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Original Research Paper

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DIFFERENTIATION OF FOCAL HEPATIC LESIONS INTO BENIGN AND MALIGNANT USING DIFFUSION WEIGHTED MR IMAGING

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ABSTRACT

Aim: To differentiate benign and malignant hepatic lesions using diffusion weighted MRI.

Methods: 82 patients detected to have focal hepatic lesions on USG, CT, MRI or PET were retrospectively analysed. Final diagnosis was confirmed by histopathology, cytology, radiological features, clinical history or follow up. The patients underwent MRI in a 1.5 T unit and Apparent Diffusion Coefficient(ADC) values were calculated. ADC values were analysed using Receiver operative characteristic(ROC) curves to calculate threshold ADC value. Test of Least Significant Difference(LSD) was applied to find out if the difference in mean ADC values of benign and malignant lesions was statistically significant or not.

Results: Out of 82 patients, 48 had benign and 34 had malignant lesions. Mean ADC value of 1.68x10-3 mm2/s was found to have the highest sensitivity and specificity for differentiating between benign and malignant lesions.

Conclusions: Mean ADC value of 1.68x10-3 mm2/sec has the highest sensitivity and specificity for differentiating between benign and malignant lesions and is recommended as the threshold value.

KEYWORDS : Magnetic Resonance Imaging(MRI), Focal Hepatic Lesion(FHL), Benign, Malignant, Apparent Diffusion Coefficient(ADC), Diffusion weighted imaging(DWI).

INTRODUCTION

Characterising and differentiating between benign and malignant liver lesions is a diagnostic challenge .Presently USG, triple phase CT and MRI are the investigations available to radiologists to characterise these lesions. MRI has emerged as a superior noninvasive modality to differentiate between benign and malignant focal liver lesions in both normal and abnormal hepatic parenchyma1. MRI sequences and post contrast dynamic MRI using gadolinated contrast media have become a mainstay for detecting and evaluating various focal hepatic lesions2,3. Inherent tissue contrast provided by MRI can not be surpassed by any other modality.

The random motion of particles in a fluid is named after Robert Brown, a Scottish botanist who observed it in 18274,5. Diffusion weighted imaging(DWI) makes use of the Brownian motion in biological tissues6. It was first used for imaging of brain and later found to be useful in imaging of other organs7,8. DWI consumes less time, no contrast is required and can be performed in a single breath hold or during free breathing9. Apparent diffusion coefficient (ADC) is a measure of the magnitude of diffusion (of water molecules) within the tissue and it calculates the combined effects of capillary perfusion and diffusion. DWI can characterise a lesion based on ADC value and differentiate between benign and malignant lesions10,11. DWI can assess response to oncotherapy12 and is being evaluated for follow up13. DWI can be done in patients with deranged renal functions and those at risk for contrast reactions14. DWI has become a cornerstone for imaging in "personalised oncology" and is having applications in "radiomics/radiogenomics"15. The aim of this study was to differentiate benign and malignant hepatic lesions using diffusion weighted MRI and the objective was to find ADC values with which to characterise these lesions.

MATERIALS AND METHODS:

This was a diagnostic study and ethics approval was obtained by our institutional review board.

Retrospective analysis of all those who had undergone liver MRI for focal hepatic lesions(FHL) from Aug 2010 to Oct 2015 for diagnostic purpose.

All patients of FHLs detected on any imaging modality (USG, CT, MRI, PET CT) who had presented to this hospital during the study period of 2010-2015 and who subsequently underwent MRI were included in this study irrespective of their age and sex. The FHLs included all infective, benign or malignant lesions, irrespective of their size. A total 82 patients and 82 FHLs were studied and the final diagnosis was confirmed either on histopathology, cytology, diagnostic radiological findings or clinical background and follow up. For patients who had more than one FHL, the FHL with largest size was taken into consideration.

Patients in whom MRI was contraindicated or DWI could not be done due to other reasons were excluded from the study. Images which were highly degraded were also excluded.

MRI TECHNIQUES:

The scanning system used was 1.5 Tesla (Symphony, Siemens Medical Solutions System) using a phased array body coil. Sequences included spin echo axial T1 WI, pre and post contrast VIBE flash 3d T1 fat suppressed axial images, T2 HASTE coronal images, Fat suppressed SE T2 WI, dynamic post contrast T1 fat suppressed images, in-phase and opposed phase images, DWI with 'b' values of 100, 500 and 750 with ADC maps. The Gradient strength was 45 mT/m.

LESION ANALYSIS:

The number, size and location of FHL visible in various sequences were noted. The segmental location of the hepatic lesions was done using Couinaud numbering system16. In patients with multiple FHLs the largest lesion with similar signal characteristics was selected.

ON DWI : Various FHLs of every patient were assessed as follows:

1. Qualitative/ Visual Assessment: The signal intensity of the FHLs on DWI were assessed using three point scale system as follows: 0- iso to hypointense, 1- Moderately hyperintense, 2- Hyperintense, to that of liver parenchyma.

THE VISUAL GRADING USED FOR TRUE RESTRICTION OF DIFFUSION IS DEPICTED IN FIGURE 1.

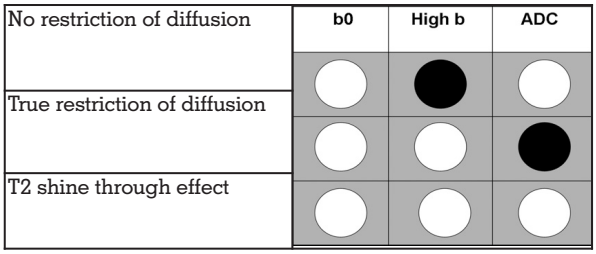

Figure 1: Visual grading used for true restriction of diffusion: Black circles - hypointense, white circles – hyperintense

2. Quantitative Assessment: ADC values were measured through gray-scale ADC maps from each lesion at b100, b500, and b750 s/ mm2 values. ADC values were calculated by drawing a Region of Interest (RIO) over the lesion. If the lesion was larger than 3 cm, ADC was measured twice using 2 circumferential regions of interests (ROI - I and II) of size 1 sq mm each and the two measurements were averaged. ADCs were measured over the largest mass detected in patients with multiple liver lesions. Necrotic portions of solid lesions detected on contrast enhanced MRI were not included in measurements.

The final diagnosis of the FHL was based on histopathology/ cytology, diagnostic radiology, clinical history, operative findings and follow-up.

DATA ANALYSIS

The various ADC values of individual lesions were analysed using ROC curve to calculate the threshold ADC value with which we could differentiate maximum number of the FHLs with high specificity and sensitivity. ROC curves were drawn for ADC values at all b values as well as for mean ADC values. Test of Least Significant Difference (LSD) was applied to determine whether the difference between the Mean ADC values of benign and malignant FHLs and Post transarterial chemoembolization(TACE) hepato cellular carcinoma(HCC) cases was statistically significant or not.

RESULTS

There were 50 men and 32 women with a mean age of 53.4 years; age range, 23–84 years. Out of 82 FHLs evaluated, 48 were benign and 34 were malignant. Patients with post TACE HCC (n=2) were taken as separate subgroup within the malignant group.

The pattern of restriction of diffusion is depicted in **Table No. 1**

TABLE NO. 1: Restriction of Diffusion in Benign Versus Malignant Lesions

Total no. of benign lesions	48	Lesions with true restriction on DWI	5
		Lesions with no true restriction on DWI	43
No. of Post TACE HCC	2	Lesions with true restriction on DWI	0
		Lesions with no true restriction on DWI	2
Total no of malignant lesions	32	Lesions with true restriction on DWI	32
		Lesions with no true restriction on DWI	0
Total	82		82

The mean ADC values obtained for the various lesions studied is shown in **Table No.2.**

TABLE NO. 2: MEAN ADC VALUES OF FHL SUBTYPES

Lesion type	Mean ADC (x10-3 mm2/s) ± SD
Simple cyst (n=11)	3.62 ± 0.06
Hydatid cyst (n=7)	3.32 ± 0.73
Hemangioma (n=14)	2.43 ± 0.13
Regenerating nodules (n=11)	2.26 ± 0.10
Hepatic abscess (n=3)	1.98 ± 0.47
Other benign lesions (n=2)	1.97 ± 0.42
Mean ADC for Benign lesions	2.66 ± 0.67
Post TACE HCC	3.5 ± 0.15
Metastasis (n=20)	1.32 ± 0.08
Hepatocellular carcinoma (n=9)	1.40 ± 0.06
Cholangio Carcinoma (n=3)	1.20 ± 0.07
Mean ADC for Malignant lesions	1.36 ± 0.20

Among the benign lesions, simple cysts had the highest and hepatic abscesses the lowest ADC values. The average ADC values for two benign lesions that showed restriction of diffusion were: 1) Atypical hemangioma – 2.0×10-3 mm2/s and 2) Infective FHL in Transitional Cell Carcinoma(TCC) urinary bladder – 1.94×10-3 mm2/s. Among the malignant lesions, HCC had the highest and intrahepatic cholangiocarcinoma and metastatic FHLs had lowest ADC values.

The ADC values for the lesions at different b values of 100, 500 and 750 is depicted in **Table No. 3.**

Table No:3 ADC values of different groups at various b values

Avg ADC (x10-3 mm2/s)		At b100	At b500	At b750	Overall ADC value				
	N	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Malignant	32	1.72 ±.23	1.40-2.80	1.32 ±.20	1.06-2.30	1.01 ±.19	0.87-2.00	1.35 ±.20	1.11-2.37
Benign	48	2.97 ±.66	1.98-3.96	2.65 ±.64	1.57-3.70	2.35 ±.74	1.29-3.48	2.66 ±.67	1.62-3.67
HCC post TACE	2	3.76 ±.07	3.71-3.81	3.46 ±.84	1.06-3.70	3.30 ±.21	3.15-3.45	3.50 ±.14	3.40-3.61
Total	82	2.49 ±.83	1.40-3.96	2.13 ±.84	1.06-3.70	1.84 ±.90	0.87-3.48	2.15 ±.85	1.11-3.67

The difference between the mean ADC values of benign and malignant FHLs and Post TACE HCC was statistically significant with p values being less than 0.05 as depicted in **Table No. 4.**

Table No. 4: ANOVA between the different groups at various b values

		Sig at b100	Sig at b500	Sig at b750
Malignant	Benign	.0001	.0001	.0001
Malignant	HCC post TACE	.0001	.0001	.0001
Benign	HCC post TACE	.044	.029	.027

On analyzing ROC curve for mean ADC values, it was seen that the mean ADC value that has highest specificity and sensitivity is 1.68X10-3 mm2/sec with specificity and sensitivity of 94.1% and 95.8% respectively. Hence, a mean ADC value of 1.68X10-3 mm2/sec if taken as a cut-off has highest specificity and sensitivity for differentiating benign from malignant lesions and can be recommended as a threshold mean ADC value.

DISCUSSION:

Literature review has shown that DWI and ADC value are useful for differentiation between benign and malignant

hepatic focal lesions. The malignant hepatic lesions are shown to have restricted diffusion due to their high vascularity and cellularity as compared to the benign hepatic lesions. Various studies have shown that the overall diagnostic ability of mean ADC value to differentiate malignant from benign FHLs is higher than its ability to differentiate between individual FHLs. We got an average ADC value for HCC at b 750 of 0.95 ± 0.097×10-3 mm2/s. For metastatic FHLs and intra-hepatic cholangiocarcinoma we got average ADC values of 1.01±0.076×10-3 mm2/s and 0.91±0.03X10-3 mm2/s respectively, at b750. The results were not significantly different from the published values by M.R. Onur et al 17 in a series of 95 patients.

The comparison in the mean ADC values obtained in our study with that by Demir et al18 is shown in **Table No 5.**

Table No 5: Comparison of the findings of Demir et al with our study

Lesion type	Mean ADC (mm^2/s) Demir et al[18].	Mean ADC values in our study
Simple cyst	3.05 ± 0.26 × 10-3	3.62 ± 0.06 × 10-3
Hemangioma	2.46 ± 0.21 × 10-3	2.43 ± 0.13 × 10-3
Hydatid cyst	2.99 ± 0.24 × 10-3	3.32 ± 0.73 × 10-3
Hepatic abscess	1.83 ± 0.28 × 10-3	1.98 ± 0.47 × 10-3
Metastasis	0.79 ± 0.11 × 10-3	1.32 ± 0.08 × 10-3
Hepatocellular carcinoma	0.90 ± 0.10 × 10-3	1.40 ± 0.06 × 10-3
Cholangiocarcinoma	0.95 ± 0.13 x 10-3	1.20 ± 0.07 × 10-3

A meta-analysis by Y. Li et al19 of eight sets of data described in six studies shows that mean ADC values can differentiate malignant FHLs from benign ones.

The mean ADC value for benign FHL we got was similar to that published by Gourtsoyianni S et al20. In case of malignant FHLs the mean ADC value was similar to that proposed by Parikh et al21.

Many studies have also reported a significant increase in the ADC value of hepatocellular carcinoma 1–2 weeks after transarterial chemoembolization . We got similar results as seen by Kamel et al. 22

One case of atypical haemangioma showed increased signal intensity on DWI even at higher b values (750 s/mm2). Increased signal intensity of haemangiomas at the higher b-value is possibly due to a fibrous tissue content, which is typically seen in hyalinised haemangiomas 23.

In our study there was a significant statistical difference ($p < 0.05$) noted between mean ADCs of benign and malignant lesions and post TACE HCC lesions (2.66±0.67x10-3 mm2/s, 1.35±0.20x10-3 mm2/s and 3.5±0.15x10-3 mm2/s respectively) when three b values were used (b = 100, 500 and 750 s/mm2; respectively) and average ADC value was calculated. Using a threshold mean ADC value of 1.68X10-3 mm2/s we were able to differentiate benign from malignant lesions with 95.8% sensitivity and 94.1% specificity. The pooled sensitivity and specificity from various studies has been found to be near to 86% and 84%, respectively24.

Despite there being significant differences in mean ADC values of benign and malignant FHLs on a group basis, characterization of FHLs by using ADCs showed overlap even in our study. Again, these results are similar to the published results and shows that ADC values cannot be used individually for characterisation of FHLs.

DWI could detect all benign and malignant FHLs visualized on other imaging modalities and other MR sequences including dynamic CEMRI. Four cases of malignant FHLs showed more number of the FHLs on DWI at lower b value (b100), particularly or small malignant lesions measuring 1 cm as compared to the T2WI. The sensitivity was 100 % in our study.

LIMITATION

Certain subgroups of FHLs, e.g. benign hepatocellular lesions, like hepatic adenoma and focal nodular hyperplasia were not seen in our study. Hence, comparison between solid benign and malignant masses or between different malignant masses could not be made. Only two cases of post TACE HCC were in our series which is low in number.

While this study was conducted with a 1.5T MRI, there are publications that report improved image quality in diffusion MRI studies with 3 Tesla MRI devices25,26,27. Recent studies have described ADC ratio as a better parameter than ADC value alone28. Further prospective studies may be planned for calculation of ADC ratio with adjacent liver parenchyma. Simple cysts were included in our study which has been reported to increase the mean ADC value. One recent study by T P Jain et al excluded simple cysts due to this reason28. Newer sequences like diffusion-weighted whole-body imaging with background body signal suppression/T2-weighted image fusion has shown to improve the detection of lesions 29,30.

CONCLUSION:

In our study, all malignant FHLs (n= 32) showed true restriction of diffusion on DWI and ADC map, with the malignant FHLs having lower ADC values than that of benign FHLs. The mean ADCs of benign and malignant lesions were 2.66 ± 0.67×10-3 mm2/s and 1.36 ± 0.20 ×10-3 mm2/s, respectively. The difference between the ADC values of benign and malignant lesions was statistically significant ($p < 0.05$).

Using a threshold value of 1.63×10-3 mm2/s for ADC we could differentiate maximum number of malignant from benign FHLS with sensitivity and specificity of 95.8% and 94.1%, respectively.

CONFLICT OF INTEREST: NONE

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