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Role of Magnetic Resonance Diffusion Imaging in Differentiation of Malignant and Benign Hepatic Focal Lesions

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Abstract
Background: *With the advances in magnetic resonance imaging (MR) technology, diffusion-weighted magnetic resonance imaging (DWI) can be used in further characterization of liver lesions and differentiating malignant and benign lesions.*
Aims: *The purpose of this study was to evaluate focal hepatic lesions using Diffusion Weighted Magnetic resonance imaging and calculate apparent diffusion coefficient (ADC) values, to determine if focal hepatic lesions could be differentiated as benign or malignant by diffusion weighted imaging and ADC maps. Histopathological correlation wherever possible.*
Material and Methods: *This study was carried out on 40 patients in Department of Radiodiagnosis, Government Medical College, Rajindra Hospital, Patiala. Patients with indeterminate hepatic masses found on USG abdomen and/ CT abdomen were included and MRI abdomen was conducted to characterize liver lesions and ADC values calculated using different b values = 0, 100, 500 and 750 s/mm^2.ADC values of benign and malignant lesions were compared.*
Results: *Mean ADC values of malignant focal lesions were significantly lower than benign mass lesions: 0.87 ± 0.15 x10^{-3}mm^2/s V/s 2.66±0.80x10^{-3}mm^2/s respectively (P<0.05). The best ADC threshold value for distinguishing benign and malignant lesions was1.50 x 10^{-3}mm^2/s with Sensitivity =100 %, Specificity = 90.9%, Positive predictive value= 93.33%, Negative predictive value =100% and p value <0.05 respectively.*
Conclusion: *DWI and ADC can better characterize focal hepatic lesions. DWI can be used as an additional sequence to the standard protocol study and not as a unique imaging series.Since there could be substantial overlap in the range of ADCs between different pathologies, the ADC should be interpreted concurrently with all available imaging before making the radiologic diagnosis.*
Keywords: *DW MRI liver; Hepatic focal lesions; ADC of hepatic focal lesions; Benign and malignant lesions; ADC cut-off.*

Introduction

Focal liver lesions (FLL) can be classified into 2 clinical categories: benign lesions and malignant lesions. Differentiation between malignant and benign focal liver lesions and establishing the correct diagnosis are of great importance in treatment planning. Imaging is an important decision-making tool in the diagnosis of FLLs as it can accurately differentiate benign from malignant lesions in most of the cases.[1]

Diffusion weighted imaging (DWI) is one of the MRI sequences that produces image contrast and depends upon the diffusion properties of water molecules in biologic tissues. Water molecules freely move in any direction in tissues like normal liver parenchyma and most of the benign liver lesions. In tissues with extracellular space densely packed with cells due to any cause like hypercellularity or cellular edema show restricted movement of free water molecules. This is called as restricted diffusion.[2]Diffusion is quantitatively measured in the form of apparent diffusion coefficient (ADC), expressed in square millimeter/second. It is called apparent because it is a mean value of diffusion contributed by movement of water molecules from the intracellular, extracellular and vascular compartments within an image voxel at different b-values. ADC calculation can be used for the characterization of focal and diffuse diseases within the liver. [3]

By using two or more b values in DW images, it allows quantification of the ADC values of tissues. The ADC calculation process is usually automated with the clinical MR systems. [4] ADC value can be obtained by one pulsate sequence using two different b values. [5]The ADC of the liver lesion calculated from diffusion acquisition can be appraised by either visual assessment of the ADC maps or by drawing regions of interest on the ADC maps to record the mean or median ADC values in the tissue of interest. ADC is routinely expressed ($x10^{-3}$) as square millimeters per second. However, quantification of ADC requires minimum acceptable SNR at higher b values.[6]

Materials and Methods

This prospective study was carried out on 40 patients (both inpatients and out patients) in Department of Radiodiagnosis, Government Medical College, Rajindra Hospital, Patiala. Continuous sampling method was used by selecting patients referred to radiology department from various other departments with indeterminate hepatic focal lesions found on USG abodomen and/ CT abdomen.

Ethical Consideration: Permission was obtained from ethical committee as per the protocol. Informed consent was obtained from all patients after full explanation of the benefits and risks of the procedure.

Inclusion Criteria: Patients with indeterminate hepatic masses based on other imaging modality such and USG and CT. Patients giving consent for MR imaging and are willing to enroll in study were included.

Exclusion Criteria: Patients having cardiac pacemaker, electromagnetic implant and Patients with blunt trauma abdomen were excluded.

Patients were subjected to clinical assessment such as recording of age, sex and clinical presentation, laboratory investigations (liver biochemical profile, renal function tests) and then Abdominal MRI. MR techniques by 1.5-T superconductive scanner (Siemens 1.5T Magnetomaera MRI machine) used were Unenhanced axial T1 weighted acquisitions, Axial and coronal T2 weighted fast spin echo sequence, Diffusion Weighted Imaging (Respiratory-triggered protocol) using different b values = 0, 100, 500 and 750 s/mm^2. Imaging Evaluation and provisional diagnosis was given.

Diffusion images were reviewed with ADC images to find out pattern of diffusion restriction. Diffusion images with ADC values were measured by applying region of interest in the lesions. In patients with multiple lesions, a maximum of 5 lesions per patient were selected for analysis (including lesions which were largest, most conspicuous and easiest to localize). The mean ADC of each detected focal lesion is

measured by drawing a region of interest (ROI) over the lesion. Final diagnosis was done by histopathological study by FNAC/biopsy, other methods like laboratory tests, clinical data and follow up with a minimum of 6 months observation period by US,CT and MRI.

Statistical Methods: ADC values of all the selected lesions were mapped and mean ADC value of each individual diagnosis were calculated. Mean ADC of all benign lesions and malignant lesions were calculated separately and compared. Independent t-test was used to know whether difference between mean ADC values of benign and malignant lesions was significant. A p value of less than 0.05 was considered significant. Statistical analysis of mean ADC values in benign and malignant hepatic lesions is done using SPSS and EPI info software. Cut-off ADC value differentiating benign and malignant lesions was obtained from receiver operating characteristic curve (ROC). The best ADC cut off value with maximum sensitivity and specificity was selected for differentiating benign and malignant lesions.

Results

Maximum percentage of cases (37.5%) were in age group of 41-60 years and minimum (12.5%) in age group 0-20 years. Malignant lesions showed male preponderance with male : female ratio of 1.8:1 and benign lesions showed female preponderance with ratio of 0.7:1. Maximum number of patients had malignant lesions than benign lesions. Out of 90 liver mass lesions 57 (63.3 %) were malignant and 33 (37.7%) were benign lesions.64 (71.11 %) lesions were found in right lobe, 26(28.89%) were in left lobe of liver. 20(50%) patients had single liver lesions and 20 (50%)had multiple liver lesions.

There were 9 hemangiomas, 15 simple cysts, 2 abscess, 6 hydatid cysts, 1 adenoma, 16 HCCs, 32 metastasis, 5 hepatoblastoma, 4 cholangiocarcinoma out of 90 lesions. The mean ADC values of different liver mass lesions in the present study were as follows: simple cysts (3.33 ± 0.29 $x10^{-3}mm^2/s$), Hemangiomas (2.29 ± 0.39$x10^{-3}$ mm^2/s), Hydatidcyst (2.90 ± 0.28 $x10^{-3}mm^2/s$), abscesses (0.69 ± 0.04 $x10^{-3}mm^2/s$), adenoma (1.32 $x10^{-3}mm^2/s$)[Table 01]. HCC (0.93 ± 0.15 $x10^{-3}mm^2/s$), cholangiocarcinoma (1.21 ±0.11 $x10^{-3}mm^2/s$), hepatoblastoma (0.85 ± 0.16 $x10^{-3}mm^2/s$) and metastasis (0.82 ± 0.08 $x10^{-3}mm^2/s$) [Table 02].

Table-01 Mean ADC for each type of Benign Liver Mass Lesions

Diagnosis	No. of Lesions	ADC x $10^{-3}mm^2/s$	
	(n=33)	Mean	SD
Abscess	2	0.69	0.11
Adenoma	1	1.32	
Hemangioma	9	2.29	0.39
Hydatid cyst	6	2.9	0.28
Simple cyst	15	3.33	0.29

Table-02 Mean ADC for each type of Malignant Liver Mass Lesions

Diagnosis	No. of Lesions		ADC x $10^{-3}mm^2/s$
	(n=57)	Mean	SD
Cholangio carcinoma	4	1.21	0.11
HCC	16	0.91	0.15
Hepatoblastoma	5	0.85	0.18
Metastasis	32	0.82	0.08

Table-03 Comparison of Mean ADC Values of Benign and Malignant Lesions

Group	No. of patients	Mean ADC x $10^{-3}mm^2/s$	SD	Std. Error Mean
Benign	18	2.69382353	0.85358785	0.14639
Malignant	22	0.87214286	0.14627141	0.01955

Independent T- test: t- Value is 15.6511. P – Value is 0.00001 In the present study the mean ADC values of malignant lesions were significantly lower than those of benign lesions (0.87 x $10^{-3}mm^2/s$ V/s 2.69 x $10^{-3}mm^2/s$). The difference between ADC values of both groups is highly significant as p value is <0.05.

Table-04 Diagnostic Validity of ADC in Differentiating Malignant v/s Benign with ADC Cut-Off=1.24 X $10^{-3}mm^2/S$ (Obtained from Receiver Operating Characteristic Analysis)

ADC x $10^{-3}mm^2/s$	Malignant	Benign	Total
<1.24	55	2	57
>1.24	2	31	33
Total	57	33	90

Sensitivity (55/57=96.49%), specificity (31/33=93.93%), positive predictive value (55/57 = 96.49%), negative predictive value (31/33 = 93.93 %) of diagnosing malignant hepatic lesions using ADC cut-off of 1.24 X $10^{-3}mm^2/S$[Table-04].

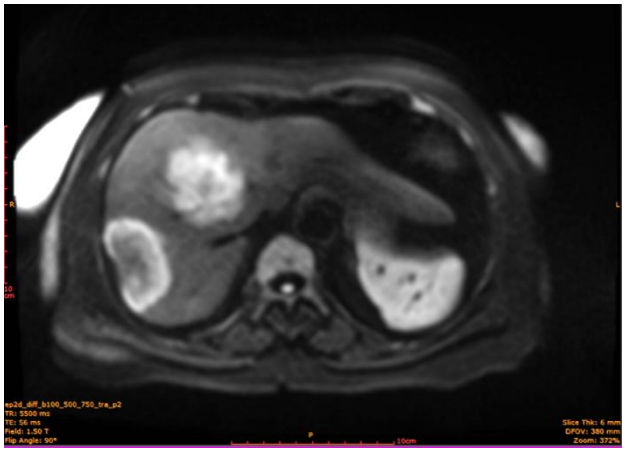
Table-05 Diagnostic Validity of ADC in Differentiating Malignant v/s Benign with ADC Cut-Off=1.50 X $10^{-3}mm^2/S$ (Obtained From Receiver Operating Characteristic Analysis)

ADC x $10^{-3}mm^2/s$	Malignant	Benign	Total
<1.50	57	3	60
>1.50	0	30	30
Total	57	33	90

Sensitivity (57/57= 100 %), specificity (30/33 = 90.9%), positive predictive value(57/60 = 93.33 %) and negative predictive value (30/30 = 100 %) of diagnosing malignant hepatic lesions using ADC cut-off of 1.50 X $10^{-3}mm^2/S$[Table-05].

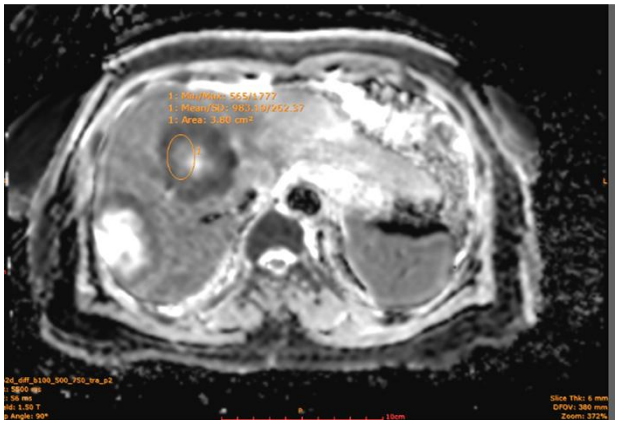
Case-1

Diffusion weighted b-750 sec/mm^2



The lesion shows peripheral hyperintensity at high b value.

ADC



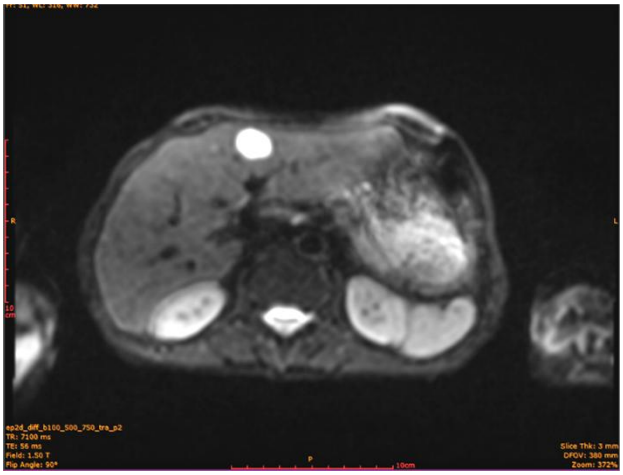
ADC: Peripherally hypointense with ADC value of $0.98x10^{-3}mm^2/s$. suggestive of malignant pathology.

Provisional diagnosis: Metastasis

Final diagnosis: Metastasis (Confirmed on Biopsy)

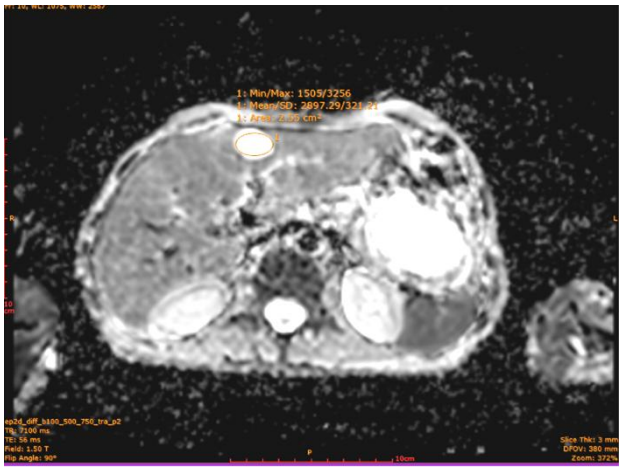
Case-2

DWI



The lesion is hyperintense on low b value (b=100)

ADC

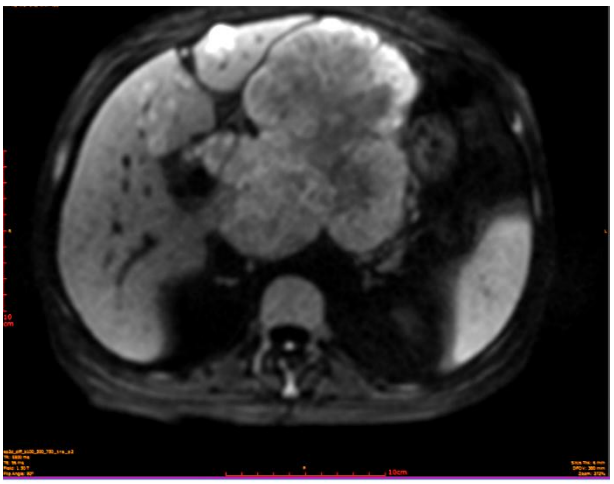


(ADC): It is hyperintense with ADC value of $2.89x10^{-3}$ mm^2/s suggestive of benign lesion.

Provisional diagnosis: Simple cyst. Diagnosis was confirmed on FNAC which revealed single layered epithelial cells suggestive of simple cyst.

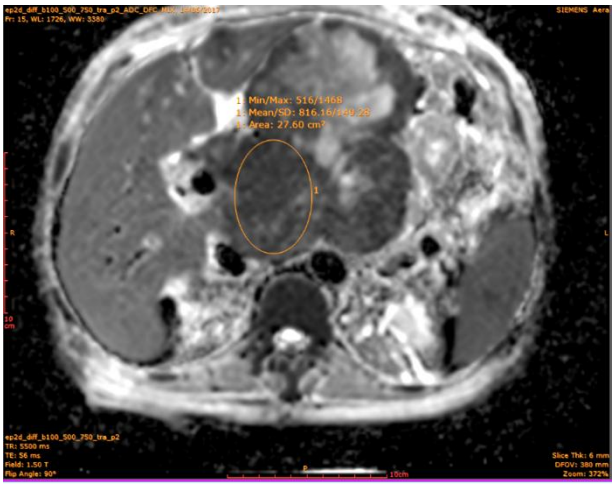
Case-3

DWI



The lesion remained peripherally hyperintense on high b value (b=750)

ADC



It is peripherally hypointense with ADC value of $0.81x10^{-3}$ suggesting malignant pathology.

Provisional diagnosis: Hepatocellular carcinoma.
Final diagnosis on histopathology: Hepatocellular carcinoma.

Discussion

In the present study, out of 40 cases, maximum number of cases were in age group of 41-60 years .Malignant lesions showed male preponderance with male to female ratio of 1.8:1 and benign lesions showed female preponderance with male to female ratio of 0.7:1,as similar to that reported in previous studies.[7-10] more number of lesions were found in right lobe of liver than left lobe, Similar to existing studies.[7,10] Out of all lesions maximum were malignant, positive correlation was seen with other studies.[8,9] which also showed predominance of malignant lesions. In the present study the number of patients having single lesion was equal to number of patients having multiple lesions and there was no predominance of either groups. Maximum number of lesions were metastasisand least in number was adenoma. Maximum number of patients had lesions in right lobe. Most common benign lesions was simple cyst and among malignant lesions was metastasis.

Quantitative analysis by ADC values of liver mass lesions: In the present study ADC values were obtained for all 90 lesions detected by DWI. Hepatic simple cysts and hydatid cysts had the highest ADC values while metastasis, abscesses and adenoma had the lowest values. The lowest ADC values among the malignant masses belonged to metastasis. Abscesses, though they are benign showed least ADC value overall $0.69x10^{-3}mm^2/s$ accounting for false positive cases resembling malignant lesions. Among the malignant lesions, the lowest ADC value was for metastatic hepatic lesion (0.82 ± 0.08 $x10^{-3}mm^2/s$).

Mean ADC values of malignant mass lesions were significantly lower than benign mass lesions: 0.87 ± 0.15 $x10^{-3}mm^2/s$ V/s $2.66\pm0.80x10^{-3}mm^2/s$ respectively ($P<0.05$), similar to available literature.[13-18] The ADC cut-off value of 1.24 ± 0.06 $x10^{-3}mm^2/s$ obtained from receiver operating characteristic analysis. With 1.24 ± 0.06 $x10^{-3}mm^2/s$ cut-off the sensitivity of 96.49 %, specificity 93.93 %, PPV of 96.49% and NPV of 93.93 % was obtained. 96.49 % sensitivity was due to 2 false positive lesions. Both of these were abscesses and showed ADC of 0.80 and 0.58 ($x 10^{-3}$ mm^2/s), characterizing these as malignant lesions. 93.93% specificity was due to 2 false negative cases (1 HCC & 1 Cholangiocarcinoma). Both of them were having ADC value of 1.25 and 1.37 ($x 10^{-3}$ mm^2/s) characterized these as benign lesions.

After overall observation and analysis of ADC value of liver mass lesions, ADC measurements

were capable of differentiating between benign and malignant liver lesions. The best ADC threshold value for distinguishing benign and malignant lesions was1.50 x 10^{-3}mm^2/s. with Sensitivity 100 % Specificity = 90.9% Positive predictive value 93.33 % Negative predictive value 100 % and p value <0.05 respectively. The area under the curve was 0.935 when receiver operating characteristic (ROC) curve of the ADC value was used for the differentiation of benign from malignant liver lesions. Similar results were obtained in previous studies[16-20] The variation in ADC cut offs is due to differences in the DW MR imaging technique applied for image acquisition, the choice of b value and the liver lesions assessed.

Table- 06 Mean ADCs of normal liver and hepatic focal lesions, ADC cut-offs, sensitivity and specificity for diagnosing malignant lesions as reported in selected studies compared with the present study.

Parameter	Taouli et al[18] (2003)	Namimoto et al[19] (1997)	Kim et al[20] (1999)	Parikh et al[21] (2008)	Miller et al[16] (2010)	Present study (2018)
No. of patients/ lesions	66/52	51/59	126/79	53/211	30/41	40/90
b values (sec/mm^2)	≤ 500	30, 1200	≤ 846	1, 50, 500	0, 1000	0, 100, 500, 750
Normal liver	1.83	0.69	1.02	-	-	1.24
HCC	1.33	0.99	0.97- 1.28	1.31	0.99	0.91
Metastasis	0.94	1.15	1.06- 1.11	1.5	0.79	0.82
Simple cyst	3.63	3.05	2.91- 3.03	2.54	3.05	3.33
Hemangiomas	2.95	1.95	2.04- 2.10	2.04	2.46	2.29
Abscess	-	-	-	1.64	1.09	0.69
Adenoma	1.75	-	-	1.49	-	1.32
Hydatid cyst	-	-	-	-	2.99	2.9
Benign lesions	2.45	1.95	2.49	2.19	2.57	2.69
Malignant lesions	1.08	1.04	1.01	1.39	0.86	0.87
ADC (x10^{-3} mm^2/s) cut-off for diagnosis of malignant lesions	1.5	-	1.6	1.6	-	1.5
Sensitivity (%)	84		98	74		100
Specificity (%)	89		80	77		93.3

Conclusion

Based on the results of our study the following conclusions can be made: Diffusion-weighted (DW) MR imaging can be used for liver lesion detection and characterization with potential additional value to routine MRI sequences. This method was very useful in differentiating malignant and benign lesions without the need for contrast agent administration. Significantly lower ADC values were seen in malignant lesions when compared with benign ones. There was however overlap between different types of lesions specially adenoma, abscess & 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. ADC thresholds applied for lesion characterization should be derived from imaging studies using similar techniques and ranges of b values for meaningful interpretation. Since there could be substantial overlap in the range of ADCs between different pathologies, the ADC should be interpreted concurrently with all available imaging before making the radiologic diagnosis.

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Conflict of Interest: None

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