setting or in very sick patients.

There are few limitations of our study. The study population was small. In addition, all the lesions were more than 2 cm (mean size being 5.2 cm on ultrasound). The efficacy of CEUS in evaluating small lesions and its comparison with CECT in small HCCs needs further evaluation. CECT was taken as gold standard as per AASLD guidelines and CEUS was compared with CECT and not with histopathology. The number of lesions misdiagnosed as HCC in both the modalities is not known. We did not perform CECT in the delayed phase of imaging.

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. On CEUS, delayed phase imaging adds confidence to the diagnosis by demonstrating washout in relative more number of lesions, without the addition of any radiation hazard.

CONFLICTS OF INTEREST

The authors have none to declare.

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