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"COMPARISON OF THE ACCURACY OF DWI AND 128-SLICE MULTIDETECTOR TRIPLE PHASE CT IN SCREENING HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC LIVER DISEASE"

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ABSTRACT **OBJECTIVE:** Compare the Accuracy of DWI and triple phase contrast enhanced 128-Slice Multidetector CT in Screening Hepatocellular Carcinoma in Patients with Chronic Liver Disease.

BACKGROUND: Liver cancer is the third most common cause of cancer related death in the world. The Hepatocellular carcinoma (HCC) is the most common primary liver cancer among the liver cancers. Therefore, HCC stays in the spotlight of many medical subspecialties. Hepatocellular carcinoma (HCC) is a neoplasm usually arising in a cirrhotic liver by a multistep carcinogenesis process. Early detection of HCC and accurate assessment of tumour burden are crucial to successful treatment planning and long-term survival.

MATERIALS AND METHOD: It is a Prospective observational study conducted at Government Stanley Medical College and Hospital, Chennai for 55 Patients with Chronic Liver Disease .

RESULTS AND OBSERVATION: DWI detected more HCC than CECT resulting in overall sensitivity of 88.6% for MRI and 80% for MDCT. There were 7 false negative cases for CECT, of which 3 cases were diagnosed by DWI.DWI showed nil false positive cases with 2 false positive for CECT resulting in 100% specificity for DWI and 90% for CECT.

CONCLUSION: The diffusion-weighted MRI sequence is a fast, non-invasive and more accurate method of screening. This method is also less time consuming and less expensive than the routine MRI. The diffusion-weighted MRI sequence can contribute to accurate diagnosis and discrimination between benign and malignant hepatic masses.

KEYWORDS : Hepatocellular carcinoma, Diffusion weighted Imaging, Chronic liver disease

INTRODUCTION:

Hepatocellular carcinoma (HCC) is a neoplasm usually arising in a cirrhotic liver by a multistep carcinogenesis process. Approximately 90% of cases of HCC develop in the setting of chronic liver disease, most commonly related to hepatitis B and C virus infection ,alcoholic cirrhosis, biliary cirrhosis, hepatic fibrosis and inherited metabolic diseases (such as hereditary hemochromatosis, Wilson disease, tyrosinemia, alpha1-antitrypsin deficiency, porphyria cutanea tarda and glycogen storage diseases) as well as non-alcoholic fatty liver disease, aromatic compounds toxic poisoning and exposure to aflatoxin[1].Early detection of HCC and accurate assessment of tumour burden are crucial to successful treatment planning and long-term survival. Hepatocarcinogenesis, the gradual transformation of non-malignant liver cells into hepatocellular carcinoma (HCC), is a complex, multistep process characterized at the molecular and cellular level by the progressive accumulation of epigenetic and genetic alterations and at the histologic level by the emergence and progression of successively more advanced precancerous, early cancerous, and overtly malignantly lesions.

Early HCC is an incipient stage of HCC development, analogous to "carcinoma in situ" or "microinvasive carcinoma" of other organs, whereas progressed HCC is an overtly malignant neoplasm with ability to invade vessels and metastasize.Key alterations during hepatocarcinogenesis include elevation of arterial flow, reduction in portal venous flow, and reduction in OATP[2] expression.

Surveillance for HCC in patients with cirrhosis or long-standing hepatitis B infection has been a common practice for many years. Serum alpha fetoprotein(AFP) testing and imaging studies are usually recommended at intervals of 6 to 12 months. This intervals based on the low incidence, typically 1–4% per year among cirrhotics , and slow growth of these tumours with a median doubling time of 117 to 150 days. Current recommendations support this practice, although the optimal interval and method for screening have been debated .

Serum AFP is the most widely used tumor biomarker in diagnosis of HCC, however its value is often considered insufficient. Serum AFP value below 20 ng/mL is considered normal, the cut-off value for malignancy is established at the level 200 ng/mL (high specificity, sensitivity of 22%) [3]. Up to 40% of patients with early stage of HCC show normal AFP values 10. Ultrasonography (US) and serum alpha-fetoprotein (AFP) assessment are the main screening methods for the early detection of HCC in patients with chronic liver disease and cirrhosis, even in the early stages. US has less capability for characterizing small lesions, particularly in the cirrhotic liver.

Magnetic resonance imaging (MRI) plays a prominent role in the evaluation of cirrhosis and screening for early HCC. In a study, dynamic MRI with IV gadolinium injection is most sensitive for imaging HCC and best reflects the actual tumour size as a screening method; however, a conventionally performed full abdominal MRI is cumbersome as well as expensive. Diffusion weighted magnetic resonance imaging (DW-MRI) allows tissue characterization by probing tissue microstructural changes, quantified as the apparent diffusion coefficient (ADC). Due to the higher microstructural density in malignant lesions, water mobility and therefore, incomplete rephrasing will be less pronounced, resulting in higher signal intensity on the native DW-MRI and lower ADC compared to benign lesions. Contrast-enhanced helical CT and MRI have been identified as accurate, noninvasive imaging techniques in the detection of HCC in a cirrhotic liver.

Although DWI has been claimed in some studies to be more specific and more sensitive than conventional MRI with dynamic scan in the detection of HCC nodule, there are few studies directly evaluating the potential role of DWI as a sensitive method in screening HCC [4,5]. Here we compare the accuracy of DWI MRI sequence with contrast enhanced CT in screening hepatocellular carcinoma in background of chronic liver disease.

MATERIALS AND METHODS

STUDY DESIGN: It is a prospective study conducted at government Stanley Medical College and Hospital, Chennai for a period of one and half years after the approval of ethical committee between January 2019 and August 2020.

STUDY POPULATION: The study group includes 55 patients referred from department of gastroenterology. Written consent was obtained from all the participants before the study.

INCLUSION CRITERIA:
Patients with Chronic Liver Disease who were referred for MRI and 128-Slice Multidetector CT with high susceptibility of HCC and high serum AFP value .

EXCLUSION CRITERIA:
Non-cooperative cases, severe ascites and contraindications for MRI and CT were excluded from the study.

IMAGING TECHNIQUES:
MRI DWI and contrast enhanced 128-Slice Multidetector triple phase CT of the liver were performed for the patients. USG guided Core needle biopsy was performed for equivocal cases found in MRI and CECT[6].

MRI DWI: All MR examinations were performed using the same fast limited protocol, with a 1.5-T clinical MR unit (Magnetom , Amira, Siemens Healthcare, Germany) with an 8-channel body phase-array coil. The liver was imaged in the axial plane in all sequences. Baseline MR images included axial half-Fourier acquisition single-shot turbo spin-echo (HASTE) images (TR/TE; 1800/72; 150° refocusing flip angle; 256 × 129 matrix; 6 mm slice thickness) and a breath-hold T1-weighted fast low angle shot (FLASH) sequence (a double echo chemical shift gradient echo sequence) (TR/first echo TE, second echo TE, 70/2.5 [opposed phase (OP)], 5 [in phase (IP)]; 70° flip angle; matrix of 256 × 137; 6 mm slice thickness; signal average one; and two acquisitions).After baseline MRI, a respiratory triggered single-shot fat-suppressed echo-planar DWI sequence in the axial plane with prospective acquisition correction was acquired using TR/TE, 2100/85 ms; 90° flip angle; 6 mm slice thickness; and matrix, 192 × 115. The gradient factors (b values) were 50 and 800 s/mm2. Depending on the respiratory efficiency of each patient, the acquisition time for this sequence ranged from 2 to 4 min. To improve the image quality, integrated parallel imaging technique (iPAT) by means of generalized auto-calibrating partially parallel acquisitions (GRAPPA) with an acceleration factor of 2 was applied. The total slices of DW-MR images were different in the base of liver length. The slice gap and field of view were occasionally changed according to the size of the liver to ensure coverage of the whole liver. Quantitative ADC maps were created on a voxel-by-voxel basis using the algorithms implemented within the Siemens Magnetom scanner software and using the b values of 50 and 800 s/mm2. On DWI, a lesion was considered malignant when it was moderately hyperintense at b 50 s/mm2, remained hyperintense at b 800 s/mm2, and showed an ADC value that was equal to or lower than that of adjacent liver parenchyma.

Triple phase contrast enhanced 128-Slice Multidetector CT : All scans were obtained on a 128-MDCT scanner (GE OPTIMA 660). The amount of IV contrast material (Omnipaque 300 [iohexol]) given was 2 mL/kg to a maximum of 200 mL. The injection rate was 5 mL/sec into an antecubital vein. The scanning parameters were as follows: collimation, 5 mm; reconstruction interval, 2.5 mm; table speed, 11.25 mm per rotation; pitch, 3; 120 kV; and 190–370 mA. Unenhanced, arterial (30 sec after injection), and portal venous (60 sec after injection) scans were obtained with a standard reconstruction algorithm.Core biopsy performed with large needles (1.1-1.6 mm outer diameter) ensures the recovery of an adequate tissue fragment; it also allows for a better preservation of tissue architecture, providing more information on the tumor tissue and facilitating certain special staining techniques[7].

Interpretation of the results was done separately by 2 independent radiologists both had experience of 15 and 10 years respectively in MRI and CT. They were blinded to the results of the other modality. Then the findings of the three modalities were correlated together. Interpretations of DWI and Triple phase 128 MDCT were compared to interpretations of Histopathology.

STATISTICAL 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. To find the significant difference between the bivariate samples in Independent groups the Unpaired sample t-test was used. The Receiver Operator Characteristic (ROC) curve analysis was used to find the Sensitivity, Specificity ,PPV and NPV on comparison of HPE with DWI & CECT. In both the above statistical tools the probability value .05 is considered as significant level.

Table 1: ADC in Tumor thrombus

Variable	Tumor thrombus	N	Mean	S.D	p-value (unpaired t -test)
ADC	Yes	5	0.90	0.25	0.004 **
	No	30	1.59	0.49	

The table shows comparison of ADC with Tumor thrombus by Unpaired t-test were t-value=3.055 , p=0.004<0.01 which shows highly statistical significant difference between ADC and Tumor thrombus.

Table 2: Receiver Operator Characteristic (ROC) curve analysis of MRI, CECT with HPE

MRI with HPE					Area	p-value
		HPE		Total		
		Yes	No			
MRI	Yes	31	0	31	.943	0.0005 **
	No	4	20	24		
Total		35	20	55		

CECT WITH HPE					Area	p-value
		HPE		Total		
		Yes	No			
CECT	Yes	28	2	30	.850	0.0005 **
	No	7	18	25		
Total		35	20	55		

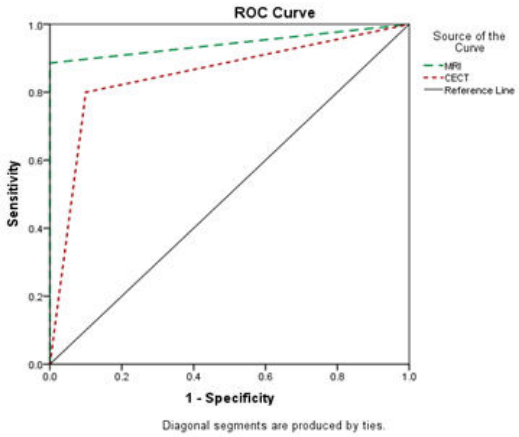


Figure 1

The table shows Receiver Operator Characteristic (ROC) curve analysis of MRI with HPE were AUC (Area Under the ROC curve)= 0.943, p=0.0005<0.01 which shows highly statistical significant difference with Sensitivity=88.6%, Specificity=100.0%, PPV=100.0%, NPV=83.3% and Accuracy=92.7%. Similarly in Receiver Operator Characteristic (ROC) curve analysis of CECT with HPE were AUC (Area Under the ROC curve) = 0.850, p=0.0005<0.01 which shows highly statistical significant difference with Sensitivity=80.0%, Specificity=90.0%, PPV=93.3%, NPV=72.0% and Accuracy=83.6%.

RESULTS AND OBSERVATIONS:

The mean ADC value of the hepatocellular carcinomas (HCC) was calculated as 1.15 +/- 0.36 x 10(-3) mm(2)/s. The mean ADC values of all the disease groups were statistically significant when compared with the mean ADC value of the normal liver 1.56 +/- 0.14 x 10-3mm2/s), (P < 0.01). The present study showed that ADC measurement has the potential to screen malignant focal hepatic

lesions. ADC values were measured in 35 HCC and other normal liver parenchyma and cirrhosis. There was high interobserver agreement in ADC measurements for all lesion types.

DWI detected more HCC than CECT resulting in overall sensitivity of 88.6% for MRI and 80% for MDCT. There were 7 false negative cases for CECT, of which 3 cases were diagnosed by DWI. DWI showed no false positive cases with 2 false positive for CECT resulting in 100% specificity for DWI and 90% for CECT.

DISCUSSION:

The diffusion-weighted MRI sequence is a useful diagnostic tool and it can contribute to accurate diagnosis and discrimination between benign and malignant hepatic masses. DWI can significantly reduce the need for intravenous administration of contrast medium in evaluation of malignancies. The CT diagnosis was based on a triphasic contrast-enhanced protocol using a 128-row MDCT scanner. All phases of the MDCT and MRI scans were independently analyzed by two independent investigators with respect to the number, size, and location of the tumours.

In order to gain the highest diagnostic sensitivity, each nodule was rated positive whenever CT or MRI or both modalities were equivocally positive by both investigators in consensus. Positive diagnosis was based on the EASL and American Association for the Study of Liver Diseases (AASLD) guidelines which require hypervascularization in arterial phase and contrast washout in the early or delayed venous phase[8]. All images were analysed on a separate workstation with magnification. Tumour diameters were sized with a measuring tool integrated in the workstation software. Additionally, the influence of HCC aetiology on tumour detection was analysed. Histopathology was considered as Gold standard for equivocal cases and DWI and CECT results were compared with HPE.

In our study, DWI detected more HCC than CECT resulting in overall sensitivity of 88.6% for MRI and 80% for MDCT. There were 7 false negative cases for CECT, of which 3 cases were diagnosed DWI.DWI showed 0 false positive cases with 2 false positive for CECT resulting in 100% specificity for DWI and 90% for CECT. There were 5 cases with tumour thrombus and there was highly statistical significant difference between ADC and Tumour thrombus.

The diagnostic imaging criteria for HCC include arterial phase enhancement with washout in the portal venous and/or delayed phases on computed tomography or magnetic resonance imaging. However, gadolinium contrast cannot be used in patients with chronic renal failure due to risk of nephrogenic systemic fibrosis and in those with history of allergy to gadolinium. This creates a need for imaging sequences without the use of gadolinium which can be used for diagnosing HCC in patients with contraindication for gadolinium. DWI can be used as an alternative for the detection and characterization of HCC. Although correct prediction of exact histopathological grade of HCC is not possible because of the large overlap among the ADC values. DWI with ADC measurement may be helpful for non-invasive and preoperative prediction of the degree of differentiation of HCC[9].

Despite the recent advent of multidetector CT (MDCT) and many technical advances, the diagnostic accuracy for identifying small HCCs is still unsatisfactory because of the difficulty in detecting and characterizing small nodules with faint or atypical enhancement. They must also be differentiated from benign lesions, such as regenerative nodules, small hemangiomas or arterioportal shunts, especially when the washout is vague on dynamic CT. Shimizu et al.[10] showed that among the small (≤ 2 cm) round or oval lesions 52% disappeared or decreased in size and were considered to be pseudo lesions, and only 28% were classified as HCC. Accordingly, false-positive results, as well as detectability, would be problematic in diagnosing small HCCs on CT.

In two studies conducted by Xu et al. and Park et al. using combined gadolinium-enhanced MRI and DWI made it possible to reliably diagnose small HCC including hypo vascular HCCs in cirrhotic patients. In a meta-analysis study of nine articles about DWI in the diagnosis of HCC, the comparison of DWI performance with that of conventional contrast enhanced MRI (CE-MRI) suggested no major differences between these two methods. DWI combined with CE-MRI had a higher sensitivity than DWI alone[11].

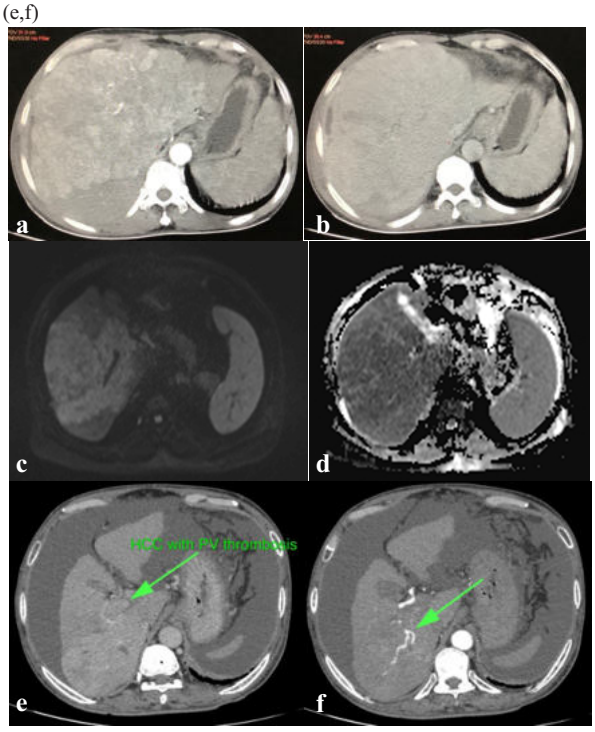
There are some limitations to our study . It could be carried out for a larger population.

Dynamic-enhanced MRI was the choice for detection of HCC; however, some studies suggested DWI as a complementary method[12] which could help in screening as non-invasive and fast method. Dynamic-enhanced MRI inclusion in study could have added additional criteria for comparative study. Triple Phase CT is an invasive study with complication related to contrast could be expected .

CONCLUSION:

The diffusion-weighted MRI sequence is a useful screening and diagnostic tool and it can contribute to accurate diagnosis and discrimination between benign and malignant hepatic masses. DWI can significantly reduce the need for intravenous administration of contrast medium in evaluation of malignancies. DWI can be used as an alternative for the detection and characterization of HCC.

Figure 3: CECT in 60yr old male patient with hepatitis B positive shows diffuse ill-defined lesion with early enhancement in arterial phase (a) and washout in cirrhotic background in portal venous phase (b) and MRI showing diffusion restriction(c,d) .Another 55yr old male patient showing arterial phase enhancing lesion with tumor thromobus (e,f)



Abbreviations: HCC-Hepatocellular carcinoma, CECT- Contrast Enhanced Computed Tomography, CT-Computed Tomography, DWI-Diffusion weighted Imaging, OATP-Organic anion transporting polypeptide, AFP-Alpha fetoprotein, US-Ultrasound, MRI-Magnetic Resonance Imaging, HASTE- Half-Fourier acquisition single-shot turbo spin-echo, ADC-Apparent diffusion coefficient, MRI-Magnetic Resonance Imaging, PPV-Positive Predictive value, NPV-Negative Predictive Value

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