ORIGINAL RESEARCH ARTICLE

Efficacy of Contrast Enhanced Ultrasound Versus Contrast Enhanced Magnetic Resonance Imaging In characterisation of Focal Liver Lesion : A Prospective Study in aTeritiary Hospital.

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Abstract:

Aims and Objectives: *a)To evaluate the focal lesions of liver by contrast enhanced ultrasonography b) To characterize the focal lesions of liver and evaluate diagnostic significance c)To evaluate the focal lesions of liver by Magnetic Resonance Imaging.d)To compare the diagnostic utility of contrast enhanced ultrasound versus Magnetic Resonance Imaging.* ***Results :*** *Out of 36 patient, majority were in the age group of 41-60 years (56%) followed by 60–80 years (33%) and least between 21-40 years (11%) with male preponderance (23 :13 ratio). benign lesions were 27% out of which, most were hemangiomas, metastasis constituted majority in present study (38.8%) and primary malignant tumours accounted for 46.1% of total malignant lesions the diagnostic accuracy of CEUSG in distinguishing malignant & benign liver lesions is comparable with that of CEMRI (p-value=0.317). The sensitivity & specificity of CEUSG in distinguishing malignant & benign focal lesions is 96.15% & 90.00% respectively & the sensitivity & specificity of CEMRI is 100 % & 90 .0% respectively. The patterns of enhancements of focal liver lesions in both CEUSG & CEMRI in the present study were comparable to the previous studies.* ***Conclusion:*** *CEUS has high sensitivity in the detection and characterization of liver lesions where biopsies can be avoided. The sensitivity of CEUS is comparable to CONTRAST MR in selected cases.*

Keywords: *Contast Enhanced Ultrasound, Enhancement Patterns, Focal Liver Lesions, Contrast Magnetic Resonance Imaging, Ultrasound Contrast Agent (SonoVue).*

Introduction

Liver is the largest abdominal organ involved in systemic and local diseases. Focal liver lesions are quite frequently discovered in daily practice in either ultrasonography,CT or MRI [1] . Clinical implications of and therapeutic strategies for focal liver lesions vary according to their causes. The main pupose of detection of focal liver lesions is their accurate characterization in order to obtain a rapid,sensitive and not very expensive diagnosis [2]. Contrast-enhanced US (CEUS) is now recognized as a highly accurate test in the detection and characterization of focal hepatic lesions [3,4,5]. It is a minimally invasive considering the required venous access ,repeatable technique that is readily available in the ultrasound suite, has high contrast and temporal resolution, and allows dynamic evaluation of lesions in real time [5,6,8]. CEUS has comparable sensitivity and specificity to CT and MRI, albeit with limitations related to the lack of panoromicity and the physical impediments to ultrasound penetration in the presence of obesity and bowel gas [6,7,8,9].

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The EFSUMB guidelines formulated indications regarding the use of CEUS and several published papers demonstrated the real practical value of this method [1].

Which is a) characterization of focal lesions in patients without chronic liver disease.

b) characterization of focal lesions detected in surveillance programs of chronic liver disease.

c) staging & follow up of cancer patients.

d) monitoring of local ablative treatment [10].

Contrast enhanced magnetic resonance imaging of the liver is considered the investigation modality of choice in detection and characterization of focal liver lesions. Only a limited number of studies in the literature have carried out a comparative study of CEUS with dynamic contrast MRI in detection and characterization of focal liver lesions.

Materials and Methods:

Patient Selection: 40 patients in the age group of 20-70 years admitted in the Department of Gastroenterology and Surgery with ultrasound diagnosis of Focal Liver Lesions were included in the study.EXCLUSION CRITERIA : Patients with Focal Liver Lesions with Diagnosis of Liver abscess, Bilioma, Liver lacerations and Hematomas & Pregnant or breast feeding women are excluded from this study i.e 4 patients were excluded from the study based on this criteria.

Method of Collection of Data:

Study sample: 36 patients.

Study period: December 2013 to August 2015.

Study area : Department of Radiodiagnosis ,Gandhi Medical College.

Study equipment: CEUSG was performed using ESAOTE MY LAB 50 and USG contrast-SONOVUE.MRI was performed on SIEMENS MAGNETOM AVANTO 18 CHANNEL 1.5 T MRI using multihance. Informed consent is taken from each patient before the procedures. Institutional ethical committee clearance was obtained.

Method of Study: Initial grey scale ultrasound (US) was performed to look for a proper acoustic window, visibility of lesion and patient co-operation. CEUS was performed on ESAOTE MY LAB 50. The vial of SonoVue was prepared 5 minutes prior to CEUS by injecting 5 ml of saline into the powdered form of the vial and shaking vigorously.After selecting contrast specific imaging mode, 2.4 ml of SonoVue was injected intravenously followed by normal saline flush of 5ml. The timer was started immediately following the contrast injection and findings recorded on cine mode. Enhancement of the mass was evaluated in three phases - arterial (15-25 seconds), portal venous (45-90 seconds) and delayed phase (180 seconds). MRI is performed using phased array surface coil and T1,T2,T2 HASTE images acquired and after the injection of the contrast, images were acquired in arterial, portal, venous phases.

Observation & Results:

Table 1 Distribution of patients according to age & gender :

		No. of Patients	Percentage
Age-Group In years	20-40	6	16.66 %
	40-60	20	55.55 %
	>60	10	27.77
Gender	Male	24	66.6%
	Female	12	33.3%

In the present study, peak age group is between 40-60 years (55.55 %). In 36 patients, males comprised majority of the present study group 24 cases (66.6%) followed by females12 cases (33.3%).

Table 2 : Clinical Presentation

Presenting Symptoms	No. of Patients [n=36]	percentage
Abdominal Pain	20	55.55 %
Mass Per Abdomen	09	25 %
Abdominal Distension	05	13.88 %
Jaundice	05	13. 88 %
Fever With Chills	O3	8.33 %
Vomitings	O3	8. 33 %
Pedal Edema	O2	5.55 %
Increased Frequency Of Stools	01	2.77 %

In this study abdominal pain was the most common presenting symptom in 20 patients .

Table 3 : Incidence of Benign and Malignant Tumours :

	No. of patients	Percentage
Benign tumours	**09**	**25 %**
Malignant tumours	**27**	**75 %**
Total	**36**	**100 %**

In the present study, benign tumours accounted for 29% cases and malignant tumours accounted for 71% cases.

Table 4: Incidence of Various Focal Liver Lesions:

TYPE OF FLL	No: Of patients	Percentage
Hemangiomas	**9**	**25.0 %**
Hepatocellular Carcinomas	**9**	**25.0%**
Cholangio Carcinomas	**3**	**8.33 %**
Metastasis	**3**	**8.33 %**
Total	**36**	**100 %**

In the present study, metastases accounted for 14 cases (38.8%) followed by hemangiomas and HCC 9(25%)

Table 5 : Malignant Focal Liver Lesions :

		No. of patients	Percentage
Malignant Focal Liver Lesions	**Hepatocellular Carcinoma**	**09**	**25%**
	Metastases	**14**	**38. 88 %**

In the present study, metastasis is the commonest malignant lesion (38.88%).

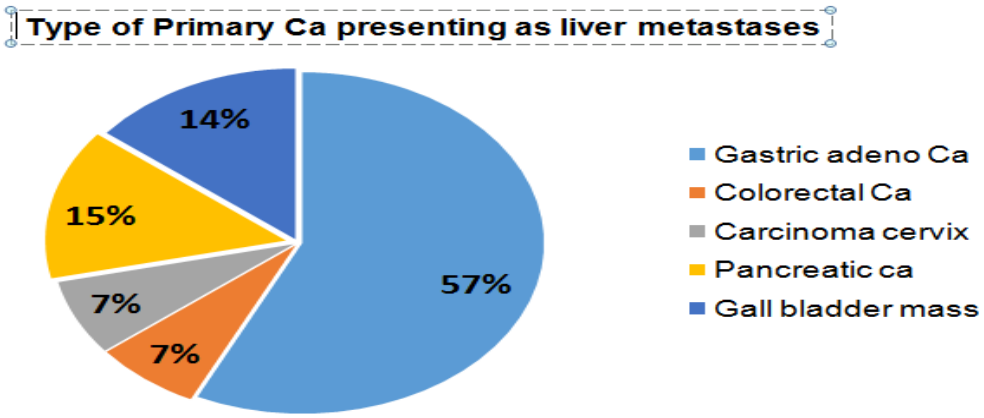

Figure 1: Type of Primary Ca Presenting as Liver Metastases

In the present, Gastric adenocarcinoma is the most commonest primary malignancy (57%) followed by other primary carcinomas.

Table 6: Contrast enhancement patterns noted

Enhancement Pattern	No. of patients	Percentage
Homogenous Enhancement in Arterial Phase	**11**	**30 .55 %**
Peripheral Rim Enhancement in Arterial Phase	**19**	**52.77 %**
Progressive Enhancement in Portal Phase	**8**	**22.22 %**
Hypoenhancing/Washout in Portal Phase	**22**	**61.11 %**
Progressive Centripetal Enhancement in Venous Phase	**5**	**13.88%**
Hypoenhancing/Wash Out in Venous Phase	**25**	**69.44 %**

In maximum 25(69.44%) cases were noted enhancement patterns of Hypoenhancing /Wash Out in Venous Phase. Also 20(61.11%) cases noted Hypoenhancing/Wash out in Portal Phase and only 08(22.22%) cases were noted Progressive Enhancement in Portal Phase.

Table 7: Sensitivity and Specificity of Diagnosis based on CEUS compared with HPE

Type of FLL	CEUS				Total Provisional Diagnosis	HPE Total Confirmed Diagnosis	Sensitivity	Specificity	PPV	NPV
	TP	FP	TN	FN						
Hemangioma	9	0	27	0	9	9	100%	100%	100%	100%
Cholangio Carcinoma	3	1	32	0	4	3	100%	96.97%	75.0%	100%
Hepatocellular Carcinoma	7	1	26	2	8	9	77.78%	96.3%	87.5%	92.86%
Metastasis	13	1	21	1	14	14	92.86%	95.45%	92.86%	95.45%
Cholangitic Abscess	0	0	35	1	0	1	--	--	--	--
Indeterminate	0	0	0	0	1	0	--	--	--	--
Malignant vs Benign FLLs	25	1	9	1	26	26	96.15	90.0%	96.15%	90.0%

The sensitivity, specificity, positive predictive value and negative predictive value of CEUS in diagnosing Hemangioma were 100%, 100%, 100% and 100% respectively

The sensitivity, specificity, positive predictive value and negative predictive value of CEUS in diagnosing HCC were 77.7%, 96.30%, 87.50% and 99% respectively.

Table 8 : Sensitivity and Specificity of Diagnosis based on CE MRI compared with HPE

Type of FLL	CE MRI Diagnosis				Total Provisional Diagnosis	HPE Total Confirmed Diagnosis	Sensitivity	Specificity	PPV	NPV
	TP	FP	TN	FN						
Hemangioma	9	0	27	0	9	9	100%	100%	100%	100%
Cholangio Carcinoma	3	1	32	0	4	3	100%	96.97%	75.0%	100%
Hepatocellular Carcinoma	8	0	27	1	8	9	88.89%	100%	100%	96.43%
Metastasis	13	1	21	1	14	14	100%	95.45%	93.33%	100%
Cholangitic Abscess	0	0	35	1	0	1	--	--	--	--
Indeterminate	0	0	0	0	1	0	--	--	--	--
Total					36	36	--	--	--	--
Malignant vs Benign FLLs	26	1	9	0			100%	90.0%	96.3%	100%

The sensitivity, specificity, positive predictive value and negative predictive value of CE MRI in diagnosing Hemangioma were 100%, 100%, 100% and 100% respectively

The sensitivity, specificity, positive predictive value and negative predictive value of CEUS in diagnosing HCC were 88.89%, 100%, 100% and 96.43% respectively.

Table 9 : Comparison between CEUS and CE MRI in differentiating malignant versus benign FLLs [McNemars Test]

CEUS	CEMRI		P-value
	Malignant Lesions	Benign Lesions	
Malignant Lesions	25 (96.1%)	0	P=0.317 Not Significant
Benign Lesions	1 (3.9%)	9 (100%)	
Total	26 (100%)	9 (100%)	

Using CEUS and CE MRI differentiating all the 9(100%) cases were Benign Lesions. This was not statistically significant.

Discussion:

The present study was done on 36 consecutive patients to characterize the focal liver lesions by CEUS in comparison with contrast enhanced MRI with histopathological examination as a gold standard. Out of 36 patients majority were in the age group of 41-60 years (20/36;56 %) followed by 60-80 years (11/36;33%) and least were from 21-40 years (4/36;11%) as shown in Table 1. Approximately two third of the study sample were males (23/36) and one third were females (13/36) as shown in Table 1. In the present study (Table 3) according to the final diagnosis 26 lesions (72.22%) were diagnosed as malignant and 10 lesions (27.78%) were benign. In a

study done by Nicolau et al in 2006 [12], out of 152 focal hepatic lesions, malignant lesions were 66.4% (101/152) and begin were 33.6% (51/151).In a large multi-centric study (DEGUM) done in 2008 [11], out of 1328 focal hepatic lesions, 56.8% were malignant lesions whereas 43.2% were benign. In the present study 12 out of 26 malignant lesions were primary lesions (46.2%) (9 HCCs and 3 Cholangio Carcinomas) and the remaining 14(53.8%) were secondaries. The higher proportion of secondary malignant lesions in the present study is similar to a large multicentric study 31 (DEGUM) done in Germany [11] in which 50.72% of hepatic malignancies were secondaries. Similar finding (secondary 53% Vs primary 47%) was also found in an Indian study done by Joshi et al [13].

Hemangiomasare the most common benign neoplasm of the liver with a prevalence of 20%, and are five times more common in women than in men. They are often multiple .CEUS has markedly improved the accurate diagnosis of hemangiomas, In the present study 9 out of 10 benign lesions were hemangiomas and the remaining one lesion was cholangitic abscess all the 9 hemangiomas were accurately diagnosed by CEUS and CEMRI. On CEUS examination, in 6 out of 9 patients (66.67%), peripheral nodular arterial enhancement could be demonstrated. Out of them, complete centripetal progressive enhancement followed by homogenous fill-in in later phases is seen in only 3 patients (33.33%) and partial centripetal progressive enhancement followed by incomplete fill-in with central non enhancing regions in later phases is seen in 3 patients (33.33%). In the remaining patients , homogenous hyper enhancement in arterial phase was followed by ISO enhancement in both portal & venous phases. In no patients could the peripheral rim-like enhancement be visualized (0 of 9, 0%), which is typically seen in metastasis. These findings were slightly different from previous studies which also showed typical enhancement pattern [14]. In the present study on MRI, all the 9 hemangiomas were hypointense on T1WI and hyperintense on T2WI. On contrast enhanced MRI 7 out of 9 patients (77.78%), a peripheral nodular arterial enhancement could be demonstrated. Out of them, complete centripetal progressive enhancement followed by homogenous fill-in in later phases is seen in 4 patients (44.44%) and partial centripetal progressive enhancement followed by incomplete fill-in with, centralnon enhancing regions in later phases is seen in 3 patients (33.33%). In the remaining 2(22.22%) patients, homogenous hyperenhancement in arterial phase was followed by iso- enhancement in both portal and venous phases . Dynamic enhancement patterns on CE MRI correlated with those on contrast-enhanced sonography in the current study. In the present study, sensitivity & specificity in diagnosing hemangiomas were found to be 100 % both in CEUS & CEMRI

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. Three types of liver involvement with HCC are It is solitary in about one half of cases, multifocal in approximately 40% and diffuse in less than 10%. Tumors possess a pseudo capsule of compressed tissue in 50% to 80% of cases. Fibrolamellar carcinoma (FCC) is a distinct subtype of HCC occurring predominantly in young adults with no underlying liver disease. In the current study 9 out of 36 focal liver leisons (25%) were diagnosed hepatocellular carcinomas on histopathology. The majority of studies done on FLLs till date showed proportion of HCCs [11]. Some studies showed higher proportions of HCC [12]. In the present study 9 out of 12 (75%) primary malignant FLLs were diagnosed as hepatocellular carcinomas on histopathology. CEUS could accurately diagnose only 7, one was misdiagnosed as multiple metastasis and another found to have no abnormality on CEUS. The case that was misdiagnosed as multiple metastasis (false negative) was multifocal on CEUS examination showing hetrogenously hyperenhancement on arterial phase and hypoenhancement in later phases, a pattern typically seen with liver metastasis. One patient on whom CEUS examination could not detect any abnormality was later diagnosed to have HCC on contrast enhanced MRI, also confirmed by histopathological examination. The diagnosis of HCC was missed in that case probably due to its sub-diaphragmatic location which was difficult to access by CEUS examination. So, the sensitivity, specificity, positive predictive value and negative predictive value of CEUS in diagnosing HCC were 77.7%, 96.30%, 87.50% and 99% respectively. In CEUS examination, 6 out of 7 cases (85.71%) showed homogenous hyper enhancement in arterial phase followed by iso enhancement in the portal phase, out of which 4 cases showed hypoenhancement in venous phase and 2 cases showed hypoenhancement with capsular enhancement in venous phase. The remaining one case (14.2%) showed heterogeneously hyperenhancement in arterial phase followed by iso enhancement in portal phase and hypoenhancement in venous phase. All the 7 cases of HCC diagnosed by CEUS showed typical enhancement patterns in accordance with the EFSUMB guidelines [10]. On CEMRI, out of 9 cases of HCC only 8 were accurately diagnosed. One case was misdiagnosed as metastases (false negative) which showed heterogeneous hyperenhancement in arterial phase followed by washout in the later phases. So, the sensitivity, specificity, positive predictive value and negative predictive value of CEMRI in diagnosing HCC were 88.89%, 100%, 100% and 96.43% respectively. Among the 8 cases of HCC accurately diagnosed by CEMRI, in arterial phase 5 out of 8 cases showed homogenous hyper enhancement, one case showed homogenous hyperenhancement and two cases showed heterogeneous hyperenhancement among which one showed central non enhancing necrotic

region. In portal phase, all the 8 cases showed iso enhancement. In venous phase, all the 8 lesions showed hypoenhancement among which 2 lesions showed delayed capsular enhancement. .

Cholangiocarcinoma : Intrahepatic or peripheral cholangiocarcinoma originates from bile ducts proximal to hilum ,seen after 60 yrs of age & is rarer than HCC . In the present study, 3 out of 12 (25%) primary malignant FLLs were diagnosed as cholangio carcinoma On CEUS examination, 2 out of 3 cases (66.67%) showed rim like hyper enhancement with central hypoenhancement in arterial phase followed by hypoenhancement in portal .and non-enhancement in venous phase. One case (33.3%) showed heterogeneously hyper enhancement with hypoenhancement in portal and non enhancement in venous phase which is an additional feature according to the EFSUMB guidelines. In the present study all 3 patients with cholangiocarcinaoma, confirmed by pathology were correctly identified by CEUS as per the EFSUMB guidelines [10], but one false positive case was detected in both CEUS and contrast enhanced MRI which was later diagnosed as cholangiticabsess on histopathology. The cholangitic abscess showed peripheral enhancement in arterial phase followed by hypoenhancement in later phases on CEUS. The pattern of contrast enhancement in CEUS in the present study was similar to those found in previous studies.

Metastasis : Metastases are the most common hepatic malignancies. On CEUS, their appearance during the arterial phase of contrast-enhancement depends on the extent of arterial perfusion Hypovascular metastases with relatively low arterial supply are common and typically occur in patients with adenocarcinoma or squamous cell carcinoma from gastrointestinal and other primaries. In the present study 14 out of 26 (53.8%) malignant FLLs were diagnosed as secondary malignant lesions. Among the secondary malignant liver lesions majority were found to have the primary lesions most - comrnonly from gastric adenocarcinoma (8/14) followed by gallbladder carcinoma (2/14), pancreatic carcinoma (2/14), colorectal carcinoma (1/14) and l carcinoma cervix (1/14). Most of the studies done previously showed similarly high proportion of patients with malignant liver lesions diagnosed as secondaries. Some studies showed lower proportions ranging from 23 to 31% .In the present study ,on CEUS examination 13 out of 14 secondaries (92.8%) were detected accurately and one lesion was misdiagnosed (false negative) as HCC but was later diagnosed as secondary malignant lesion on both contrast enhanced MRI and histo pathological examination. One case was false positively diagnosed as metastasis both on CEUS and CEMRI but later confirmed as HCC on histopathological examination .So, the sensitivity, specificity, positive predictive value and negative predictive value of CEUS in diagnosing metastases were 92.86%, 95.45%, 92.86% and 95.45% respectively . Majority of the lesions showed typical enhancement pattern on CEUS (12 out of 13, cases i.e, 85.8%) which is peripheral rim enhancement in arterial phase followed by hypoenhancement in both portal and venous phases (washout). One case showed hyperenhancement in arterial phase followed by hypoenhancement in later phases During these phases, hypo enhancement is characteristic of and common to all metastases, regardless of eventual enhancement in the arterial phase because the liver tissue retains the UCA, while the metastases present a rapid and marked "washout". The observed hypoenhancement could be due to the absence of portal supply to metastases and hence a lower vascular volume in the metastases compared with the liver parenchyma. Incidental benign focal liver lesions can present with hypo enhancement at CEUS and thus the careful evaluation of any lesion is required when the liver is examined for the first time. On plain MRI, all the 14 lesions showed showed hypointense signal on T1WI and hyperintense signal with one lesions showing additional hypointense rim on T2WI. Contrast enhanced MRI could accurately characterize all the 14 secondary malignant liver lesions. Out of them 10 lesions (71.43%) showed peripheral rim enhancement in arterial phase followed by peripheral washout in the later phases, 2 lesions (14.29%) showed homogenous hyperenhancement in arterial phase followed by washout in the later phases. The remaining two lesions (14.29%) showed hypoenhancement in the arterial phase followed by washout in the later phases. One case was false positively diagnosed as metastasis both on CEUS and CEMRI but later confirmed as HCC on histopathological examination. So, the sensitivity, specificity, positive predictive value and negative predictive value of CEMRI in diagnosing metastases were 100%, 95.45%, 93.33% and 100% respectively.

Diagnostic performance of CEUS versus CEMRI : In the present study sensitivity ,specificity ,positive predictive value and negative predictive value of CEUS in distinguishing malignant from benign FLL are 96.15 % ,90.00%96.15 % and 90.00 % respectively. The sensitivity, specificity, positive predictive value and negative predictive value of CEMRI in distinguishing malignant from benign FLL are 100 % ,90.00% , 96.30 % & 100.0 % respectively. Considering the small sample size, it was found that both the diagnostic modalities were comparable in the diagnostic performance overall with no significant difference in the values obtained.

Limitations:

Penetration of contrast-specific imaging modes is usually limited to 12-15cm. Fatty change of the liver aggravates the problem of limited penetration and in severe fatty infiltration, large parts of the liver may not be assessable by CEUS. Very small FLL may be overlooked. Sub diaphragmatic lesions, especially

those in segment VIII, may not be accessible to conventional US or CEUS.

Conclusion:

CEUS has high sensitivity in the detection and characterization of liver lesions where biopsies can be avoided. The sensitivity of CEUS is comparable to CONTRAST MR in selected cases.

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