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Original research article

Efficacy of Diffusion Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) in Characterizing Hepatic Lesions and Differentiating Regenerating Nodules from HCC in the Case of Liver Cirrhosis -An Observational Study

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Abstract

Purpose: Evaluating the efficacy of DWI and Apparent Diffusion coefficient (ADC) value in characterizing hepatic lesions and in differentiating regenerating nodules from HCC in the background of liver cirrhosis.

Methods: In this observational study 40 patients with malignant liver lesions and 19 patients with benign liver lesions were included. Out of these 59 patients, 35 patients had a history of cirrhosis. DWI was used to characterize these lesions. Hepatic lesions in patients with cirrhosis were categorized into hepatocellular carcinomas (HCC) and regenerative nodule. The different ADC values obtained in these proven cases were used to derive a cut off ADC value to differentiate malignant from benign lesions. All these patients were referred to the department of radio diagnosis at Amrita Institute of Medical Science and research centre, Kochi, Kerala, India. Data were collected from June 2019 to June 2021 prospectively.

Results: In the current study we could derive an ADC value which can be effectively applied to categorize lesions into malignant and benign. However there was no significant difference in ADC values between malignant lesions with considerable overlap in ADC values of HCC and other malignant lesion. Therefore, application of ADC value to differentiate between malignant lesions was not useful. ADC value was insufficient to further sub-characterize the malignant lesions into HCC and other malignant lesions even in the background of cirrhosis. However, it is useful in differentiating regenerating nodules from HCC in the case of liver cirrhosis. ADC values of different malignant lesions were nearly same with a decimal difference and hence a cut off to differentiate between these malignant lesions were not possible. Similarly, there was no significant difference between the ADC values of benign solid lesions by which we could subcategorize them. In this study ADC cutoff value of 1.45x10-3 mm2 /s was used to differentiate benign from malignant lesions.

Conclusion: This study showed that application of the derived ADC cut off value of 1.45 was effective to differentiate malignant from benign lesions and it was also useful in differentiating regenerating nodules from HCC in the background of cirrhosis. It was not applicable to further subcategorize the malignant and benign lesions as obtained by histopathology. With the help of DWI, existing gold standard involving liver biopsy and its complications can be avoided in patients having a risk of contrast allergy and severe renal failure.

Keywords: Apparent diffusion coefficient, Diffusion weighted imaging, hepatocellular carcinomas, magnetic resonance, regenerative nodule

Introduction

Diffusion weighted magnetic resonance (MR) imaging is reaching its potential for clinical use in the abdomen with the application of stronger diffusion gradients and faster imaging sequences. DWI is an effective method for the diagnosis of liver cirrhosis because it is easy to implement and process without the need for contrast agents. Apparent diffusion coefficient (ADC) has been shown to be a promising diagnostic marker of cirrhosis[1]. Diffusion MR Images is characterized based on the signal in diffusion-weighted images (DWI) at different b value strengths and its corresponding signal in apparent diffusion coefficient (ADC) which can be quantified based on ADC values. The principle of DWI is based on the assessment of random motion of water molecule in a tissue. DWI provides information at the molecular level of the tissue. Thus it helps in assessing the structures and function of the tissue. DWI provides information about tissue microenvironment including its cellularity, tissue viscosity and cell membrane status. ADC is calculated by performing DWI in two or more b values and magnetic resonance imaging systems automatically generates the ADC values. The ADC signal and the value derived in lesions can be used for lesion detection. One of the benefits of DWI is the early evaluation and detection of diffuse liver diseases, particularly in the detection of cirrhosis[2].

DWI does not have contrast media allergy and the risk of renal dysfunction[3]. Patients have the risk of worsening renal failure with iodinated CT contrast and risk of developing nephrogenic systematic fibrosis with Gadolinium based contrast [4]. DWI without contrast is a reasonable option for these patients but non-contrast protocols do not have a diagnostic accuracy comparable to multi-phase contrast MRI. DWI does not require administration of intravenous contrast. The diagnostic performance of DWI has been tested in metastatic liver disease and HCC, and the results were comparable to contrast MRI. Therefore, DWI is a useful technique to detect and monitor hepatic lesions and also it is effective in differentiating regenerating nodules from HCC in the case of liver cirrhosis, thereby avoiding the existing gold standard involving triple phase imaging or liver biopsy and its complications[5].

In this study we assessed the role of DWI and ADC in focal hepatic lesions detection. Also we analyzed the efficacy of DWI in differentiating regenerating nodules from HCC in the case of liver cirrhosis by calculating Apparent Diffusion coefficient (ADC) value.

Methodology

In this observational study 40 patients with malignant liver lesions and 19 patients with benign liver lesions were included. Out of these 59 patients, 35 patients had a history of cirrhosis. DWI was used to characterize these lesions. ADC values were also calculated and recorded. Subsequently lesions in cirrhosis patients were categorized into hepatocellular carcinomas (HCC) and regenerative nodule based on the typical imaging findings in contrast enhanced triple phase CT/MRI and the other cases of hepatic lesions without cirrhotic were identified based on histopathological report after image guided biopsy. The different ADC values obtained in these proven cases were used to derive a cut off ADC value to differentiate malignant from benign lesions. An attempt was also made to study if there was any significant difference between the ADC values of malignant lesions with which we could differentiate HCC from other malignant lesions based on ADC value. All these patients were referred to the department of radio diagnosis at Amrita Institute of Medical Science and research centre, Kochi, Kerala, India. Data were collected from June 2019 to June 2021 prospectively. The lesions were studied with diffusion weighted MR imaging and the measurement data were collected. All patients with USG or CT detected lesions were imaged with DWI and their ADC

values were calculated for lesion characterization. In our study all of the MR imaging was performed in 1.5T MR Imaging HDXT Machine, GE Medical Systems, Milwaukee, Wisconsin.

Inclusion criteria*:* Inclusion criteria consists of the following:
(1)All patients referred for MRI with USG or CT detected liver lesions.
(2) Chronic liver disease referred for MRA as part of pre transplant work up.

Exclusion criteria*:* Exclusion criteria consists of the following:
(1)Patients having cardiac pacemakers, MRI incompatible prosthetic heart valves, cochlear implants or any metallic implants.
(2)Claustrophobic patients
(3)Patients who do not have histological proof / gold standard imaging

Sample size: Based on the sensitivity (87.5%) of ADC cut off value of 1.43 x 10 ^-3sec/mm2 in malignant lesions observed in an earlier study by Madhu SD et al. and with 95% confidence and 20% precision and based on the prevalence of malignant hepatic lesions, the total sample size was derived to be 59. Informed consent was taken from each patient before the preparation for MRI measurements and data collection. All 59 patients with focal liver lesions were evaluated with diffusion weighted MR imaging for a period of 2 years. Histopathology and standardized imaging criteria were taken into consideration for final diagnosis of liver lesions.

MR Imaging*:* All patients were imaged in 1.5T MR Imaging HDXT Machine, GE Medical Systems, Milwaukee, Wisconsin. Patients were given instructions about the examination and its time, and how to take a rhythmic breath. In supine position with arms extended above the head, Torso XL coil surface coil was placed over the upper abdomen. Respiratory-gated acquisitions were used wherever necessary.

Recommended Sequences*:* Fat suppressed single shot respiratory triggered EPI DWI sequence was performed in axial plane with 3D diffusion gradients by using three different b values (b=0 s/mm2, b=500 s/mm2 and b=1000 s/mm2). Region of interest was drawn on ADC map to calculate ADC value.

Result

In this study 40 patients with malignant lesions and 19 patients with benign liver lesions were included. ADC value for each lesion was calculated by performing DWI. Out of these 59 participants, 50 participants were males and 9 participants were females. Age of the study patients was in the rage of 18 years to 83 years. The mean age of the participants was 54.51 + SD 17. 25 years. Most of these patients were from the age group of 51years to 70 years (44.07 %). Based on ADC values these lesions were categorized into benign and malignant. The current study observed that lesions with highest mean ADC value greater than 1.45 ×10-3 mm2 /sec were benign lesions. There were 19 benign lesions and 40 were malignant lesions
A total of 59 participants were included in this study. Out of total 59 cases 35 (59.3%) participants were cirrhotic and 24 (40.7%) of the participants were non cirrhotic. (Table 1)

diagnosis * Cirrhotic / Non cirrhotic Cross tabulation					
			Cirrhotic / Non cirrhotic		Total
			Cirrhotic	Non cirrhotic	
Diagnosis	Cholangiocarcinoma	Count	2	1	3
		% within diagnosis	66.7%	33.3%	100.0%
		% within Cirrhotic / Non cirrhotic	5.7%	4.2%	5.1%
		% of Total	3.4%	1.7%	5.1%
	Cystadenoma	Count	0	2	2
		% within diagnosis	0.0%	100.0%	100.0%
		% within Cirrhotic / Non cirrhotic	0.0%	8.3%	3.4%
		% of Total	0.0%	3.4%	3.4%
	FNH	Count	0	4	4
		% within diagnosis	0.0%	100.0%	100.0%
		% within Cirrhotic / Non cirrhotic	0.0%	16.7%	6.8%
		% of Total	0.0%	6.8%	6.8%
	Granuloma	Count	0	1	1
		% within diagnosis	0.0%	100.0%	100.0%
		% within Cirrhotic / Non cirrhotic	0.0%	4.2%	1.7%
		% of Total	0.0%	1.7%	1.7%
	HCC	Count	25	5	30
		% within diagnosis	83.3%	16.7%	100.0%
		% within Cirrhotic / Non cirrhotic	71.4%	20.8%	50.8%
		% of Total	42.4%	8.5%	50.8%
	Hemangioma	Count	1	6	7
		% within diagnosis	14.3%	85.7%	100.0%
		% within Cirrhotic / Non cirrhotic	2.9%	25.0%	11.9%
		% of Total	1.7%	10.2%	11.9%
	Hydatid cyst	Count	0	1	1
		% within diagnosis	0.0%	100.0%	100.0%
		% within Cirrhotic / Non cirrhotic	0.0%	4.2%	1.7%
		% of Total	0.0%	1.7%	1.7%
	Metastasis	Count	3	4	7
		% within diagnosis	42.9%	57.1%	100.0%
		% within Cirrhotic / Non cirrhotic	8.6%	16.7%	11.9%
		% of Total	5.1%	6.8%	11.9%
	Regenerative nodule	Count	4	0	4
		% within diagnosis	100.0%	0.0%	100.0%
		% within Cirrhotic / Non cirrhotic	11.4%	0.0%	6.8%
		% of Total	6.8%	0.0%	6.8%
Total		Count	35	24	59
		% within diagnosis	59.3%	40.7%	100.0%
		% within Cirrhotic / Non cirrhotic	100.0%	100.0%	100.0%
		% of Total	59.3%	40.7%	100.0%

Out of total 35 cirrhotic cases, 25(71.5%) of the lesions were found to be Hepatocellular carcinoma lesions and 4(11.4%) of the lesions were found to be regenerative nodule.
Most of the patients had HCC ie, 30 patients (50.8 %) followed by 7 patients with hemangioma (11.9%) , 7 patients had metastases (11.9%), FNH in 4 patients (6.8%) , regenerative nodule in 4 patients (6.8%) and rest of the cases included cholangiocarcinoma, cystadenomas, granuloma and hydatid cyst.

Out of 19 benign lesions, Cystadenoma had shown maximum mean ADC value of 2.7×10-3 mm2 /sec followed by Hemangioma having mean ADC value of 2.09×10-3 mm2 /sec. Mean ADC value of Regenerative nodule was 1. 90×10-3 mm2 /sec and FNH mean ADC value was 1.58 ×10-3 mm2 /sec. In granuloma and hydatid cyst, ADC value was constant and hence was omitted.

Out of 40 malignant lesions, metastasis had shown lowest mean ADC value of 0.84×10-3 mm2 /sec while HCC had shown mean ADC value of 0.88×10-3 mm2 /sec and Cholagiocarcinoma had mean ADC value of 0.90×10-3 mm2 /sec.
Table 2 shows the mean ADC values of all the lesions. Using Independent sample t test for unequal variances, p-value was less than 0.05(p value is 0.000***) therefore there was highly significant difference between mean ADC values for benign and malignant lesions.
ADC cut-off value of 1.45x10-3 mm2 /s was obtained by normal distribution (mean±2SD). SPSS Version 26 was used for ROC curve analysis to determine sensitivity and specificity. With 1.45x10-3 mm2 /s ADC cut-off value, the sensitivity of 97.5 % (39/40), specificity of 84.2% (16/19), positive predictive value of 92.2% (39/42) and negative predictive value of 94.1% (16/17) were obtained.

Table 2:

Type Number Of lesions		ADC in 10-3 mm2 /s		p value
		Mean	SD	
Malignant	42	.87	.284	0.000***
Benign	17	1.93	.470	

Diagnosis	No of lesions	Mean ADC (x 10−3 mm2 / sec)	SD	95% Confidence Interval for Mean		Min ADC	Max ADC
				Upper bound	Lower bound	x 10−3 mm2 /s)	x 10−3 mm2 /s)
HCC	30(50.85)	0.88	0.25	0.97	0.78	0	1
Metastasis	7(11.9)	0.84	0.46	1.27	0.42	0	2
Hemangioma	7(11.86)	2.09	0.37	2.43	1.74	2	3
FNH	4(6.8)	1.58	0.22	1.93	1.22	1	2
Regenerative nodule	4(6.78)	1.90	0.356	2.47	1.33	1	2
Cystadenoma	2(3.4)	2.70	0.42	6.51	-1.11	2	1
Cholangiocarcinoma	3(5.1)	0.90	0.10	1.15	0.65	1	1
Granuloma	1(1.7)						
Hydatid cyst	1(1.7)						

Discussion

In the current study, out of total 35 cirrhotic cases, 25(71.5%) of the lesions were found to be Hepatocellular carcinoma lesions and the rest 4(11.4%) were found to be regenerative nodule. In our study, among the 30 hepatocellular carcinomas, 25 had background cirrhosis and five were non cirrhotic. All of the five lesions with non-cirrhotic background were diagnosed using histopathology. Out of the 25 patients with cirrhotic background, 10 did not have typical enhancement pattern of HCC and were subjected to biopsy for diagnosis. The mean ADC value of 30 hepatocellular carcinomas was 0.88±0.25 x10 $^{-3}$ mm^2/sec in our study. In a study by Filipe et al[6], the mean ADC value of HCC was found to be 1.1 x10 $^{-3}$ mm^2/sec and they concluded that malignant lesions like HCC and metastasis had significantly lower ADC values as compared to benign lesions like haemangioma and cysts ($p < 0.001$).In our study also all, except two hepatocellular carcinomas showed diffusion restriction by visual qualitative assessment based on the signals in high b value acquisition and the ADC maps, however with the quantitative analysis applying the derived cut off value of 1.4 mm2/sec both of these missed lesions could be effectively tagged as malignant . Fibrolamellar variant of HCC had an ADC value of 1.1 x 10 -3 mm2/sec and the other HCC had an ADC value of 1.4 1 x 10 -3 mm2/sec. In a study by Javadrashid et al[7] , which included 93 patients, the lowest ADC value was recorded for metastasis which was 0.49 x10 -3 mm2/sec. This study by Javadrashid et al[7] also showed a significant difference between ADC values of benign and malignant lesions (p= 0.001) with a sensitivity of 97.6 % and a specificity of 98.7% of ADC cut off value in differentiating benign and malignant liver lesions. In our study also, the lowest ADC was observed in a metastatic lesion which was 0.3 x10 -3 mm2/sec .Our study included seven metastatic lesions with a mean ADC value of 0.84±0.46x10 -3 mm2/sec. However, one of the metastatic lesion in our study had a relatively higher ADC value of 1.8 x10 -3 mm2/sec though it was showing diffusion restriction. This might have resulted due to severe movement due to poor breathing in a sick patient while imaging and hence poor ADC mapping with tissue overlap. In this case it was particularly difficult to trace the lesion in ADC map due to to poor quality of the acquired images. Poor or incorrect area of interest must have resulted in a higher ADC. Two cholangiocarcinoma were included both of which, showed diffusion restriction with a mean ADC value of 0.85 x 10^{-3}sec/mm2. Both the cholangiocarcinomas were found in cirrhotic liver and had ADC values of 0.8 x10 $^{-3}$ mm^2/sec and 0.9 x10 $^{-3}$ mm^2/sec. In our study, four of the benign lesions showed diffusion restriction and they were - granuloma, hydatid cyst and two FNH. Only 15 out of 19 were stated as true negative with a relatively lower specificity of 78.9%.However, with the application of a cut off value of 1.45mm2/sec the specificity could be increased to 89%. One of the FNH and a granuloma which showed suspicious diffusion restriction had a relatively higher ADC value of 1.5 each and this ADC cut off value would be better in differentiating such lesions. All the benign lesions, except for haemangiomas and regenerative / dysplastic nodules were seen in non-cirrhotic liver. Four FNH were included in our study, with a mean ADC value of 1.57 x10 -3 mm2/sec. Four regenerative / dysplastic nodules included in the study had a mean ADC value of 1.9 x10 -3 mm2/sec. All seven haemangiomas, except one showed hyper intense signals in low, intermediate as well as high b value acquisitions with bright signal on ADC maps , suggesting T2 shine through effect. The mean ADC value of haemangioma was found to be 2.08 x 10 -3 mm2/sec. The benign cystic lesions in our study consisted of biliary cystadenoma, cystic/necrotic granuloma and a hydatid cysts and they had a mean ADC value of 2.05 x 10-3sec/mm2.

In a previous work by Madhu SD et al [8], hydatid cyst showed maximum ADC value of 2.9 x10 -3 mm2/sec followed by simple cysts with an ADC value of 2.3 x 10 -3 mm2/sec. However in our study, the Hydtid cyst showed diffusion restriction with a relatively lower ADC value of 1.3X 10 -3 mm2/sec, both of which are not suggestive of a benign lesion. This could have

resulted due to a highly viscous microenvironment with high protein, sodium chloride and lipid content within the cyst along with an excessive number of scoleces as stated by a study conducted by Ekrem Karakas[9]. In our study, the benign lesion with the highest ADC value was observed in biliary cystadenoma (3 x 10-3sec/mm2).

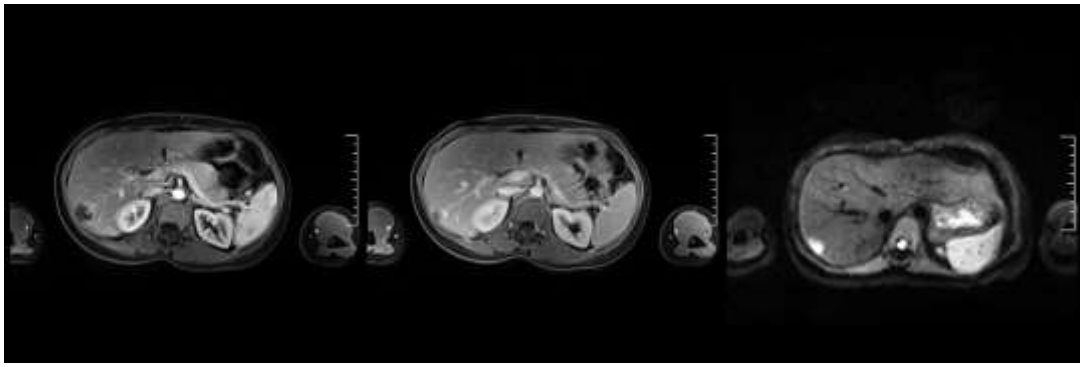

Fig 2A Fig 2B Fig 2C

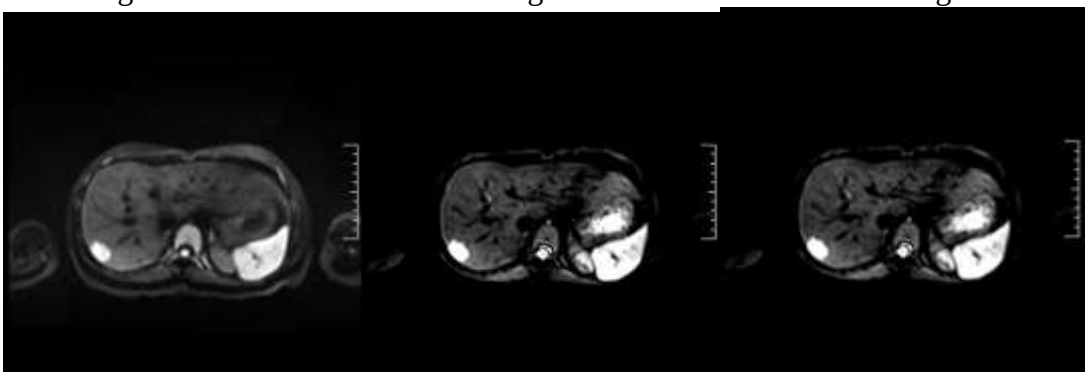

Fig 2D Fig 2E Fig 2F

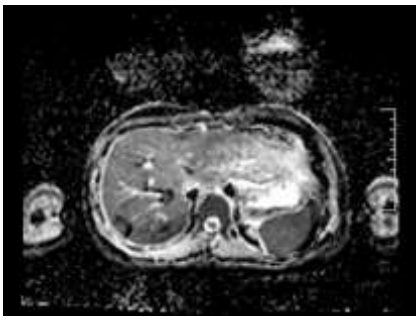

Fig 2G

Hemangioma in right lobe of liver showing typical peripheral nodular enhancement in arterial phase (Figure 2A) and progressive filling of contrast in venous phase (Figure 2B).Hyperintense signals are seen in DWI images in low(Figure 2D), intermediate(Figure 2E) and high (Figure 2F) b values. ADC maps(Figure 2G) show no dark signals suggesting no diffusion restriction.

Fig3A Fig 3B Fig 3C

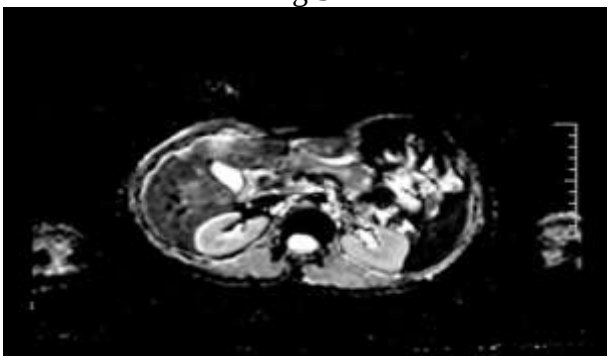

Fig 3D

Focal nodular hyperplasia involving segment V of liver .DWI images in low(Fig 3A), intermediate (Fig 3B)and high (Fig 3C)b values shows hyperintense signals .ADC maps (3D) shows hyperintense signals , suggesting facilitated diffusion.

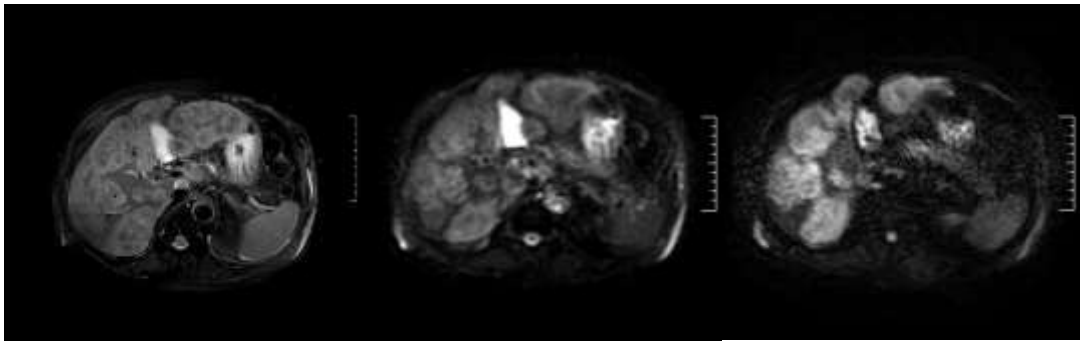

Figure 4A Figure 4B Figure 4C

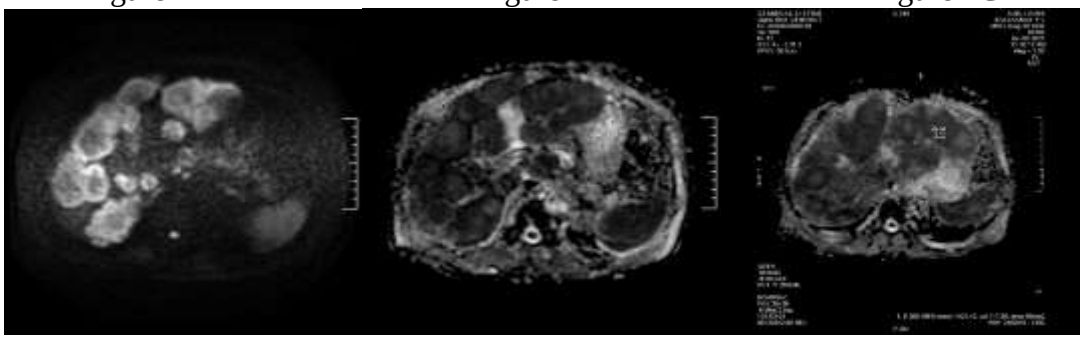

Figure 4D Figure 4E Fig 4F

Liver metastasis. T2WI (Fig 4a) shows multiple hyperintense lesions scattered in liver parenchyma. DWI images at low(Fig 4B), intermediate(Figure 4C) and high b values (Figure 4D)show hyperintense signal with ADC mapping(Figure 4E and 4F) showing hypointense signals and low ADC values , suggesting diffusion restriction and high probability of malignant lesion. It was proven to be adenocarcinoma metastasis on histopathology.

Conclusion

This study showed that application of the derived ADC cut off value of 1.45 was effective to differentiate malignant from benign lesions and it was also useful in differentiating regenerating nodules from HCC in the background of cirrhosis. It was not applicable to further subcategorize the malignant and benign lesions as obtained by histopathology. A further study focusing on a larger number of such lesions may be helpful to subcategorize these lesions especially in the background of cirrhosis. DWI with ADC values is a useful technique for the earlier identification and characterization of malignant from benign lesions especially in cirrhotic patients where it can differentiate regenerating nodule from HCC. It is of utmost importance in cases where contrast administration is contraindicated. Contrast can be avoided in patients with history of allergy to contrast media and in cases with severe Renal failure who stands the risk of permanent Renal dysfunction with the use of iodinated contrast and the risk of developing Nephrogenic systematic fibrosis with Gadolinium based MR contrast media. Therefore, with the help of DWI, the existing gold standard involving triple phase dynamic CT/MRI or liver biopsy and their respective complications can be avoided in patients having a risk of contrast allergy and severe renal failure.

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