DIAGNOSTIC ACCURACY OF CONTRAST ENHANCED ULTRASONOGRAPHY IN FOCAL LIVER LESIONS DETECTED BY CONTRAST ENHANCED COMPUTED TOMOGRAPHY

Radio Diagnosis

Sathyan Gnanasigamani	Professor, Department of Radio diagnosis, Govt. Stanley medical college, Chennai-600001.
Amarnath Chellathurai	Professor and Head of the department, Govt. Stanley medical college, Chennai-600001.
Priya	Assistant professor, Department of Radio diagnosis, Govt. Stanley medical college, Chennai-600001.
Sivakumar*	Assistant professor, Department of Radio diagnosis, Govt. Stanley medical college, Chennai-600001. *Corresponding Author.
Karthikrajan	Junior Resident, Department of Radio diagnosis, Govt. Stanley medical college, Chennai-600001.

ABSTRACT

Context: Contrast enhanced Ultrasonography (CEUS) has improved the detection and characterization of focal liver lesions, offering comparable results to those with contrast CT when ultra-sound exploration is technically satisfactory. The vascular property of the lesion in arterial, portal and delayed phases by enhancement and washout is used in this technique. **Aim:** The aim of the study is to interpret the use of contrast-enhanced ultra-sound (CEUS) in characterising the focal liver lesions and compare the diagnostic accuracy of the contrast-enhanced ultra-sound with contrast enhanced CT. **Materials and Methods:** This is a cross sectional analytical study in patients with focal liver lesions detected by USG/CECT coming to Department of Radio diagnosis in Government Stanley Hospital. The duration of the study is two and a half years from January 2017 to July 2019. Sample Size was total of 51 patients detected by CECT/USG as focal liver lesions registered in Govt. Stanley Medical College Hospital between January 2017 to July 2019. **Results:** Diagnostic accuracy for CEUS is 76.46 % and CECT is 83.9%. Sensitivity, specificity, PPV, NPV and Diagnostic accuracy of the CEUS is almost near equal or comparable with that of CECT. **Conclusion:** CEUS has ability to detect and characterise of focal liver lesions with no risk of radiation exposure and aids in real time imaging assessment. The study parameters like sensitivity, specificity and diagnostic accuracy of the CEUS are comparable with that of CECT. CEUS can be used to characterise the focal liver lesions in patients where CECT is contraindicated.

KEYWORDS

Contrast enhanced ultrasound, microbubbles, focal liver lesions, , contrast wash out patterns, Contrast enhanced computed tomography.

INTRODUCTION

Contrast enhanced ultra-sound is the application of ultrasound contrast medium to the traditional medical sonography. Prevalence of focal liver lesions in general population is 15.25%. Contrast media are gas filled micro bubbles that are administered intravenously followed by dynamic real time imaging by ultrasound using a contrast specific software (1). It is difficult to characterize a focal liver lesion by conventional B mode and doppler ultrasound because the character of a malignant lesion may be similar to a benign lesion. CEUS has improved the detection and characterization of focal liver lesions (2), offering comparable results to those with contrast CT when ultra-sound exploration is technically satisfactory. The vascular property of the lesion in arterial, portal and delayed phases by enhancement and washout is used in this technique.

AIM OF THE STUDY

The aim of the study is to interpret the use of contrast-enhanced ultra-sound (CEUS) in characterising the focal liver lesions and compare the diagnostic accuracy of the contrast-enhanced ultra-sound with contrast enhanced CT. The objective of the study is to explain the pattern of enhancement and washout of malignancy in a focal liver lesion by CEUS.

MATERIALS AND METHOD

Study design

This study is a cross sectional analytical study in Patients with focal liver lesions detected by USG/CECT coming to Department of Radiodiagnosis in Government Stanley Hospital. The duration of the study is Two and a half years from January 2017 to July 2019. Sample Size was Total of 51 patients detected by CECT/USG as focal liver lesions registered in Govt. Stanley Medical College Hospital between January 2017 to July 2019.

INCLUSION CRITERIA

All patients diagnosed as focal liver lesions by USG and CECT.

EXCLUSION CRITERIA

Previous history of allergy to sulpha containing agents. Patients with pulmonary hypertension. Patients with acute respiratory distress syndrome. Patients with uncontrolled systemic hypertension. Multifocal liver lesions and any focal lesions with previous treatment and surgery.

METHODOLOGY

Ultrasound machine (Mind ray M6 model) with contrast specific software with low mechanical index dual mode both B-mode and contrast specific mode is used. Before CEUS, a thorough conventional ultrasound assessment of the liver lesion on B-mode imaging and by means of color doppler ultra-sound examination of the entire liver was performed. All 51 patients are subjected to plain ultrasound, Contrast Enhanced ultrasound and Contrast enhanced CT and also underwent histopathological analysis. HPE is the gold standard investigation for diagnosing the focal liver lesions. In CEUS, we used 1.5-2 mL of third generation micro bubble contrast agent sulphur hexafluoride (sonovue). It is rapidly injected via an antecubital vein followed by a 10-mL saline flush. Image processing & generation is done by contrast-specific software integrated in ultrasound scanners cancels the linear ultra-sound signal from tissues and uses the non-linear responses from microbubbles (3). Cine mode is used for recording of video of the entire study for about 5 minutes. Timing zero starts from injection of saline flush. Single clip will record upto 3 minutes and after that intermittent still images can be captured when needed. The phases of contrast enhancement is similar as that of CECT protocol i.e., Early arterial (15-20secs), late arterial (35-40secs), Portal (60-70 secs) and equilibrium phase (beyond 3 minutes). The bubbles will get destroyed after 5 minutes from the field of view.

ANALYSIS

The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean and standard deviation were used for continuous variables. To find the efficacy of the tools on comparison with HPE the Sensitivity, Specificity, PPV & NPV were used.

Table 1: Cross tabulation between CEUS and CECT with comparison of number of positive and negative cases with positive and negative cases in histopathology as reference standard.

Contrast Enhanced Us Vs Histopathology			Contrast Enhanced Ct Vs Histopathology		
CEUS	Histopathology	Total	CECT	Histopathology	Total
	Positive			Positive	
Positive	34	37	Positive	36	38
Negative	7	14	Negative	5	13
	41	51		41	51

Table 2 : Table showing parameters expressed in percentage used to compare the CEUS and CECT observed results.

	CEUS %	CECT %
Sensitivity	82.93	87.80
Specificity	70.00	80.00
PPV	91.89	94.74
NPV	50.00	61.54
Diagnostic Accuracy	76.46	83.90

Fig 1 : Gender and age distribution of the study sample

ROC CURVE

Case processing summary

HISTOPATHOLOGY	VALID N
Positive a	41
Negative	10

Diagonal segments are produced by ties

Fig 2: ROC curve depicting both CEUS and CECT is above the reference line.

Test Result Variable(s)	Area	Std error	Asymptotic Sig	Asymptotic 95% Confidence Interval	
				Lower bound	Upper bound
USG and DOPPLER	0.344	0.092	0.129	0.164	0.524
CONTRAST ENHANCED ULTRASOUND	0.765	0.092	0.010	0.584	0.945
CONTRAST ENHANCED CT	0.839	0.080	0.001	0.684	0.996

Table 3:Area under the curve in ROC

The test result variable (s): USG and DOPPLER , CONTRAST ENHANCED ULTRASOUND, CONTRAST ENHANCED CT has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

- Under the nonparametric assumption
- Null hypothesis: true area = 0.5

Table 4:Mcenemar's chisquare test

	CECT positive	CECT negative	CECT total
CEUS positive	32	5	37
CEUS negative	6	8	14
CEUS total	38	13	51

RESULTS

In 51 patients with focal liver lesions detected by conventional USG, 34 cases are detected as true positives by CEUS and 36 patients are detected as true positives detected by CECT. Histopathological diagnostic results showed 41 cases to be positive for both benign and malignant lesions. (Table 1)

Negatively proven cases in Histopathology are 10 out of which True negatives in CECT is 8 and True negatives in CEUS is 7. Specificity and Sensitivity of the CECT is slightly higher

Lesions	Number Of Cases	CEUS			CECT		
		Sensitivity	Specificity	Ppv	Sensitivity	Specificity	Ppv
Total	51						
Hemangioma	9	85	87	96	88	89	98
FNH	6	82	72	94	92	81	97
Hepatic adenoma	2	75	69	96	82	74	97
HCC	13	89	86	96	93	94	98
Metastasis	16	74	71	92	83	77	95
Intrahepatic cholangio ca	5	83	84	91	79	81	89

Table 5 : Individual case based tabulation with comparison of parameters expressed in percentage.

than that of CEUS. Negative predictive value of the CECT is also higher than of the CEUS.(Table 1).Diagnostic Accuracy for CEUS is 76.46 % and CECT is 83.9%. Sensitivity, Specificity ,PPV ,NPV and Diagnostic accuracy of the CEUS is almost near equal or comparable with that of CECT(Table 2).ROC curve values of CEUS is fair(0.70-0.80 = fair) but inferior to CECT(0.80-0.90 = good) in this study(Table 3).

The P-value in McNemar's Chi-square test (Table 4) is 1 which implies there is no statistical significance between the discordant test results of CECT and CEUS ,hence the diagnostic performance of CEUS is comparable to CECT in detection of focal liver lesions.

Fig 3: (From left to right) 36 years old male with focal liver mass in segment 2 detected by USG is subjected to CEUS and CECT. In CEUS post contrast injection at 19 seconds , shows peripheral nodular discontinuous enhancement in the lesion which shows

some centripetal filling at 40 seconds. and the lesion ,at delayed phase 170 seconds , shows central filling This case was found to be slow filling type of hemangioma.

Fig-4: (From above downwards) A 72 years old male with focal liver mass in near the confluence of the hepatic veins detected by USG is subjected to CEUS and CECT.

In CEUS Post contrast arterial phase at 28 seconds , demonstrates enhancement of lesion homogeneously and rapid washout at 64 seconds

In CECT the enhancement pattern of the lesion shows discordance with that in the CEUS, the lesion contrast resolution here was poor to delineate the washout pattern.

This case was found to be a metastatic lesion in HPE.

Fig -5: (from right to left) 58 years old male with focal liver mass in segment 7 detected by USG is subjected to CEUS and CECT.

In CEUS post contrast injection at arterial phase some areas of the

lesion shows arterial phase enhancement within the lesion and, at delayed phase there is washout seen inside the areas which enhanced in arterial phase lesion, there is also a central non enhancing areas in the lesion.

In CECT the enhancement pattern of the lesion is similar to that in the CEUS, so there is concordance imaging finding between CECT and CEUS.

This case was found to be HCC in HPE.

DISCUSSION

A threshold size of 1-cm for characterization of lesions with CEUS is valuable and accepted by the Liver Imaging Reporting and Data System (LI-RADS) working group(4) , but in our experience, the lesions that can be seen well at gray-scale US can be accurately and confidently evaluated, especially to exclude malignancy.

Out of 51 cases in our study, 9 cases were diagnosed to be Hemangioma, 13 cases were diagnosed to be Hepato cellular carcinoma and 16 cases were found to be Focal liver Metastasis , 5 cases were diagnosed to be intra hepatic cholangio carcinoma, 6 cases were Focal nodular hyperplasia and 2 cases were benign Hepatic adenoma(Table 5)

In Bhayana et al non hepato cellular malignancies (ie, metastases, cholangio carcinoma, and lymphoma) shows early washout, typically before 1 minute; and HCC generally begins washing out later (after 1 minute). The Mechanical index for CEUS is calculated from the amplitude of the ultrasound pulse, which is proportional to the peak negative pressure of the ultrasound beam(5).

The Algorithm for Enhancement pattern for Liver lesions presented in this study has been developed from many years of experience of the radiologists at five separate Canadian academic centers: University of Calgary, University of Toronto, University of Vancouver, Université de Montréal, and the University of Western Ontario. The schematic diagram in my discussion is based on the previous work of Wilson and Burns published in 2006(6).

With CEUS and other contrast-enhanced imaging modalities, washout is a feature of malignancy. Though, Bhayana et al (7) has shown that washout occurred in 97% of malignant lesions and 37% of benign lesions evaluated by CEUS. Of the benign lesions that showed washout in the study by Bhayana et al (7), many exhibited characteristic arterial phase enhancement patterns that defined them as benign lesions. In addition, washout in these benign lesions often occurs late in the examination and is often vague compared with that in malignant lesions, in which washout is more pronounced.

The DEGM study the reference standard diagnosis was made by means of liver biopsy in 75% of cases and by contrast-enhanced CT in the other cases. The accuracy of CEUS for the diagnosis of focal liver lesions was 90.3%.

According to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines , CEUS is indicated for lesion characterization when a lesion or suspected lesion is detected with ultrasound in patients with a known history of malignancy, as an alternative to CT or MRI, or when CT and MRI are contraindicated or inconclusive. (8)

In total cases in our study most commonly diagnosed focal liver lesions was focal liver metastasis, hemangioma and HCC. Least diagnosed focal liver lesion in my study is benign hepatic adenoma(Table 5) .

Cavernous hemangiomas are the most common benign liver tumor, with an incidence of approximately 2%–20%, with a slight female predominance (9). Many gray-scale US imaging features of hemangiomas have been described, and hemangiomas are often categorized as typical or atypical on the basis of these features. In asymptomatic patients without risk factors for malignancy, many hemangiomas appear as a uniformly hyper echoic mass and can be diagnosed by using the combination of conventional gray-scale and Doppler US alone (10). Large hemangiomas or hemangiomas with an unusual appearance on gray-scale US images often require further evaluation. Similarly, in a patient at risk for malignancy, a lesion with gray-scale US imaging features suggestive of hemangioma cannot be

dismissed as such, because HCC can be similar in appearance to hemangioma, and further assessment is required to exclude the possibility of malignancy (11).

In our study, most of the Hemangioma shows progressive peripheral nodular enhancement with centripetal progression in CEUS (Fig 3), occurring rapidly or slowly. This pattern is characterized by discontinuous pooling of hyperenhancing contrast agent around the periphery of the lesion in a nodular fashion. This pattern correlates nicely with the well-described enhancement pattern of hemangiomas on CT images. Both small and large hemangiomas demonstrate this characteristic pattern of enhancement. At any time, contrast enhancement progresses centrally, filling the lesion either completely or partially.

In our study two cases showed a pattern of flash filling type of hemangioma which is a common variation of hemangioma. Flash-filling hemangiomas account for approximately 16% of all hemangiomas and are most common with smaller lesions; 42% of hemangiomas measuring less than 1 cm are flash-filling lesions. CEUS is an excellent modality for the evaluation of flash-filling hemangiomas owing to the unique real-time arterial phase imaging capabilities of CEUS. Classic peripheral nodular enhancement is also observed in the early arterial.

HCC is the most common primary malignant neoplasm of the liver and occurs usually in patients with a background of chronic liver disease (12). Ultrasound is the most common screening modality for HCC in at-risk patients. Unfortunately, the gray-scale US appearance of HCC is nonspecific, and further evaluation is required. Two arterial phase enhancement characteristics of HCC are arterial phase hyper enhancement and dysmorphic vessels. In arterial phase hyper enhancement is one of the essential components for the noninvasive diagnosis of HCC, along with nodule size of more than 10 mm and late weak washout. Disorganized arterial phase enhancement of tubular vascular structures within a lesion is suggestive of malignant neovascularity and is a well-described early arterial phase feature of HCC (13). This pattern is observed in our study (Fig 5). The fill-in pattern does not always follow a strictly centrifugal or centripetal pattern and proceeds in an indifferent disorganized fashion with somewhat tortuous vessels. A basket-weave pattern of disorganized centripetal neovasculature has been described in HCC and, when present, is a specific sign of HCC (14).

This observation is demonstrated in our study. Rarely, well-differentiated HCC will show isoenhancement in the arterial phase. These lesions may continue to demonstrate dysmorphic vascular enhancement with portal venous or late phase washout. In addition, CEUS can be used to assess the hepatic and portal venous structures for the presence of tumor thrombus and vascular invasion. Tumor thrombus is highly suggestive of HCC; however, tumor thrombus has been increasingly recognized as a less-common feature of nonhepatocellular malignancies such as cholangiocarcinoma.

The common forms of non-hepatocellular malignancy in the liver are metastases, cholangiocarcinoma, and lymphoma. In our study metastasis occurred commonly (Table 4), each of these lesions is difficult to diagnose on the basis of gray-scale US alone, and the arterial phase enhancement patterns are nonspecific. Three arterial phase enhancement patterns are described for these lesions; diffuse hyperenhancement is the most commonly encountered arterial phase appearance of nonhepatocellular malignancy (15).

An arterial phase enhancement variation that is more suggestive of non-hepatocellular malignancy is a hyperenhancing rim with central non-enhancement or hypo-enhancement. Finally, some non-hepatocellular malignancies will demonstrate enhancement less than that of the adjacent liver in the arterial phase. These three arterial phase enhancement patterns (hyperenhancement, rim enhancement, and hypo-enhancement) are not suggestive of a specific type of nonhepatocellular malignancy.

In our study most of the cases in Metastatic liver lesion showed hyperenhancement in early arterial phase and rapid wash out (Fig 4). Then two cases showed non enhancement in all three phases and diagnosed to be cystic metastasis from colonic adeno carcinoma.

Focal nodular hyperplasia is a hepatocellular-based lesion and it

represents the second most common benign hepatic tumor. Focal nodular hyperplasia is a hyperplastic mass thought to be secondary to an underlying vascular abnormality (16). Focal nodular hyperplasia is typically an asymptomatic lesion seen most commonly in women between the ages of 30 and 50 years. Pathologically, a typical lesion of focal nodular hyperplasia is composed of a central scar with radiating fibrous septae containing arterial structures. This pathologic appearance correlates well with the enhancement characteristics (16). Because focal nodular hyperplasia is thought to relate to an arterial vascular abnormality, focal nodular hyperplasia is a hyperenhancing lesion in the arterial phase at CEUS. Real-time assessment of focal nodular hyperplasia demonstrates a spoke-wheel pattern of enhancement with an inside-to-outside, or centrifugal, filling pattern. The spoke-wheel pattern reflects the presence of arterial structures within the radiating fibrous septae. The centrifugal progression of enhancement at CEUS makes focal nodular hyperplasia appear to grow during the arterial phase. Bubble-tracking techniques optimally show the spoke-wheel pattern of vascularity in focal nodular hyperplasia.

In our study in a case of FNH there is no central enhancement of the scar in all three phases in both CECT and CEUS, there is concordance between the CECT and CEUS in imaging findings in this case but the classical pattern of FNH is not demonstrated in this study.

In many well-documented studies, CT with Contrast imaging enhancement patterns are reproduced with CEUS. Classic arterial phase hyperenhancement and washout in HCC and discontinuous peripheral nodular enhancement in a hemangioma are examples of concordant imaging features across the two contrast-enhanced modalities which is explained in our study (Fig 3).

The dominant difference between CEUS and CECT is the method of image acquisition. CEUS is a dynamic real-time imaging technique that can demonstrate enhancement regardless of the timing or duration of enhancement. This feature is well demonstrated in the example of a flash-filling hemangioma, in which early arterial phase imaging shows classic peripheral nodular enhancement and later arterial phase imaging shows diffuse enhancement. The ability of CEUS to image the arterial phase in real time allows accurate diagnosis of hemangioma, which may have been more difficult on the contrast-enhanced portions of CT imaging examinations (17).

The second unique feature of CEUS is the entirely intravascular nature of the microbubbles. Iodine- and gadolinium-based contrast agents diffuse into the interstitium, resulting in some sustained lesion enhancement that is not directly related to the vascularity of the lesion, which may reduce the conspicuity of washout (18). In comparison, the individual CEUS microbubbles are too large to diffuse into the interstitium; and, therefore, CEUS enhancement reflects only the vascular properties of the lesion being assessed. This property leads to a situation in which CEUS may show washout of a malignant lesion, and CT imaging may show increasing enhancement. This discordant appearance is best described for tumors such as cholangiocarcinoma with a permeable endothelium and a fibrous stroma.

The real time imaging helps in accurate determination of early arterial enhancement and late wash out and to overcome the discordance with CT. The micro bubbles are intra vascular in nature but the CT contrast agents diffuse to interstitium, so specific in determining the vascularity of the lesion. The recognition of specific arterial phase enhancement patterns of common benign lesions that can be used as an aid in clinical practice for characterization of focal liver lesions with CEUS.

In addition, the good sensitivity of Ultrasound to a microbubble contrast agent allows depiction of smaller differences in contrast agent concentration in a lesion, compared with that of the background liver parenchyma. These two features make CEUS extremely sensitive in the assessment of washout.

Limitations

The Major limiting factor is Unlike CT it is impossible to scan multiple organs or Multifocal pathology at same time in CEUS, also CEUS cannot be used for staging. As it is real time technique proper sequence of steps is required to be deployed for accurate results. Operator dependence and handling of probe varies person to person and it results in inter observer variation. A reconstituted vial cannot be used

later. Moreover, with a high MI tissues produce harmonics, that are superimposed to those coming from micro-bubbles, so this produces artifact. Cost factor is also additional limiting factor for this study.

CONCLUSION

CEUS has ability to detect and characterise of focal liver lesions with no risk of radiation exposure and aids in real time imaging assessment. The study parameters like sensitivity, specificity and diagnostic accuracy of the CEUS are comparable with that of CECT. CEUS can be used to characterise the focal liver lesions in patients where CECT is contraindicated.

ABBREVIATION:

CEUS-Contrast enhanced ultrasound, CT – Computed Tomography, CECT-Contrast enhanced computed tomography, HPE-Histopathology, FNH-Focal nodular hyperplasia, HCC-hepatocellular carcinoma.

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