Section: Radiology

Original Research Article

ROLE OF DIFFUSION WEIGHTED MRI IN IDENTIFICATION AND CHARACTERIZATION OF FOCAL LIVER LESIONS

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Received *: 13/03/2025*
Received in revised form *: 06/05/2025*
Accepted *: 24/05/2025*

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DOI: 10.70034/ijmedph.2025.2.308

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (2); 1719-1725

ABSTRACT

Background: The aim of the present study was to assess the role of diffusion weighted MRI in identification and characterization of focal liver lesions.
Materials and Methods: This prospective study was done in the Department of Imaging Science & Interventional Radiology of Meenakshi mission hospital & research centre, Madurai, Tamil Nadu after getting approval from Ethical & Scientific committee of hospital from March 2013 to May 2014.
Results: We analyzed 100 focal lesions which included 65 malignant (HCC n=25 & Metastasis n=40) and 35 benign (hemangioma n=15, cysts n=10, adenoma n=6 & FNH n=4) lesions. Major part of our patients was between 41-71years of age group (total 61 patients (71.7%). The average age of the patients was 56years (range 18-85years). Out of total 85 patients 43 patients were female while 42 patients were male. Major part of the focal lesions was between 2-4cm with size range 2.5-18 cm with average size of lesions 7.8 cms. 95% sensitivity was due to 3 false negative lesions. There was no significant difference between ADC values of HCCs & metastases (p=0.19). ADC values of FNHs showed no significant difference from adenomas (p=0.066). HCCs and metastatic lesions presented significantly lower ADC values compared to haemangioma, adenoma, FNH and cysts (p<0.001) and ADC values of cysts were significantly higher when compared to all other lesions (hemangiomas, adenomas and FNHs, HCCs and metastasis (p<0.001).
Conclusion: In conclusion, quantitative and qualitative evaluations of ADC values of hepatic parenchyma and focal hepatic lesions better fulfils our criteria included in aims and objectives of our study. Qualitative and quantitative analysis of ADC can better characterize hepatic lesions & is very useful for the differentiation between malignant and benign lesions. Significantly lower ADC values are seen in malignant lesions when compared with benign ones. But there is also overlap between different types of lesions specially FNH, adenoma, normal liver parenchyma & malignant lesions with few benign lesions showing restriction of diffusion and may look like malignant lesions. So DWI alone should not be taken as a stand-alone procedure.
Keywords: Diffusion weighted MRI, HCC, focal liver lesions.

INTRODUCTION

Diffusion simply means free mobility of molecules in water known as Brownian motion.[1] It is directly related with tissue properties, such as the size of the extracellular space (like the rate of relatively unhindered moving water protons), viscosity and cellularity.[2] In simple words water molecules are free to move in any directions in tissues like normal liver parenchyma and most of benign lesions. While

when extracellular space is densely packed with cell due to any cause like cellular edema or hypercellular tissue, water molecules are restricted from freely moving called as restricted diffusion.[3-10]

Diffusion imaging is characterized by its b value(s/mm2) which is strength of the diffusion sensitizing gradient. Diffusion imaging can be performed using various techniques like spine echo (SE), fast spin echo (FSE), gradient echo or echo planar imaging (EPI). Scan can be performed using breath hold or free breathing or respiratory triggering (RT). Respiratory triggered DWI can give as high quality images within short duration (4-6min). A study compared respiratory triggered and breath-hold DW-SS-EPI for liver imaging, and respiratory gated DW-SS-EPI (Diffusion weighted single shot echo-planar imaging) showed overall better image quality and a significantly higher lesion-to liver contrast ratio & that's the reason we have used respiratory gated diffusion method for our study.[3,11-20]

Proton molecules within vessels are highly mobile and readily lose signal at low b values while on the other side in slow-flowing blood molecules will not lose signals as they have moved very subtle distance from its original position & may show features of highly cellular lesion and appear hyper intense on DW images. At b value of 0 sec/mm2 where there is no diffusion sensitizing gradient, free water molecules have high signal intensity because it is based on T2 weighting. Small b values (50–100 sec/mm2) will show signal loss in highly mobile water molecules like molecules in vessels. The water molecules will have moved quickly over relatively longer distances by the time the rephasing gradient is applied, and consequently will not regain their original phase information after application of the rephasing gradient giving the "black-blood" images, as a result of the signal loss in the fast-flowing blood within vessels.[4,21-30]

DW MR imaging gives us both qualitative and quantitative information of tissue diffusivity (apparent diffusion coefficient) without the use of any contrast material like gadolinium chelates making it a highly attractive technique, especially in patients with severe renal dysfunction who are high risk for nephrogenic systemic fibrosis. Diffusion weighted MRI also have role in diagnosis of breast, adnexal, head and neck malignancies.[5,6]

The aim of the present study was to assess the role of diffusion weighted MRI in identification and characterization of focal liver lesions.

MATERIALS AND METHODS

This prospective study was done in the Department of Imaging Science & Interventional Radiology of Meenakshi mission hospital & research centre, Madurai, Tamil Nadu after getting approval from Ethical & Scientific committee of hospital from March 2013 to May 2014.

Study Population: After getting informed consent of patients, we did respiratory gated non contrast MRI examination (DWI, T1WI & T2WI) of total of 95patients (85 patients with focal liver lesions and 10 normal healthy volunteers) who were referred for MRI examinations to our department with focal lesions diagnosed by other methods (like USG or CT) or incidentally diagnosed unknown lesions. Normal healthy volunteer were examined to know the mean ADC value of normal liver parenchyma.

Study tools: MRI (PHILIPS MULTIVA 1.5 Tesla, (16 channels) with 16channel torso (body) coil & respiratory sensor for Respiratory triggered imaging.

Inclusion Criteria

- Patients already diagnosed with focal liver lesion by ultrasonography.
- Patients with findings suggestive of focal liver lesion on contrast CT examinations.
- Patients referred to the Radio Diagnosis Department with strong clinical suspicion of focal lesion of liver including those with primary malignancy elsewhere.
- Incidentally diagnosed lesions(like cyst, hemangioma) in patients referred for MRI examination for other reasons
- Focal lesions >2cm size were included.

Exclusion Criteria

- Infiltrative liver lesions like fatty liver, cholangiocarcinoma.
- Infective or Inflammatory lesions as we want to evaluate and characterise exclusively benign and malignant lesions only.
- Patients with mass lesions infiltrating the liver from outside the liver.
- Patients with traumatic injury to liver.
- Patients with general contraindication to MRI such as those with pace makers, cochlear implants and other electromagnetic implants in body.
- Lesions <2cm size to avoid partial volume effect errors.
- Those already on or taken treatment chemo or radiotherapy for malignancy.

Study Protocol

1. A detailed history of the patient including signs and symptoms, detailed physical examination, biochemical investigations and radiological investigations were recorded and tabulated as in the proforma shown.
2. A written & informed consent was taken.
3. It was made sure that the patient doesn't have any contraindication for MRI scanning and is not in possession of any metallic objects.
4. The patient was then placed on the gantry table in supine position.
5. A 16 channel torso coil was then placed over the upper abdomen with the superior surface 5 cms below the level of the nipple along with a respiratory trigger fixed just below the xiphisternum.

MRI Imaging: MR Imaging was performed by using PHILIPS MULTIVA 1.5 Tesla machine with 16 channel torso coil.

		TE (ms)	TR (ms)	Slice Thickness	Intersect ion Gap	Matrix
DWI (b=0,50,300,600)	SE-SSEPI	59	1230	6mm	1mm	124x100
T1W	SS TFE	4.6	100	6mm	1mm	224x224
T2W	SS TSE	80	800	6mm	1mm	240x240

	Flip Angle	Respiratory Triggered by Sensor	Acquisitions Time	Fat Supression	Fov (mm)
DWI (b=0,50,300,600)	90	YES	5.18min	SPIR	375x305
T1W	15	YES	3min	NO	375x307
T2W	90	YES	4min	NO	375x305
Total scan duration			12.18min		

ADC calculation was done automatically by MRI machine and ADC map was generated automatically

Image Analysis:

Visual Qualitative characterization: Images were evaluated with b values of 0, 50, 300 and 600 sec/mm2 by using criteria like lesion morphology, signal intensity, degree of signal intensity decrease with increasing b values and qualitative assessment of ADC maps.7-8 A lesion was characterised as benign if the lesion was iso or hyperintense on T2-weighted images and on DW images at b =0 sec/mm29,10 and showed a strong signal intensity decrease at b =500 sec/mm2 and in ADC map lesion was iso or hyperintense compared to that of the liver.8 Those lesions showing hyperintensity on T2W images11-13 and on DWI b=0 and maintained hyperintensity compared to liver parenchyma at b=300 & 600 sec/mm2 images and which showed hypointense signals on ADC, were labelled as malignant.[1,8]

Quantitative analysis: Lesion evaluation was done for lesions measuring > 20 mm. Single region of interest with approximate diameter of 1cm2 was drawn over the lesion and ADC values were shown on monitor. We selected the most hypo intense part of the lesion for drawing region of interest because it is the area which will represent the most hyper cellular part of lesion. Necrotic areas were not included in region of interest. And in case of two or more lesions showing same signal intensity, larger lesion was evaluated. Final diagnosis was confirmed by histopathological examination which was available for all malignant lesions, adenoma and FNH. Cyst and Haemangioma were confirmed by their typical signal intensities on T1 and T2W imaging and already established criteria10,14,15 for them with stability of the lesion over at least 6 months duration. We had done DWI of ten normal healthy volunteers with normal liver parenchyma. The mean ADC value for normal liver was 1.40x10-3 mm2/s. Taking 1.40x10-3 as a cut off value we characterized lesions with ADC value <1.40x10-3 mm2/s as malignant lesion and ≥1.40x10-3 mm2/s as benign lesion.

Statistical Methods Employed

All data was collected and was put into master chart. All continuous variables were summarised using the following descriptive statistics: Mean, SD, Minimum & maximum. The frequency and percentages of observed levels were reported for all categorical measures. Statistical analysis was performed with STATA software (version 11.1 college station, TX USA). The t- test was used to calculate the significance of differences in the ADC values of different FHL and the differences between benign and malign lesions. A p-value of <0.05 was considered as significant. All statistical analysis is performed for cases only (85 patients with 100 focal lesions). Only Mean ADC value & mean age of normal healthy volunteers was calculated.

RESULTS

Table 1: Patient characteristics

Age group(years)	No of cases	Percentage
18-30	2	2.4%
31-40	10	11.2%
41-50	21	24.7%
51-60	19	22.4%
61-70	21	24.7%
71-80	10	11.2%
81-90	2	2.4%
Gender		
Males	42	49%
Females	43	51%
Size of the Lesion(cm)		
2-4	35	35
4.1-6	17	17
6.1-8	20	20

8.1-10	13	13
10.1-12	7	7
12.1-14	2	2
14.1-16	3	3
16.1-18	3	3

Major part of our patients was between 41-71years of age group (total 61 patients (71.7%). The average age of the patients was 56years (range 18-85years). Out of total 85 patients 43 patients were female while 42 patients were male. Major part of the focal lesions was between 2-4cm with size range 2.5-18 cm with average size of lesions 7.8 cms

Table 2: Patients with focal liver lesions

Total no. of patients with focal liver lesions n = 85			
Total no. of focal liver lesions n = 100			
Benign lesions n= 35		**Malignant lesions n =65**	
Hemangioma	n = 15	HCC	n =25
cysts	n = 10	Metastasis	n = 40
Adenoma	n = 6		
FNH	n = 4		

We analyzed 100 focal lesions which included 65 malignant (HCC n=25 & Metastasis n=40) and 35 benign (hemangioma n=15, cysts n=10, adenoma n=6 & FNH n=4) lesions. There were 40 cases of metastasis which included metastasis from Ca Colon (n=15), Periampullary Carcinoma (n=4), Ca Breast (n=6), Ca Cervix (n=4), Ca Ovary (n=3), Ca Endometrium (n=2), Ca Prostate (n=3), Ca Esophagus (n=2), Ca Buccal mucosa (n=1).

Table 3: Accuracy of MRI (T1 & T2WI) to differentiate between benign & malignant lesion

MRI Characterization	**Final Diagnosis**		
	M	**B**	
M	61 (TP)	4 (FP)	65
B	04 (FN)	31 (TN)	35
	64	36	100

Sensitivity: TP/TP+FN = 61/65 = 94% SPECIFICITY: TN/TN+FP = 31/35 =89% PPV: TP/TP+FP = 61/65 =94% NPV: TN/TN+FN = 31/35 = 89%

Table 4: Accuracy of DWI (ADC VALUE) to differentiate between benign & malignant lesion

DWI Characterization (By ADC Value)	**Final Diagnosis**		
	M	**B**	
M	63 (TP)	2 (FP)	65
B	03 (FN)	32 (TN)	35
	66	34	100

95% sensitivity was due to 3 false negative lesions. All of them were adenoma and showed ADC of 1.29, 1.33 & 1.29(x 10-3 mm2/s) making them to be characterized as malignant lesion. 94% specificity was due to 2 false positive cases (1 HCC & 1 Metastasis). Both of them were having ADC value of 1.5x10-3mm2/s which made them to be characterize as benign lesion.

Table 5: Accuracy of qualitative assessment OF ADC map to differentiate between benign & malignant lesion

Qualitative Characterization by ADC Map	**Final Diagnosis**		
	M	**B**	
M	59 (TP)	6 (FP)	65
B	05 (FN)	30 (TN)	35
	64	36	100

92% sensitivity in our study was due to 5 false negative lesions, 4 of which were adenoma and one was hemangioma which appeared hypointense to normal parenchyma on ADC so they were wrongly characterized as malignant lesion. 83% specicity in our study was due to iso to slight hyperintense appearance of 6 (3 metastasis & 3 HCC) false positive lesions which made them to be characterized as benign lesions.

Table 6: Mean ADC values of lesions and Mean ADC values of Benign & Malignant lesions

FOCAL Lesion	**Mean ADC value (x 10-3mm2/s)**
HCC (n=25)	0.89 ± 0.25
METASTASIS(n=40)	0.97 ± 0.23
HEMANGIOMA(n=15)	2.14 ± 0.39
SIMPLE CYSTS(n=10)	2.92 ± 0.21

ADENOMA(n=6)	1.37 ± 0.07
FNH(n=4)	1.45 ± 0.03
NORMAL LIVER PARENCHYMA	1.40 ± 0.03
Mean ADC values of Benign & Malignant lesions	MEAN ADC Value (x 10-3mm2/s)
BENIGN (n=35)	2.15 ± 0.64
MALIGNANT(n=65)	0.94 ± 0.24

The mean ADC values of the focal lesions were as follows (×10−3mm2/s): hepatocellular carcinoma (HCC) 0.89±0.25; metastases 0.97±0.23; hepatocellular adenoma 1.37±0.07; focal nodular hyperplasia (FNH) 1.45±0.003; hemangioma 2.14±0.39 & cyst 2.92±0.21. Mean ADC value of the 35 benign lesions was (2.15 ± 0.64) ×10−3mm2/s, while mean ADCvalue of the 65 malignant lesions was (0.94 ± 0.24) ×10−3mm2/s. The mean ADC value of malignant lesion was significantly lower than those of benign lesions (p<0.001)

Table 7: Significance of difference between Individual lesions

Difference Between ADC Values of Focal Lesions	p VALUE	Significant(p<0.05)/ Insignificant(p≥0.05)
HCC & Metastasis	0.19	Insignificant
Metastasis & Adenoma	<0.001	Significant
HCC & Adenoma	<0.001	Significant
HCC & FNH	<0.001	Significant
FNH & Metastasis	0.0002	Significant
FNH & Hemangioma	0.0024	Significant
HCC & Hemangioma	<0.001	Significant
Metastasis & Hemangioma	<0.001	Significant
Cyst & Adenoma	<0.001	Significant
CYST & FNH	<0.001	Significant
CYST & HEMANGIOMA	<0.001	Significant
CYST & METASTASIS	<0.001	Significant
CYST & HCC	<0.001	Significant
FNH & ADENOMA	0.066	Insignificant

There was no significant difference between ADC values of HCCs & metastases (p=0.19). ADC values of FNHs showed no significant difference from adenomas (p=0.066). HCCs and metastatic lesions presented significantly lower ADC values compared to haemangioma, adenoma, FNH and cysts (p<0.001) and ADC values of cysts were significantly higher when compared to all other lesions (hemangiomas, adenomas and FNHs, HCCs and metastasis (p<0.001).

DISCUSSION

Using a small b value less than 100–150 sec/mm2 nulls the intrahepatic vascular signal producing black-blood images, which increases the detection chances of focal liver lesions.[16-19] High b values (>500 sec/mm2) are useful for focal liver lesion characterization.[8,9] That is the reason we have done study with b values 0, 50, 300 & 600 sec/mm2 which includes both low b value for lesion detection and high b value for lesion characterization.

ADC value of normal liver parenchyma in our study is (1.40±0.03)x10-3 mm2/s which is close to value by Muller et al20 (1.39x10-3mm2/s) and slightly higher than study done by Bruegel et al,[22] (1.24±0.15 mm2/s). Various literatures until 201421 show variable mean ADCs for normal liver parenchyma ranging from 0.69 to 2.28 ×10−3mm2/s. This might be because of the differences in MR scanners and due to no standardized protocol followed for DWI.[22,23] Sensitivity & specificity of quantitative ADC value for our study considering 1.40x10-3 mm2/s as cut off value was 95% and 94% respectively. 95% sensitivity was due to 3 false negative lesions. All of them were adenoma and showed ADC of 1.29, 1.33 & 1.29(x 10-3 mm2/s) making them to be characterized as malignant lesion. 94% specificity was due to 2 false positive cases (1 HCC & 1 Metastasis). Both of them were having ADC value of 1.5x10-3mm2/s which made them to be characterize as benign lesion.

As expected cysts showed the highest ADC values because of their fluid content and high cellular malignant lesions like HCCs and metastases showed the lowest ADC values. Benign lesions showed an average intermediate ADC value which overlaps with normal liver parenchyma but, despite this, values were significantly different when compared with other solid hepatic lesions, especially HCCs. Like other previous studies, no overlapping of ADC values was seen between the ADCs of cysts and solid lesions. All simple cysts showed higher ADC values than the mean ADC value of hemangiomas. Metastases showed significantly (p< 0.001) lower mean ADC values than benign lesions. We got partial overlapping of ADC values of FNH & adenoma with metastasis and HCC. No overlapping was seen between hemangioma & malignant lesions (p<0.001). We are more concerned about overlapping of hemangiomas with malignant lesions because necrotic metastases may be strongly hyperintense24-26 and hemangiomas may hyalinize and show low signal intensity on T2-weighted images.27 Some hemangiomas may also demonstrate atypical contrast enhancement patterns and look like hypervascular metastases.[22] So it is necessary to differentiate

between them and ADC evaluation (both quantitative and qualitative) performs its job better.

Sensitivity and specificity values of our study are slightly lower than those of Gourtsoyianni et al28 and Taouli et al,[29] but the reason for that is they have studied very few (almost none) number of lesions containing adenoma & FNH which are the main lesions showing overlapping with benign and malignant lesions and with normal parenchyma. Qualitative analysis of ADC map is performed in study by Holzapfel et al. In their study qualitative analysis was performed by two separate readers and they found 96.6% sensitivity and 89.8% specificity by one reader and 96.6% sensitivity and 87.8% specificity by another reader for diagnosis of malignancy. In our study we got 92% sensitivity & 83% specificity which is slightly lower than by Holzapfel et al,[30] 92% sensitivity in our study was due to five false negative lesions, 4 of which were adenoma and one was hemangioma which appeared hypointense to normal parenchyma on ADC so they were wrongly characterized as malignant lesion. 83% specicity in our study was due to iso to slight hyperintense appearance of 6 (3 metastasis & 3 HCC) false positive lesions which made them to be characterized as benign.

On comparing our study with various studies with breath hold method it seems that Ichikawa et al6 probably overestimated the ADCs by using very low b values(<55 sec/mm2). On the other side low ADCs reported by Namimoto et al,[8] are possibly underestimated because they used very large b values (1200 sec/mm2). ADC for normal liver parenchyma is close to our study in Muller et al,[20] while Kim et al,[9] showed slight lower value. On the other side ADC values of focal liver lesions (both benign and malignant lesions) is seen more close to our values in Kim et al,[9] study especially with b < 450 sec/mm2. While ADC values for focal liver lesions are slightly on higher side in study by Muller et al than our study. But it should be kept in mind that Muller et al did study with very small number (n=9) of focal liver lesions.

CONCLUSION

In conclusion, quantitative and qualitative evaluations of ADC values of hepatic parenchyma and focal hepatic lesions better fulfils our criteria included in aims and objectives of our study. Qualitative and quantitative analysis of ADC can better characterize hepatic lesions & is very useful for the differentiation between malignant and benign lesions. Significantly lower ADC values are seen in malignant lesions when compared with benign ones. But there is also overlap between different types of lesions specially FNH, adenoma, normal liver parenchyma & malignant lesions with few benign lesions showing restriction of diffusion and may look like malignant lesions. So DWI alone should not be taken as a stand-alone procedure. Cysts showed the highest ADC values because of the free movement of water molecules within their fluid contents, on the other side HCCs, metastases & adenoma showed the lowest ADC values probably due to their high cellularity. A lesion with available region of interest above 1 cm2 can give us accurate ADC values in supra-centimetric homogenous lesions. Other lesions should be studied and future cut offs for lesion characterization should be obtained, using a standardized DWI protocol to overcome differences between studies.

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