Original Article

Roles of contrast-enhanced ultrasound and diffusion-weighted magnetic resonance imaging and their comparison in solid space-occupying lesions of the liver – Microbubbles and micromovements in imaging

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Abstract

Aims: This study aims to establish the role of contrast-enhanced ultrasound (CEUS) and diffusion-weighted (DW) magnetic resonance imaging (MRI) in the characterization of solid liver lesions.

Settings and Design: An analysis of 22 patients undergoing CEUS and DW MRI following identification of 1 or more solid liver lesions on conventional ultrasonography.

Subjects and Methods: The study is carried in a standard Doppler ultrasound machine with contrast ultrasound capabilities and 1.5T MRI machine over a period of 2 years from July 2015 to June 2017. After baseline US examination, a bolus of 1.0–2.4 ml of ultrasound contrast agent was administered intravenously followed by 10 ml of saline flush. CEUS images were obtained during arterial, portal venous, and delayed phases. After CEUS, patient is transferred to MRI scanning room where the DW imaging (DWI) sequence is taken. The CEUS and DW MRI diagnosis were compared to other imaging modalities, histopathology, and/or clinical follow-up after 12 months.

Statistical Analysis Used: Sensitivity, specificity, positive predictive value, negative predictive value, accuracy rate and receiver operating characteristic analysis curve was performed using Statistical Package – SPSS ver. 17.0. Statistical evaluation of qualitative analysis between benign and malignant lesions was performed using the Fisher's exact test.

Results: CEUS correctly identified malignant liver lesions in 13 out of 14 cases, with the final diagnosis confirmed by histopathology in 6 cases, by other imaging modalities in 7 cases and follow-up in 1 case. Eight patients were correctly identified as benign liver lesions on CEUS imaging, with all these cases confirmed on other imaging modalities and/or follow-up and two cases by histopathology. In the detection of malignancy, the sensitivity is 86.7% and specificity is 100%. On the DW images the Mean apparent diffusion coefficient (ADC) value for benign lesions is 1.5 and mean ADC value for malignant lesions is 0.7. The ADC was significantly higher in benign lesions than in malignant lesions ($P < 0.01$).

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Access this article online	
Quick Response Code:	Website: www.wajradiology.org
	DOI: 10.4103/wajr.wajr_18_18

How to cite this article: Rai SP, Reddy T, Gopal S, Shenoy S. Roles of contrast-enhanced ultrasound and diffusion-weighted magnetic resonance imaging and their comparison in solid space-occupying lesions of the liver – Microbubbles and micromovements in imaging. West Afr J Radiol 2019;26:69-79.

Conclusions: In our experience, CEUS and DWI with ADC values are highly accurate in confirming benign lesions, early detection of malignant lesions, and metastases in known primary malignancy patients. Other advantage of CEUS and DW MRI is that it is also cost-effective as compared to simultaneously performing individual investigations and can be performed in renal insufficiency patients. Hence, we conclude that CEUS and DW MRI sequence should be used in routine practice.

Keywords: Contrast-enhanced ultrasound, diffusion-weighted magnetic resonance imaging, liver

INTRODUCTION

The effective noninvasive detection and characterization of focal liver lesions (FLLs) can significantly alter patient management.[1] Early detection of primary or secondary liver malignancies increases the possibility of curative surgical resection or successful percutaneous ablation. Ultrasound is a widely used modality for imaging liver pathology. It is relatively inexpensive, does not expose the patient to ionizing radiation, and is widely available. In cases of incidental findings, FLLs can be characterized by conventional B-mode and color Doppler ultrasound when a typical pattern is identified, as in the case of homogeneously hyperechoic hemangiomas[2] or focal nodular hyperplasia with a spoke-wheel-shaped central vascular pattern on color Doppler ultrasound,[3] but the accuracy of the final definitive diagnosis can be limited. Limitations of conventional ultrasound in the detection and characterization of FLLs[4] are (a) especially when the lesions are small (<2 cm), (b) in the setting of cirrhosis, or (c) in patients undergoing chemotherapy.

The aim of this study was to establish the role of contrast-enhanced ultrasound (CEUS) and diffusion weighted (DW) magnetic resonance imaging (MRI) in the characterization of solid liver lesions.

CEUS techniques show great potential in the diagnosis of focal and diffuse liver disease.[5-7] Globally, there are three kinds of ultrasound contrast agent (UCA) which can be used in liver imaging: Levovist (air with a galactose/palmitic acid surfactant; SH U 508A; Schering, Berlin, Germany), SonoVue (sulfur hexafluoride with a phospholipid shell; BR1; Bracco, Milan, Italy) and Sonazoid (perfluorobutane with a lipid shell; NC100100; Amersham Health, Oslo, Norway).[8] SonoVue (sulfur hexafluoride) and Sonazoid (perfluorobutane) contain low solubility gases and show higher microbubble stability than Levovist which contains air. These are different types of contrast but all of them consist of a gas microbubble stabilized with a phospholipid membrane.

The UCAs are microbubbles with an approximate size of red blood cells that circulate into vessels but not through the vascular endothelium into the interstitium.[9] This property helps to provide accurate information about the vascularity of the lesion. The contrast works as a signal enhancer. The interface between microbubble and aquatic medium reflects the ultrasonic wave improving the contrast between the blood and hepatic tissue around. Contrast agents are safe and produce very few adverse effects. Severe anaphylactoid reactions have been described in 0.001% of abdominal explorations, similar to those described in MRI contrasts (gadolinium) and fewer than allergic reactions to CT iodized contrast.[10]

The liver, with its dual blood supply, shows first enhancement in the arterial phase as the contrast agent fills the hepatic artery, with progressive enhancement as it arrives to the portal vein. The arterial phase (10–35 s after the injection) gives information about the amount and type of the lesion's microvascularization. The portal (30–120 s after the injection) and late phases (over 120 s after the injection) give more information about the elimination of the contrast in the lesion than about that of the rest liver parenchyma. The portal and late phase enhancement can give important information about the lesion's behavior.

The majority of malignant lesions present a lower enhancement than the rest liver parenchyma, while the majority of benign solid lesions present a higher than or the same enhancement as the rest liver parenchyma.[6]

The parallel objective was to prove the advantage of CEUS and DW MRI as cost-effective alternative to multiple investigations and can be performed in renal insufficiency patients.[8]

DW MRI is a widely accepted technique in brain imaging for detecting early ischemia in cerebrovascular accidents, characterization of brain tumors, and evaluation of intracranial infections. Its use in other parts of body, particularly in the abdomen for liver lesions is gaining importance. In abdominal imaging, its application had been limited owing to problems related to motion and susceptibility artifacts. However, with continuous advancement in MRI technology, namely multichannel

coils, fast gradients, and parallel imaging (which has helped in enabling reduction in echo time, k-space filling time, and echo train length), the data acquisition has become faster with reduction in number of artifacts, due to which the image quality has been significantly improved and so is its use in body applications. DW MRI is an attractive technique for its usage in liver imaging because of the following reasons:[11] (i) it can add potentially useful information to conventional imaging sequences for achieving a proper diagnosis; (ii) no need of contrast administration for this sequence, thus easy to repeat, and useful in patients with severe renal failure who will be at risk for nephrogenic systemic fibrosis.[12-15]

The use of DW imaging (DWI) in imaging of liver pathologies is relatively new, but very promising for the detection, characterization, and differentiation of benign and malignant lesions, imaging for staging in cancer patients before treatment, and for follow-up after treatment to know the status of the liver lesions and secondary spread to liver from the primary malignancy.[16] Besides this, DW MRI is also capable of predicting the response to therapy for malignant tumors (especially following chemotherapy). Results of several studies[17] have shown that DW MRI along with apparent diffusion coefficient (ADC) values can help characterize FLLs into benign and malignant lesions.

SUBJECTS AND METHODS

This is an analytical study done from July 2015 to June 2017 for a period of 2 years. The study includes 22 patients (6 women, 16 men) with a mean age of 60 years (25–75 years) who was referred to the department of radiodiagnosis following identification of 1 or more solid liver lesions on conventional ultrasonography.

This study was done in the Department of Radiodiagnosis at KMC Hospital, Ambedkar circle, Mangalore over a period of 2 years from August 2015 to July 2017.

The study was approved by the institutional ethics committee. Data were collected from all age group patients including inpatients, outpatients who were investigated in the department with one or more solid FLLs detected on conventional gray-scale ultrasound, and/or multiphase contrast-enhanced computed tomography (CECT).

Excluded were all the patients with contraindications for contrast SonoVue administration which include (a) right-to-left shunts of heart, (b) severe pulmonary hypertension (pulmonary artery pressure >90 mmHg), (c) uncontrolled systemic hypertension and (d) in patients with adult respiratory distress syndrome, (e) SonoVue should not be administered during pregnancy and lactation.

Patients with general contraindications for MRI which included intracranial aneurysm clips and intraorbital metal fragments; any electrically, magnetically, or mechanically activated implants (including cardiac pacemakers, biostimulators, neurostimulators, cochlear implants, and hearing aids) were excluded.

Contrast-enhanced ultrasound technique

CEUS study performed using ultrasound machine "LOGIQ e7 expert" (GE healthcare, USA) using 3–5 MHz curvilinear probe with gain 40 and mechanical index 0.15 for all the patients included in the study.

Contrast used for CEUS in this study is SonoVue (manufactured by Bracco, Geneva, Switzerland). SonoVue Kit contains (i) 1 vial containing 25 mg of lyophilized powder, (ii) 1 prefilled syringe containing 5 ml sodium chloride (0.9%), and (iii) mini spike transfer system. The microbubble dispersion is prepared by 5 ml sodium chloride and lyophilized powder. The vial is then shaken vigorously for a few seconds until the lyophilisate is completely dissolved. Approximately 1–2.4 ml of the dispersion is drawn into a syringe and then administered immediately into a peripheral vein by injection followed by a flush with 10 ml of sodium chloride (0.9%) solution. In our study, contrast is injected through antecubital vein in all the patients. CEUS images were obtained during arterial (10–35 s after the injection), portal venous (30–120 s after the injection), and late phases (over 120 s after the injection).[5]

Diffusion-weighted magnetic resonance imaging technique

DW MRI study is done with 1.5T MRI machine "MAGNETOM SIEMENS AVANTO." All the patients are subjected to DW MRI sequence with ADC mapping in axial plane using multisection single-shot echoplanar sequences. Cardiac gating/respiratory triggering was not used during acquisition of images. Parameters for DWI sequences include: TR/TE - 5800/83 ms; section thickness - 6 mm; spacing - 1.2 mm; FOV of 380 × 382 mm; bandwidth - 1736 Hz/pixel; number of excitations - 6; water excitations with b values of 50,400 and 800 mm^2/s. ADC maps were generated with the software supplied by manufacturer on a pixel-by-pixel basis from the DWI. Regions of interest were defined in areas with abnormal signal intensity on max b value DWI and copied to the ADC map.

The CEUS and DW MRI diagnosis were compared to each other and with other imaging modalities, histopathology, and/or clinical follow-ups for a period of 12 months.

Data analysis

Digital recordings of unenhanced sonography and contrast-enhanced sonography were reviewed by on-site junior radiologist and one blinded senior radiologist who are having at least 2-year experience with hepatobiliary imaging.

The subsequently acquired DW MR images were viewed in a dedicated workstation (ADW - 4.5 advantage windows, General Electric, Milawaukee, United States). The images were reviewed independently and retrospectively by two experienced radiologists (who are blinded) with at least 5–7 years of experience in reporting such studies. All the images along with reports are archived, and the analysis was done after the completion of the study.

Sensitivity, specificity, positive predictive value, negative predictive value, accuracy rate and receiver operating characteristic (ROC) analysis curve was performed using Statistical Package – SPSS ver. 17.0 (SPSS Inc., Chicago, Illinois, US).

Statistical evaluation of qualitative analysis between benign and malignant lesions was performed using the Fisher's exact test.

RESULTS

The patients who are having solid liver lesions with size more than 1 cm are selected for the study. The final diagnosis was based on classic CECT findings or fine needle aspiration cytology (FNAC)/biopsy of the lesions. The study included 2 groups [Table 1]. First group comprises of 8 cases of benign lesions of which 7 cases are hemangiomas (6 cases are below 60 years and 1 case is above 60 years, 3 cases are females, and 4 cases are males) and 1 case of forming abscess with thick internal debris. Among the seven cases of Liver hemangioma, 6 cases are pathognomically proven with CECT scan showing classic features of peripheral nodular enhancement in arterial phase, gradual centripetal filling in venous and delayed phases of contrast imaging. Although in 1 case, FNAC is done due to atypical features on CECT scan which is proven to be hemangioma. One case of forming abscess is confirmed by aspiration and culture was done showing growth of *Klebsiella pneumoniae*. Second group comprises of 14 malignancy cases which include 6 cases of hepatocellular carcinoma (HCC), 7 cases of metastases, and 1 case of cholangiocarcinoma. All HCC cases are above 60 years and were males. Among metastases cases, 4 cases are below 60 years and 3 cases are above 60 years (3 cases are females and 4 cases are males). In HCC subgroup, 4 cases are histopathologically proved and remaining 2 cases are confirmed on CECT scan with classic features of HCC showing enhancement in arterial phase and washout in venous phase of contrast images. The other subgroup is metastases which include metastasis from carcinoma stomach, breast, lung, and colon. 5 cases are known case of malignancies and remaining 2 cases underwent histopathological evaluation and proved to be metastases from adenocarcinoma. One of the patients who was a known case of breast carcinoma whose CECT scan detected two solid liver lesions suggesting metastases showed increased number of lesion on follow-up ultrasonography after 6 months.

Table 1: Distribution of cases in our study

Liver lesions	Number of cases
HCC	6
Hemangioma	7
Metastases	7
Abscess	1
Cholangiocarcinoma	1
Total	22

HCC – Hepatocellular carcinoma

Data analysis of CEUS shows sensitivity of 92.86, specificity 100, positive predictive value 100, and negative predictive value of 88.89 which matches the studies referred in the review of literature.

Apparent diffusion coefficient values

Among the total 22 cases, all the 14 malignant cases were showing diffusion restriction and all the 7 benign cases were not showing diffusion restriction. However the one case of forming abscess is showing diffusion restriction as it is an established feature of abscess but with higher ADC values compared to malignancy (mean ADC value for abscess in our case is 1.1×10^{-3} mm^2/s).

In our study, mean ADC value for malignant liver lesions is 0.7×10^{-3} mm^2/s, mean ADC for benign liver lesions is 1.5×10^{-3} mm^2/s, and cut off for diagnosis of malignant liver lesions is 0.98×10^{-3} mm^2/s with sensitivity 100% and specificity 99.93%.

All the 8 benign lesions are correctly diagnosed by CEUS and 7 cases of hemangiomas are correctly diagnosed as benign by DW MRI with ADC values. Mean ADC value for hemangioma is $1.5 \pm 0.21 \times 10^{-3}$ mm^2/s [Table 2]. One case of pyogenic liver abscess which is showing diffusion restriction with higher mean ADC value of 1.15×10^{-3} mm^2/s is wrongly interpreted as malignancy.

Table 2: Mean apparent diffusion coefficient with standard deviation in benign and malignant liver lesions

	n	Mean±SD	95% CI for mean		*t*	*P*
			Lower bound	Upper bound		
Malignant	14	0.7000±0.15671	0.6053	0.7947	10.311	0.9
Benign	8	1.5156±0.21528	1.250	1.6810		(HS)
Total	21	1.0336±0.44738	0.8353	1.2320		

SD – Standard deviation; CI – Confidence interval; HS – Highly significant

Among 14 malignant cases, CEUS correctly diagnosed 13 cases and DW MRI with ADC values correctly identified all 14 cases. One case of cholangiocarcinomas wrongly diagnosed by CEUS as benign due to its persistent heterogeneous enhancement.

DISCUSSION

During routine clinical practice, majority of FLLs are detected incidentally or patient may present with vague abdomen pain. An ultrasound examination is the most frequently used diagnostic study for screening of abdomen. The lesions that are considered benign and are clinically insignificant or asymptomatic can be suggested for follow-up, and unnecessary surgeries can be avoided. However, sometimes, it is difficult to narrow down the differential diagnosis or to characterize the lesion as benign or malignant entity. CEUS is proven extremely helpful in such cases as it is radiation free, and most of the cases with suspected malignancy, if proved likewise, have to undergo a series of imaging consisting of preoperative work up, postoperative images, and subsequent later follow-up, hence obviating the cost of an added imaging modality and cost of an invasive procedure.[8] The cost of an added CECT Liver and FNAC is mitigated. An added advantage of this modality is it can be done in patients with raised creatinine values/altered glomerular filtration rate with no adverse effects.[10,18] As compared to the excretion of Iodinated contrast media and gadolinium, ultrasound contrast is not nephrotoxic, does not affect thyroid metabolism, and can be repeated if necessary with excellent tolerance.[10] Imaging characterization of a focal liver mass is largely dependent on its enhancement characteristics after the injection of a contrast agent. Portal venous phase behavior on CECT and MR studies is complicated by diffusion of the contrast agents from the vascular space into the interstitium. The enhancement pattern after administration of a contrast agent is the key to characterizing FLLs using dynamic CT or MRI. The enhancement pattern of tumoral vascularity evaluated with sonography after the injection of contrast agents has many advantages such as real-time evaluation, no exposure to radiation, absence of iodinated contrast agents, and a probable reduction of the time to achieve a final diagnosis.

Newer contrast agents like SonoVue which is used in the present study show an excellent nonlinear response to insonation at a low mechanical index and thereby allow continuous real-time assessment using all phases after contrast injection and show no Kupffer cell uptake. Unlike other contrast agents, it does not have late liver parenchymal uptake (beyond 5 min), but at 3 min after contrast agent injection, it enhances the liver parenchyma well.[19] Because of their relatively large size (2–5 μm), microbubbles are purely intravascular; therefore, their signal is purely vascular in origin. Several early studies of CEUS identified the importance of washout (negative enhancement) in the late phase for the detection of malignant liver lesions.[20]

Most of the lesions in our study exhibited definite enhancement patterns on dynamic CEUS. Principal difference between benign and malignant liver lesions found in our study is their appearance during the late phase of contrast enhancement which is comparable to several studies on delayed phase of CEUS.[20] Data analysis matched sensitivity, specificity, positive predictive value, and negative predictive value as mentioned in the studies referred in the review of literature.[21-24]

According to Dietrich *et al*.,[21] ultrasound contrast has been shown to be particularly advantageous in the differentiation of benign and malignant liver tumors and therefore possibly represents a new cost-effective competitive alternative to other liver imaging modalities (e.g., CT and MRI). They also mentioned that liver tumors known to be hyperperfused (e.g., focal nodular hyperplasia, hepatocellular adenoma and carcinoma, and hyperperfused metastases) can be better detected and characterized in the arterial phase, and hypoperfused tumors (e.g., liver metastases of the gastrointestinal tract) can be recognized in the portal venous phase as less perfused "blackspots."

Wilson and Burns[22] developed a simple diagnostic algorithm for interpretation of microbubble-enhanced sonography which provides sensitive and accurate diagnosis of commonly encountered liver masses. In their study with total of 96 cases, they found that portal phase enhancement comprises the first step of the algorithm, with positive or sustained enhancement identifying 48 (92%) of 52 benign lesions and negative enhancement or washout present in 41 (93%) of 44 malignancies. Sustained portal phase enhancement with arterial phase peripheral nodularity and centripetal progression predicted 24 (92%) of 26 of the hemangiomas. While diffuse arterial phase enhancement greater than the liver identified 19 (95%) of 20 of the focal nodular hyperplasia. With negative portal phase enhancement, arterial phase information was less effective

at differentiating HCC (25 [86%] of 29 cases) from another hepatic malignancy (11 [73%] of 15 cases).

In our study, washout in venous and delayed phases in all the HCCs which is comparable to the results of CECT/CEMRI [Cases in Figures 1-4]. Similar results are seen in a study done by Guang *et al*.,[23] who showed that diagnostic value of FLLs with CEUS has no significant difference compared with CECT and CEMRI. They also stated that CEUS is highly sensitive and specific in the characterization of FLLs to support an effective diagnostic method.

Among the 7 cases of hemangiomas, typical patterns of peripheral nodular enhancement in arterial phase with gradual centripetal filling in venous and delayed phases were observed in all the cases of hemangioma proving that CEUS

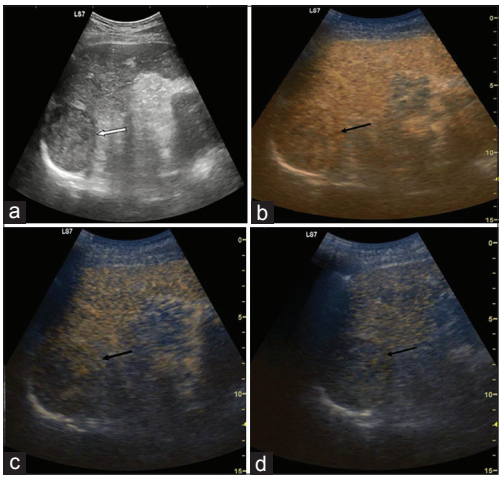

Figure 1: A 64-year-old male patient; case of chronic parenchymal liver disease. On follow-up conventional ultrasound (white arrow a), the patient is found to have space-occupying lesion and portal vein thrombosis. Serum alpha feto protein (AFP) level is 9727 ng/ml. Contrast-enhanced ultrasound is done targeting the larger lesion in the right lobe of the liver showing enhancement of the lesion in arterial phase at 22 seconds after contrast injection (black arrow, b) and washout in venous phase at 74 seconds (black arrow, c) and complete washout at delayed phase at 175 seconds (black arrow, d). Diagnosis is confirmed as hepatocellular carcinoma by biopsy

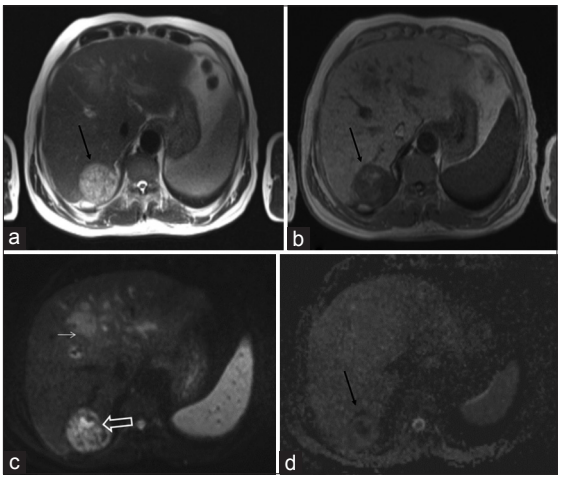

Figure 2: Magnetic resonance imaging of the same patient as Figure 1. The lesion is hyperintense on T2-weighted imaging (black arrow, a) and hypointense on T1-weighted imaging (black arrow, b). The lesion is showing diffusion restriction as evident on the diffusion series (open white arrow, c) and apparent diffusion coefficient mapping images (black arrow, d) and mean apparent diffusion coefficient value is 0.53×10^{-3} mm^2/s. Diagnosis is confirmed as hepatocellular carcinoma by biopsy. There was mild patchy altered signal intensity in the parenchyma – likely due to portal vein thrombosis (small white arrow, c)

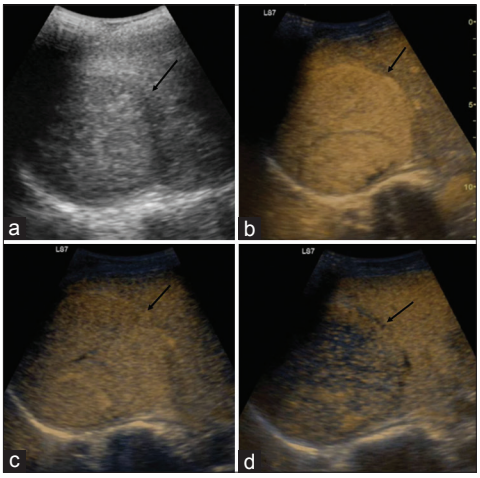

Figure 3: A 36-year-old male - screening ultrasound, multiple large heterogeneously hyperechoic lesions in both lobes of liver, largest in the right lobe in the subdiaphragmatic location (black arrow a). Contrast-enhanced ultrasound is done targeting the larger lesion in the right lobe of the liver showing significant enhancement of lesion in arterial phase at 20 s after contrast injection (black arrow, b) and washout in venous phase at 70 s (black arrow, c) and delayed phase at 180 s (black arrow, d)

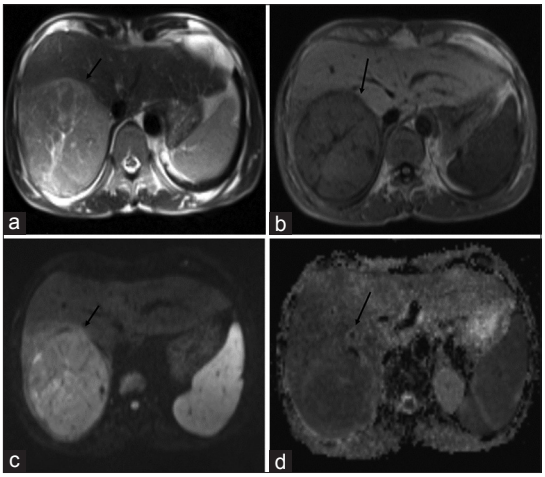

Figure 4: Magnetic resonance imaging of the same patient as Figure 3. Axial T2-weighted image showing large hyperintense lesion (black arrow, a) in the right lobe and appearing heterogeneously hyperintense on axial T1-weighted image (black arrow, b). The lesion is showing diffusion restriction appearing hyperintense the axial diffusion-weighted imaging series (black arrow, c) and appearing hypointense on the apparent diffusion coefficient mapping – (black arrow, d) mean apparent diffusion coeffi cient value is 0.9×10^{-3} mm^2/s. Diagnosis is confirmed as hepatocellular carcinoma by biopsy

is a very good investigating modality for benign lesions like hemangioma and can be used as 2nd line of investigation immediately after conventional gray scale ultrasound [Cases in Figures 5-9]. Performing CEUS before CECT has advantages such as prevention of unnecessary radiation to patients in benign conditions such as haemagnioams and also in avoiding injection of iodized contrast agents which is particularly useful in renal failure patients.

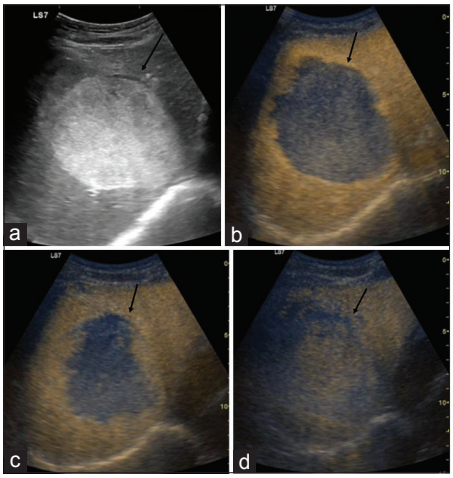

Figure 5: A 60-year-old male patient presented with diffuse abdominal pain. On screening ultrasound, well-defined large hyperechoic lesion in the liver (black arrow, a). Contrast-enhanced ultrasound is done targeting the lesion showing peripheral nodular enhancement in arterial phase at 25 s after contrast injection (black arrow b), gradual centripetal filling in venous at 90 s after contrast injection (black arrow, c), and near complete enhancement after 210 s after contrast injection in the delayed phases (black arrow, d)

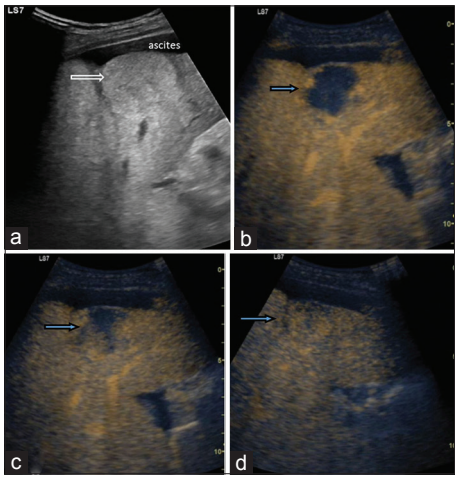

Figure 7: A 58-year-old case of chronic parenchymal liver disease. Ultrasound shows iso to hyperechoic lesion in the left lobe of the liver in the subcapsular region (open white arrow, a). Contrast-enhanced ultrasound is done targeting the lesion showing peripheral nodular enhancement in arterial phase at 20 s after contrast injection (open arrow, b), gradual centripetal filling in venous phase at 85 (open arrow, c), and near-complete enhancement after 232 s (open arrow, d). The lesion was confirmed as hemangioma and is on follow-up. AFP was normal, and there was no e/o diffusion restriction with mean apparent diffusion coefficient value 1.6×10^{-3} mm^2/s

In our study, 6 out of 7 cases of metastases remained hypoechoic with minimal peripheral vascularity throughout all phases although one case showed arterial enhancement with rapid washout in delayed phase [Case in Figures 10 and 11]. Most liver metastases usually are hypovascular or weakly enhanced during the arterial phase (15–35 s after contrast injection), with enhancement, when present, more pronounced

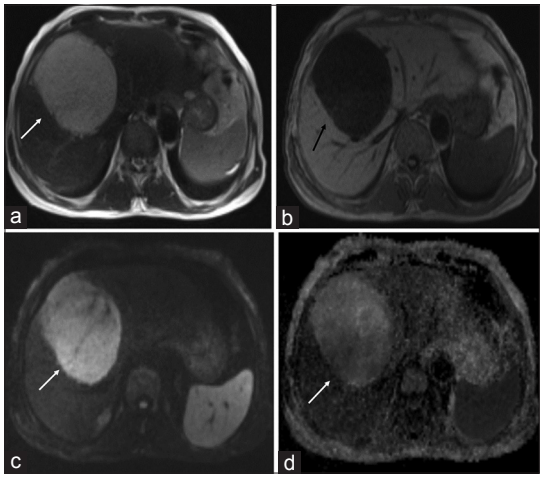

Figure 6: Magnetic resonance images of the same patient as Figure 5. Axial T2-weighted showing large homogeneously hyperintense lesion in the liver (white arrow, a) and homogeneously hypointense on T1 images (black arrow, b). Axial diffusion-weighted magnetic resonance image showing heterogeneously hyperintense signal in the lesion (white arrow, c) and apparent diffusion coefficient map showing hyperintense signal corresponding to the diffusion-weighted imaging (white arrow, d) which signifies no e/o diffusion restriction within the lesion and mean apparent diffusion coefficient value 1.55×10^{-3} mm^2/s. Later, multiphase contrast-enhanced computed tomography was done which is showing typical features of hemangioma

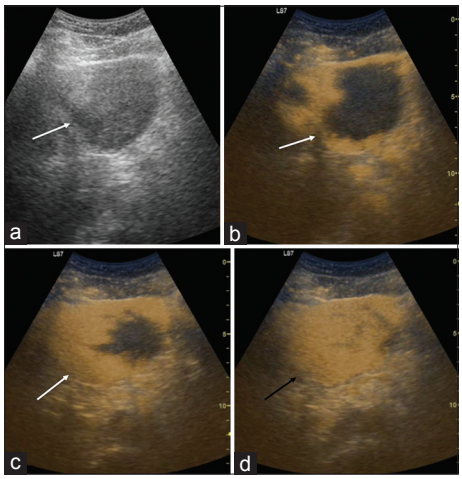

Figure 8: A 54-year-old male patient who is a known case of chronic renal failure presented with mild abdominal pain from 1 week. Routine screening ultrasound shows a large hypoechoic lesion with irregular margins in the left lobe of the liver (white arrow, a). Contrast-enhanced ultrasound done targeting the lesion is showing peripheral nodular enhancement in arterial phase (white arrow, b), gradual centripetal filling in venous (white arrow, c) and complete filling in the delayed phases at 150 s after contrast injection (black arrow, d)

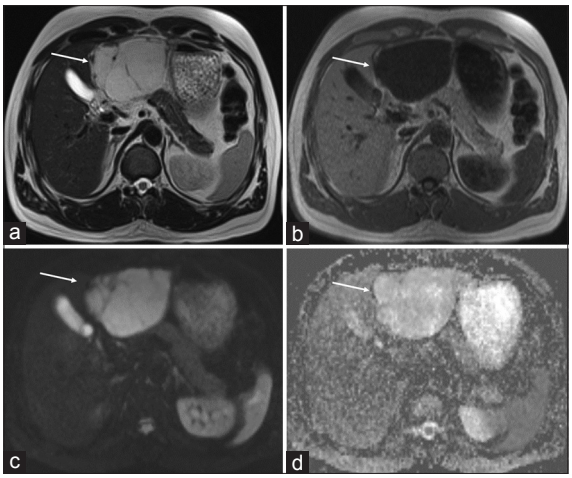

Figure 9: Magnetic resonance images of the same patient as Figure 8. Axial T2-weighted images showing large homogeneously hyperintense lesion with few septae in the left lobe of the liver (white arrow, a) and appearing homogeneously hypointense on T1 images (white arrow, b). Axial diffusion-weighted magnetic resonance image showing homogeneously hyperintense signal in the lesion (white arrow, c) and apparent diffusion coefficient map showing hyperintense signal corresponding to diffusion-weighted imaging suggesting no e/o diffusion restriction within the lesion (white arrow, d) with mean apparent diffusion coefficient value 1.68 × 10^{-3} mm^2/s

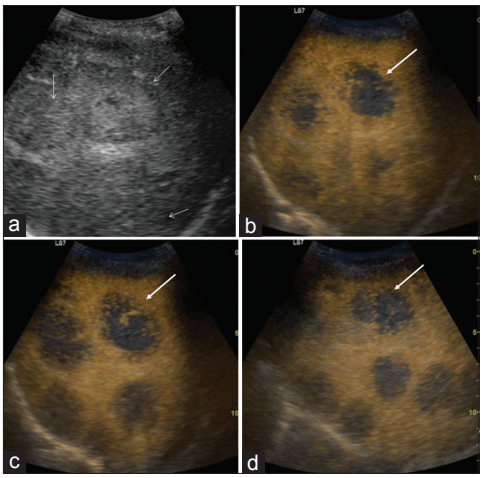

Figure 10: A 62-year-old male patient presented with pain abdomen and loss of appetite from 2 months. On ultrasound, multiple well-defined iso to hypoechoic lesions in the right lobe of the liver (thin white arrows, a). Contrast-enhanced ultrasound done targeting few of the lesions, which are showing peripheral enhancement in arterial and venous phases (white arrow, b and c), there is minimal washout in the peripheral enhancing areas in delayed phases and no central filling suggesting metastases (white arrow, d). Subsequently, biopsy from stomach growth proven to be adenocarcinoma by histopathological evaluation

at the periphery of the lesion.[8] This phase of hypervascularity is often undetected on CT and MRI because of its brevity (its washout usually takes place after 20 s from the injection of the contrast medium whereas the arterial phase of MRI and CT starts after about 40 s from the injection). On the other hand, CEUS enables a real-time dynamic lesion study, with continuous target lesion monitoring.

In our study, we analyzed the usefulness of this late hepatic sinusoidal phase of SonoVue for differentiation between benign and malignant FLLs and found an accuracy of 95.45%. None of the benign lesions showed washout in the venous and delayed phases in our study.

According to a prospective study on 67 patients with FLLs done by von Herbay *et al*.,[24] contrast-enhanced sonography has greater specificity and sensitivity than baseline sonography for the differentiation of benign and malignant liver lesions. In their study, for the discrimination of malignant versus benign liver lesions, contrast-enhanced sonography improved sensitivity from 85% to 100% and specificity from 30% to 63%, as compared with baseline sonography. ROC analysis revealed a significant improvement in this discrimination (Az = 0.692 ± 0.065 at baseline sonography, Az = 0.947 ± 0.037 with contrast-enhanced sonography, $P < 0.001$).

One case of cholangiocarcinoma encountered in our study showing heterogeneous enhancement in arterial and portovenous phases, hence considered as indeterminate/benign according to CEUS. According to Xu *et al*.,[25] 4 enhancement patterns were observed in the arterial phase for mass-forming intrahepatic cholangiocarcinomas: peripheral rim-like hyperenhancement, heterogeneous hyperenhancement, homogeneous hyperenhancement, and heterogeneous hypoenhancement.

The solitary case of abscess encountered in our study showed persistent peripheral enhancement in arterial, venous, and delayed phases of CEUS with well-defined smooth margins [case in Figures 12 and 13].

Contrast enhancement ultrasound has a great role in cancer patients with incidentally detected FLL on follow-up. It helps in confirming the benign or malignant nature of the lesion with added advantages like cost-effective compared to CECT/CEMRI, avoiding unnecessary radiation which really matters in patient who is already undergoing radiotherapy for any primary malignancy elsewhere.

As a general observation, both benign and malignant solid lesions may demonstrate residual high signal intensity on higher b value images and would be difficult to characterize with visual assessment of the DW MR images alone. Hence, once a cellular hepatic lesion is identified visually, further characterization usually relies on conventional morphologic (with or without contrast enhancement) imaging, supplemented with ADC measurements. Specifically, in malignant lesions, DW MRI is useful in distinguishing the

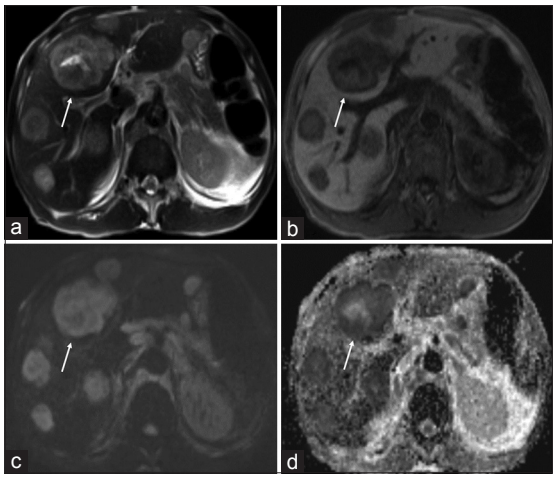

Figure 11: Magnetic resonance images of the same patient as Figure 10. Target-like lesions scattered in the liver parenchyma appearing heterogeneously hyperintense on T2 (white arrow, a) and heterogeneously hypointense on T1 (white arrow, b) and showing predominant peripheral diffusion restriction (white arrow, c and d)

different components of tumors (cystic and/or necrotic vs. solid components). On visual inspection of diffusion images alone, false-positive identification of malignant disease may result from T2 shine-through, partial volume effects from adjacent structures, and cellular benign lesions (e.g., focal nodular hyperplasia, adenoma, and abscess). False-negative findings may result from image artifacts, which could obscure lesion visualization. In our experience, lesion characterization as benign or malignant was correct in 100% of lesions using DW MRI with visual assessment excluding the case of abscess.

In our study, mean ADC value for malignant liver lesions is 0.7×10^{-3} mm^2/s, mean ADC for benign liver lesions is 1.5×10^{-3} mm^2/s, and cutoff for diagnosis of malignant liver lesions is 0.98×10^{-3} mm^2/s with sensitivity 100% and specificity 99.93%. These results are comparable to a study done by Namimoto *et al*.[26] with results almost near to our ADC values. In their study, mean ADC value for malignant liver lesions is 1.04×10^{-3} mm^2/s and mean ADC value for benign liver lesions is 1.95×10^{-3} mm^2/s.

One case of pyogenic liver abscess showing diffusion restriction is wrongly diagnosed as malignancy [Figure 12]. The mean ADC value for pyogenic liver abscess in our study is 1.1×10^{-3} mm^2/s which is slightly higher than the mean ADC values for malignancies. Both pyogenic hepatic abscesses and malignancies demonstrate restricted diffusion centrally with hyperintense signal on DWI and corresponding low ADC values. Although both types of lesions may exhibit peripheral hyperintense rims on DWI at a high b value (600–800 s/mm^2), most pyogenic abscesses, in contrast to malignant lesions, demonstrate high ADC

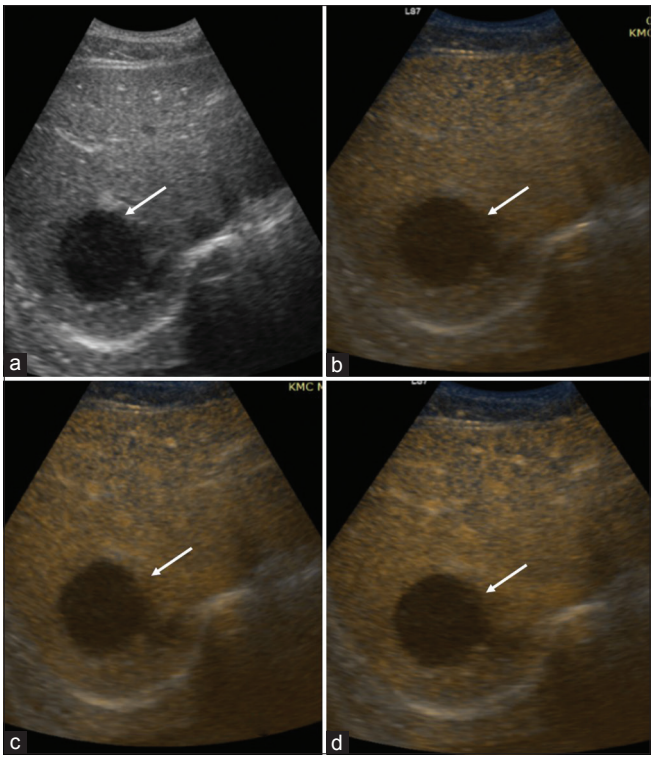

Figure 12: A 25-year-old male patient presented with fever and right upper quadrant pain. Ultrasound showing hypoechoic lesion in the liver (white arrow, a). Contrast-enhanced ultrasound of the same lesion showing no enhancement of the lesion at 25 s (white arrow, b) after contrast injection (arterial phase). Contrast-enhanced ultrasound of the same lesion showing mild peripheral enhancement at 85 and 160 s (white arrow, c and d) (portovenous and delayed phases) suggesting abscess. Later, the diagnosis is confirmed by aspiration and culture showing growth of *Klebsiella*

values along the periphery. This phenomenon, referred to as T2-shine through, is a valuable finding to differentiate a pyogenic hepatic abscess from a malignant lesion. Pyogenic abscess may demonstrate the "double target" sign, which reflects various layers of signal on T2-weighted imaging within the lesion. Central pus due to liquefaction necrosis results in mild T2 hyperintensity. Surrounding this is a inner granulation and outer collagenous layer which is T2 hypontensity and a peripheral compensatory hyperemia that appears as T2 hyperintensity. Hence, for diagnosis of liver abscess, DWI alone is not sufficient for diagnosis and should be compared and analyzed along with conventional MR sequences.[27]

The main limitations of DW MRI related to image quality and ADC reproducibility. Single-shot SE echo-planar DW MRI still has limited image quality, including poor SNR, limited spatial resolution, and echo-planar imaging-related artifacts (mainly distortion, ghosting, and blurring). For example, parallel imaging should be used systematically to reduce susceptibility artifacts and decrease the echo time to improve SNR**.** It is important to emphasize that DW

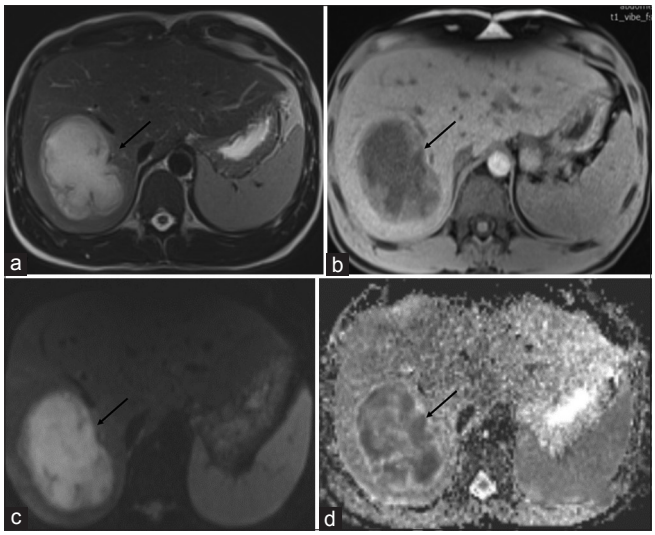

Figure 13: Axial T2 weighted MR image showing large hyperintense lesion with Hypointense rim in right lobe of liver (black arrow, a). Axial T1 weighted MR image showing large homogenously hypointense lesion with hyperintense rim in right lobe of liver (black arrow, b). Axial DW MR image showing hyperintense signal in the lesion (black arrow, c). ADC map showing heterogeneously hypointense signal corresponding to hyperintense signal areas on DWI within the lesion which signifies diffusion restriction (black arrow, d)

MRI is an imaging technique that still often requires varying degrees of optimization to ensure consistent high-quality performance.

The results of this study indicate that CEUS and DW MRI in general practice have high sensitivity and specificity in early detection of malignant liver lesions. Contrast-enhanced ultrasonography using a low mechanical index is the sonographic modality of choice for the detection of liver malignancy. In our experience, contrast-enhanced ultrasonography is having great role mainly in case of incidentally detected liver lesions on routine screening with conventional gray scale ultrasound. The use of CEUS can be used as a second diagnostic step after ultrasound detection of indeterminate FLLs to immediately establish the diagnosis, especially for benign liver lesions, such as hemangiomas, avoiding further and more expensive examinations. CEUS imaging is highly accurate in characterizing malignant and benign FLLs with the fact that none of the benign lesions showed washout in the venous and delayed phases in our study. CEUS is having great advantage in confirming incidentally detected liver lesions, particularly renal failure patients. In our experience, there are few limitations regarding use of CEUS in the liver:

1. There is limitation of resolution of CEUS regarding size that the smallest detectable lesions are 5mm in diameter[28]
2. Subdiaphragmatic lesions, especially those in segment VIII of right lobe of liver, may not be accessible to conventional grey scale US or CEUS.Intercostal scanning and positioning of the patient in left decubitus position can help reduce this limitation
3. Since CEUS has limited penetration, especially in case of steatosis, sometimes deep-seated lesions may not be accessible. Further scanning in the left lateral decubitus position can help to reduce this limitation by manoeuvring the Liver forward and closer to the transducer; and this can be incorporated in the routine survey
4. The falciform ligament and surrounding fat can cause an enhancement defect that may be sometimes confused with a FLL
5. Since ultrasound is an operator-dependent investigation, CEUS has the limitations of being subjective to the operators' skills. In addition to this, only one lesion can be studied at one injection, which would have to repeat for multiple lesions.

Benign lesions have higher mean ADC values than malignant lesions. However, ADC values of forming abscess are nearer to malignant lesions (metastases and HCC) limiting the value of DWI alone for differentiating solid liver masses. Hence, DW MRI along with conventional MR sequence is more accurate in detecting malignant lesions.

Comparing both the modalities, CEUS with DW MRI and their role in solid liver lesions; CEUS scores over the latter in characterization of the type of benign and malignant lesions.

Limitation of our study was the number of cases. CEUS has to be repeated when lesions are multiple.

In our experience, CEUS and DWI with ADC values are highly accurate in confirming benign lesions, early detection of malignant lesions, and metastases in known primary malignancy patients without radiation. Other advantages of CEUS in particular are its cost-effectiveness. Hence, we conclude that CEUS and DW MRI sequence should be used in routine practice.

CONCLUSION

This study aims to establish the role of contrast-enhanced ultrasound and diffusion-weighted MRI in the characterization of solid liver lesions.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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