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Original research article

Evaluating the sensitivity and specificity of Diffusion Weighted Imaging (DWI) in Diagnosing and Differentiating Hepatic Lesions: A Prospective Study in a Tertiary Care Hospital in South India

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Abstract

Background: Diffusion weighted MR is an attractive technique which uses both quantitative and qualitative data to differentiate benign and malignant lesions. The purpose of this study was to evaluate the sensitivity and specificity of Diffusion weighted imaging (DWI) and Apparent Diffusion Coefficient (ADC) in diagnosing hepatic lesions and to evaluate the efficacy of DWI and ADC mapping to differentiate benign lesion from malignant hepatic lesions.

Aims: To evaluate the sensitivity and specificity of diffusion weighted imaging in diagnosing benign and malignant hepatic lesions.

Settings and design: The diagnostic accuracy study was conducted for one year duration starting from July 2019 to July 2021 after the date of approval from the thesis protocol review committee (Scientific, Ethical & Financial), Amrita institute of medical sciences and research Centre, Kochi, Kerala.

Method: In this observational study, a total of 59 patients with liver lesions were enrolled. All detected liver lesions in USG/CT were imaged with DWI and their corresponding ADC values were calculated and recorded. Sensitivity and specificity of ADC mapping and DWI in differentiating benign lesions from malignant lesions were evaluated.

Result: 59 hepatic lesions were imaged with DWI which was performed at three different b values of 'b' 50, 'b' 500 and 'b' 1000 sec/mm^2. By performing DWI, ADC values were also calculated for each lesion. For differentiating benign lesions from malignant lesions, we used the ADC cutoff value of 1.45x10-3 mm^2/s. As per the study result,19 lesions were benign and 40 lesions were malignant. ADC value had a sensitivity of 97.5% and specificity of 84.2%, whereas DWI MRI had a sensitivity of 97.5 % and specificity of 78.9 %.

Conclusion: This study showed that malignant and benign liver lesions can be differentiated by using DWI and ADC mapping technique. ADC value had a sensitivity of 97.5% and specificity of 84.2%, whereas DWI MRI had a sensitivity of 97.5 % and specificity of 78.9 %. It is difficult to trace and target the small or deeply situated lesions for FNAC/biopsies and it stands a risk of bleeding. Using DWI and ADC mapping technique, these lesions can easily be traced and characterized into benign and malignant. This study demonstrated that with the help of DWI, dependency on FNAC/biopsy for differentiating malignant lesion from benign can be reduced and biopsies may be further restricted to a subset of those suspected to be malignant.

Keywords: ADC, DWI, HCC

Introduction

Human body is composed of 75% water allocated in three different compartments: intravascular, intracellular, and extracellular. For the study of tumors, movement of water molecules in the extracellular space is extremely helpful. Rate of movement of water molecules in a tissue is determined by the number of cells, the integrity of membranes and the viscosity of tissue. Benign tumors generally have less cellularity, therefore the movement of water molecules is free and diffusion will not be restricted. Malignant tumors have higher cellularity; therefore the movement of water molecules is limited, and diffusion will be restricted. MRI is the only method that can detect and measure molecular diffusion in human beings [1]. Diffusion weighted imaging (DWI) is a technique of signal contrast generation based on random translational molecular motion of water . Diffusion weighted MR imaging is reaching a potential for clinical use in the abdomen, particularly in the liver. It is an attractive technique as both quantitative and qualitative data can be incorporated into conventional imaging sequences .The applications of DWI are increasing every day and it has been undergoing rapid technical evolution. The degree of diffusion sensitization is defined by b value. It is possible to obtain pure maps of water diffusion by acquiring two images with different b values. Lesion differentiation into benign and malignant can be obtained independent of T1 and T2 and without the need for contrast agents by quantifying diffusion effects via apparent diffusion coefficient (ADC) measurements [2][3]. Appropriate treatment planning for patients with liver neoplasms require accurate differentiation between malignant and benign focal liver lesions and establishing the correct diagnosis for avoiding unnecessary liver biopsies. Imaging is an important decision-making tool, as it can accurately differentiate benign from malignant lesions in most of the cases[4]. 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 systems automatically generates the ADC values. ADC values are expressed in mm^2/sec. These ADC value measurements in lesions can be used for lesion detection and lesion characterization. This study evaluated the sensitivity and specificity of DWI and ADC in diagnosing hepatic lesions.

METHODS

SELECTION AND DESCRIPTION OF STUDY PARTICIPANTS:

In this observational study a total of 59 patients with single liver lesions were enrolled. These lesions were measured with diffusion weighted MR imaging. All detected liver lesions in USG/CT were imaged with DWI and their corresponding ADC values were calculated and recorded. All these patients were referred to the department of radio diagnosis at Amrita Institute of Medical Science hospital, Kochi, Kerala, India. Data were collected from June 2019 to June 2021 prospectively. Sensitivity and specificity of ADC mapping and DWI in differentiating benign lesions were evaluated. For the study all MR imaging was performed in 1.5T MR Imaging HDXT Machine, GE Medical Systems, Milwaukee, Wisconsin.

Inclusion criteria:

(1) Patients referred for MRI with USG or CT detected liver lesions.
(2) Patients with chronic liver disease referred for MRI as part of pre transplant work up.

Exclusion criteria:

(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 based on AASLD/EASLD.

Sample size:
In this study, a total of 59 patients with single hepatic lesions were enrolled. Total sample size was derived to be 59 based on the sensitivity (87.5%) of ADC cut off value of 1.43 x $10^3 mm^2$/sec in malignant lesions observed in an earlier study by Madhu SD et al [5] and with 95% confidence and 20% precision based on the prevalence of malignant hepatic lesions.

TECHNICAL INFORMATION:
Primary objective: To derive the sensitivity and specificity of diffusion weighted imaging and apparent diffusion co-efficient in detection of benign and malignant hepatic lesion by correlation with histopathology/standardized imaging criteria.

Secondary objective: To derive the ADC cut off value in differentiating benign and malignant hepatic lesions

Materials and methods:
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. Patients were given instructions about the examination and its time. Also, patients were given instructions regarding taking and keeping deep 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. All data were measured in control console.

The imaging parameters of diffusion weighted MRI with SE-echo planar imaging (EPI) sequence were set as follows:

TR/TE, 2,300/70 ms; matrix, 204 X 160; slice thickness, 8 mm; intersection gap, 1.6 mm; field of view, 380 X 380 mm; &2 min acquisition time. Three different b values (b=50mm2/, 500, 1 000 mm2/s) and three directions were used. Total acquisition time was 40 sec. ADC maps were calculated automatically from all diffusion weightings on a voxel-by-voxel basis.

The review of all MR images and previous imaging studies were performed on a PACS workstation and the review of the clinical histories of the patients were performed using the internal database from the institution. Size of lesions were determined by measuring their greatest axial diameter, as displayed on b = 50 s/mm2 images. For lesion evaluation, a circular ROI of standardized size of 1 cm^2 was placed randomly inside the lesion. Because of software limitations, only circular ROIs were drawn. For comparing lesion ADC variations, we used the ADC values of the ROI. When the lesion was difficult to recognize on the ADC map, the T2-weighted image, the contrast enhanced T1- weighted images and the b50 images served as a roadmap for accurate ROI placement. The choice of the b values was based on previous works that showed that intermediate b values are not required in the detection and differentiation of focal hepatic lesions.

STATISTICS
For statistical analysis IBM SPSS Software version 21.0 was used. Data was entered in Microsoft excel. Diagnostic measures such as sensitivity, specificity, predictive value positive,

predictive value negative and accuracy of diffusion weighted imaging and ADC values were calculated. McNemar's Chi square test was used to compare the findings of DWI with the final histopathological / standardized imaging criteria, while student T test was used to compare mean parameters betweek two groups. To find the statistically significant cut off of ADC value of benign and malignant lesions, ROC curve analysis was applied.

RESULT

In this prospective study, a total of 59 patients with single hepatic lesions were enrolled. These participants were referred to the department of Radio diagnosis at Amrita institute of medical science hospital, Kochi, Kerala, India (a tertiary care center). Participant's data were collected from June 2019 to June 2021 prospectively. There were 50 males and 9 females. The mean ±SD age of the participants were 54.51 + SD 17.25 years, the age rages from 18 years to 83 years. All participants underwent DWI at three different b values of b 50, b 500 and b 1000 and corresponding ADC were calculated for each lesion. Based on the ADC values, these hepatic lesions were differentiated into two: benign lesions and malignant lesions. As per the result, out of 59 lesions, 19 lesions were benign, and 40 lesions were malignant.

Out of total 59 lesions, 39 (72.2 %) were malignant and 16(28.8 %) were benign lesions based on ADC values. Mean ±SD of ADC Value 1.621±0.609 × ($10^{-3}mm^2$/sec).

All 40 malignant lesions showed hyper intense signal intensity at higher b value of 1000 s/mm^2 and on ADC map it showed restricted diffusion. All benign lesions showed hyperintense signal on DWI at lower 'b' values and on ADC map, they showed no restricted diffusion.

In DWI MRI , 71.1% (42) of the total lesion showed diffusion restriction and 28.8% (17) of the lesions showed no diffusion restriction. 67.7% (40) of the total number lesions were found to be malignant and 32.2% (19)of the lesions were found to be benign. *P value* obtained was more than 0.05, which showed that there was no significant difference between histopathology/ standardized imaging criteria as compared to DWI MRI. 66.1% of total lesions showed ADC values less that 1.4 x 10^{-3} mm^2/sec and were malignant based on ADC values.16% of the total lesions showed ADC values more than 1.4 x 10^{-3} mm^2/sec and were benign based on ADC value. *P value* obtained was more than 0.05, which showed that there was no significant difference between histopathology/ standardized imaging criteria as compared to ADC values. ADC value had a higher accuracy as compared to DWI in differentiating benign and malignant lesions.

The best cut off value which has the highest true positive rate together with lowest false positive rate was derived as 1.45x10^{-3} mm^2/sec. Here the area under the curve = 0.987 which denotes our diagnostic tool is excellent .*P value* <0.001 is also significant.
Lesions with ADC values 1.9316±.47029 were considered as benign lesions and with ADC values 0.8740±.28440 were considered as malignant with ADC cut-off value of 1.45x$10^{-3}mm^2$/sec. Mean ADC value of the 19 benign lesions (1.9316) was significantly higher than the ADC value of the 40 malignant lesions (0.8740) with a *P value* less than 0.000***.

Table 1: Distribution of various characteristics in imaging

SN	Variables	Characteristics	n(%)
1	Cirrhotic	Yes No	35(59.3) 24(40.7)
2	DWI at 50	Hyper intense Hypo intense Isointense	55(93.2) 3(5.1) 1(1.7)
3	DWI at 500	Hyper intense Hypo intense Isointense	56(94.9) 2(3.4) 1(1.7)
4	DWI at 1000	Hyper intense Hypo intense Isointense	53(89.3) 3(5.1) 3(5.1)
5	Lesion Based on DWI/ADC	Benign Malignant	17(28.8) 42(71.2)
6	Lesion based on ADC Cut of value (>1.45<	Benign (ADC greater than 1.45)	19(32)
		Malignant (ADC greater than 1.45)	40 (68)

Table 2: Mean ADC of benign and malignant lesions

Type **Number Of lesions**		**ADC in 10-3 mm2 /s**	
		Mean	SD
Malignant	40	.87	.284
Benign	19	1.93	.470

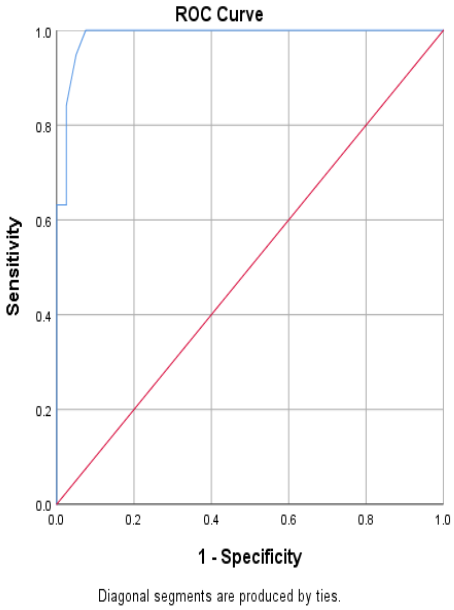
Using Independent sample t test for unequal variances, *P-value* was less than 0.05 (*P value* is 0.000***) therefore there was highly significant difference between mean ADC values for benign and malignant lesions.

Table 3 : ADC with Histopathological diagnosis

	Histopathological diagnosis-Malignant lesion	**Histopathological diagnosis-Benign lesion**	**Total**
ADC value less than 1.45(Malignant lesion)	39 (66.1%)	3 (5%)	42(71.1%
ADC value greater than 1.45 (Benign lesion)	1 (1.6%)	16 (27.1%)	17(28.8%)
Total	40 (67.7%)	19 (13.2%)	59(100%)

Table 4 : DWI with Histopathological diagnosis

	Histopathological diagnosis-Malignant lesion	**Histopathological diagnosis-Benign lesion**	**Total**
DWI (Malignant lesion)	38 (64.4%)	4(6.7%)	42(71.1%)
DWI (Benign lesion)	2(3.3%)	15(25.4%)	17(28.8)
Total	40(67.7%)	19(32.2%)	59(100%)



Graph 1: ROC Curve

Area	Std. Error	Asymptotic Sig.b	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.987	.011	.000	.966	1.000

The best cut off value which has the highest true positive rate together with lowest false positive rate was derived as $1.45x10^{-3}$ mm^2/sec. Here the area under the curve = 0.987 which denotes our diagnostic tool is excellent .P value <0.001 is also significant.

(A) **(B)**

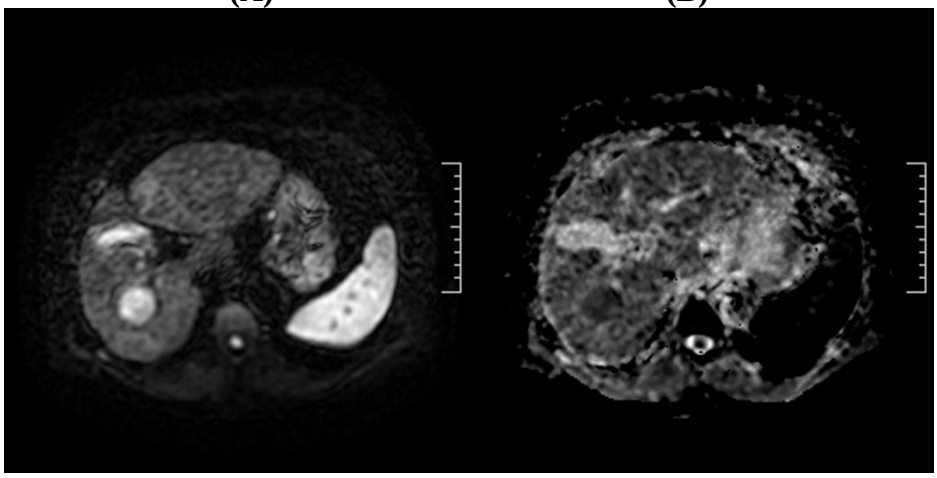


Figure 1:
A: DWI image showing hyperintense lesion in right lobe.
B: ADC mapping shows a corresponding hypointense signal, suggestive of a malignant etiology. Lesion was diagnosed to be HCC on histopathology

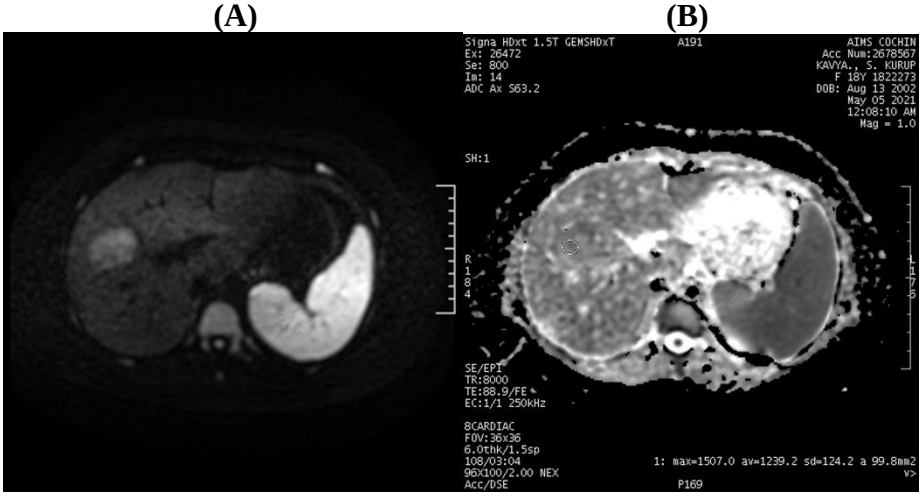


Figure 2:
A: DWI imaging showing a hyperintense lesion in the right lobe of liver.
B: ADC maps showing a corresponding lesion with no hypointense signals and no diffusion restriction. Lesion was diagnosed to be FNH on histopathology.

DISCUSSION

In this prospective study, we evaluated the sensitivity of DWI and ADC in diagnosing and characterizing focal hepatic lesions. A total of 59 hepatic lesions were imaged with DWI in this study. All 59 patients underwent DWI at three different b values of 'b' 50, 'b' 500 and 'b' 1000 and corresponding ADC were calculated for each lesion. These 59 hepatic lesions were categorized into two: (1) benign lesions and (2) malignant lesions based on diffusion characteristics in imaging and the ADC values. In our study there were19 benign lesions and 40 malignant lesions.

In 39 patients (66.1%) right lobe of the liver was involved and left lobe of liver was involved in 20 patients (33.9%). There was no significant difference in involvement between the right and left lobes. All focal liver lesions showed higher signal intensity compared to surrounding liver parenchyma, predominantly on lower b value DWI images, enabling lesion detection. Further DWI in different b values along with generated ADC maps were used for differentiation of liver lesions. The qualitative and subjective assessment of a lesion into benign and malignant was done by two Radiologists and were initially blinded to the final diagnosis. A lesion was defined to be malignant if it showed hyper intense signal in higher b value images with corresponding hypo intense signal in ADC mapping. Final derivation was with mutual consent. The quantitative/objective evaluation of the lesion into benign and malignant was based on the ADC values as represented by the region of interest drawn as a circle of one cm^2 over the lesion. Hence based on their signal in DWI and ADC mapping 38 out of 59 were found to show diffusion restriction indicating either a highly viscous microenvironment as seen in an abscess or a highly cellular tissue as is to be expected in malignancy. DWI had a sensitivity of 95% (38 out of 40 malignant cases). Our DWI results were slightly different when compared to the study by Badawy et al [6] which demonstrated that all the malignant liver lesions showed restricted diffusion with persistent high signal at higher b values and corresponding low signals on ADC.As a general rule, significantly higher ADC values have been demonstrated for benign lesions compared with malignant lesions, with variable overlap.

The ADC values were calculated for each of the benign and malignant lesions by drawing a circumference of $1cm^2$ on the ADC maps. Using ROC curve, an ADC cut-off value of $1.45x10^{-3}$ mm^2 /sec 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 mm^2 /sec as the 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. Here the area under the curve was 0.988 and this denotes that our diagnostic tool was excellent. *P value* was 0.001 and was significant. These observations were comparable to the ADC cut off value obtained in an earlier publication by Madhu SD et al [5] where a cut off value of 1.4845 x 10^{-3} mm^2/sec was obtained. The ADC values for various focal hepatic lesions in our study were similar to previous studies with a mean ADC value of 1. x 10^{-3} mm^2/sec for benign lesions and 0.87 x 10^{-3} mm^2/sec for malignant lesions. The ADC values of benign lesions were found to be significantly higher than malignant lesions. In a study by Taouli et al [7] on DWI in focal liver lesions , the benign solid lesions showed ADC values, which ranged from 0.9 to 1.5 x 10^{-3} mm^2/sec and benign cystic lesions showed ADC values which ranged from 2.5 to 3.6 x 10^{-3} mm^2/sec.

The cut off value to differentiate malignant from benign lesions observed in an earlier publication by Javadrashid et al [8] was 1.1 x 10^{-3} mm^2/sec, but this lower value would significantly decrease the sensitivity especially if a larger number of cystic/necrotic lesions are to be characterized. Yet another similar study by Testa et al [9] with 67 patients showed a ADC cut off value of 1.5 x 10^{-3} mm^2/sec in differentiating benign lesions including cysts from malignant liver lesions with an accuracy of 78%.However , to distinguish metastasis from benign solid lesions, the cut off value dropped to 1.2 x 10^{-3} mm^2/sec and with an accuracy of 71 %. Our study showed that diffusion weighted MRI was a sensitive and suitable method for differentiating benign and malignant lesions and an additional evaluation using ADC value with a cut off of 1.45 x 10^{-3} mm^2/sec would improve the differentiation of lesions

Limitations:

In our study most of the lesions were either solid or cystic. In certain lesions like Hepatic abscess, which though benign would show a restricted diffusion as a result of highly viscous micro tissue environment. We did not have even a single case of abscess in our patient database and this could be one of the reasons for getting excellent results with significant difference in the ADC cut-off values between benign and malignant lesions. A larger study incorporating more numbers of abscess may be required to derive ADC values to differentiate between abscess of mostly infective or inflammatory etiology from malignant masses, both of which tend to diffusion restrict for their own microenvironments.

Conclusion

This study showed that malignant and benign liver lesions can be differentiated by using DWI and ADC mapping technique. It is difficult to trace and target the small or deeply situated lesions for FNAC/biopsies and it stands a risk of bleeding. Using DWI and ADC mapping technique, these lesions can easily be traced and characterized into benign and malignant. ADC value had a sensitivity of 97.5% and specificity of 84.2%, whereas DWI MRI had a sensitivity of 97.5 % and specificity of 78.9 % in detection of benign and malignant liver lesions. The best cut off value which has the highest true positive rate together with lowest false positive rate was derived as 1.45x10^{-3} mm^2/sec in differentiating benign and malignant lesions. This study demonstrated that with the help of DWI, dependency on FNAC/biopsy for differentiating malignant lesion from benign can be reduced and biopsies may be further restricted to a subset of those suspected to be malignant.

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