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The Egyptian Journal of Radiology and Nuclear Medicine (2014) **45**, 299–308

Egyptian Society of Radiology and Nuclear Medicine

The Egyptian Journal of Radiology and Nuclear Medicine

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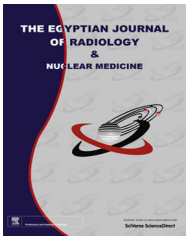

ORIGINAL ARTICLE

The role of MR diffusion in differentiation of malignant and benign hepatic focal lesions

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Received 19 July 2013; accepted 19 December 2013
Available online 22 January 2014

KEYWORDS

DWI;
ADC maps;
Malignant liver lesions;
Benign hepatic focal lesions;
MRI

Abstract *Aim:* To determine if focal liver masses could be differentiated as benign or malignant by DWI and ADC maps.

Methods and materials: Sixty focal liver lesions were scanned using 1.5 T MRI. DWI was performed with *b* 0, *b* 500 and *b* 1000 gradients with ADC measurements. Comparison of mean ADC values between each benign and malignant lesion was done. Reference standard of diagnosis was obtained by correlating DWI with histopathologic findings and imaging follow-up. The accuracies of DWI and ADC values were assessed with the Student's t test, and cut-off values were determined with receiver operating characteristic curve analysis.

Results: When ADC value of 1.0×10^{-3} mm^2/s was used as a threshold value for differentiation of malignant tumors from benign lesions, sensitivity was 90.3%, specificity 78.57% and accuracy 86.7%. The best result was obtained with the use of ADC cut off value (at *b* 500) of 1.5×10^{-3} mm^2/s and ADC cut off value (at *b* 1000) of 1.0×10^{-3} mm^2/s, with 90.3% sensitivity, 92.86% specificity, 91.1% accuracy, 96.6% positive predictive value and 81.3% negative predictive value.

Conclusion: DWI and ADC map is a useful tool in differential diagnosis of malignant from benign liver lesions.

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Abbreviations: DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient; T, tesla; MRI, magnetic resonance imaging; ROC, receiver operating characteristic curve; FNH, focal nodular hyperplasia; HCC, hepato-cellular carcinoma; CT, computed tomography; DWMRI, diffusion-weighted magnetic resonance imaging; DWI, diffusion-weighted imaging; *n*, number; FLL, focal liver lesions; FSPGR, fast-spoiled gradient echo; SSFSE, single shot fast spin echo; S, second; TR, repetition time; TE, echo time; FOV, field of view; cm, centimeter; ASSET, array spatial sensitivity encoding technique; mm, millimeter; ROI, region of interest; SD, standard deviation; SI, signal intensity; DW-EPIs, diffusion-weighted-echo planar imagings; SNR, signal to noise ratio; mm/s, millimeter/second.

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Peer review under responsibility of Egyptian Society of Radiology and Nuclear Medicine.

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1. Introduction

The differential diagnosis between malignant and benign focal liver lesions remains a diagnostic challenge for every radiologist. For detection and characterization of focal liver lesions, many different modalities have been proposed; including multi-phase contrast-enhanced CT (1), MRI (2), CT portography (3) and perfusion studies using dedicated ultrasound or CT or MRI contrast agents (4). Of these modalities, magnetic resonance imaging is considered the most accurate imaging technology because it has high resolution for soft tissue and has the potential to characterize a lesion on various data acquired, such as T1, T2, and early and late post-gadolinium images (5,6).

Magnetic resonance imaging (MRI) has been used in both the detection and characterization of focal hepatic lesions. With the advent of the echo-planar MR imaging technique, diffusion weighted imaging (DWI) of the abdomen has become possible with fast imaging times which minimize the effect of gross physiologic motion from respiration and cardiac movement (7). Thus, DWI became a valuable technique for evaluating focal hepatic lesions in addition to conventional MRI sequences (8). More recently, apparent diffusion coefficient (ADC) value has been introduced in quantitative measurements as an adjunct to DWMRI. ADC is a quantitative parameter measuring the rate of diffusion of water molecules in biological tissues. There are several reports regarding the use of ADC in diagnosis and characterization of focal hepatic lesions (7–10). However, the efficacy of ADC values in diagnosing and characterization of solid benign and solid malignant lesions has not been well described. Similarly, lesion and diffusion gradient variabilities were also limited in these studies (8–10). Usage of ADC measurements in various types of focal hepatic lesions at different diffusion gradient values may define the role of ADC values in radiological evaluation of focal hepatic lesions (11).

The expanding role of DWI in evaluation of liver lesions can increase confidence in differentiation between benign and malignant lesions. DW sequences can be performed on most modern MRI machines with relative ease, in a short time period and without the need for contrast medium (12).

2. Patients and methods

2.1. Patients

Between June 2011 and December 2012, a total of 60 focal hepatic lesions in 60 consecutive patients were evaluated by abdominal MRI with informed consent was taken from them. Patients with hepatic neoplasms who had undergone chemotherapy or radiation therapy within the last 3 months prior to the MR examination were excluded from our analysis in order to ensure that ADC measurements were reflective of the natural state of the liver lesions. In addition, patients without sufficient confirmation of the nature of the lesions were excluded. The final study population consisted of 60 patients (43 men, 17 women; age range 20–70 years, mean age 45 years).

There were 9 patients with history of an extra-hepatic primary malignancy and suspected liver metastases (colorectal cancer [$n = 3$], breast cancer [$n = 2$], gastric cancer [$n = 1$], and pancreatic cancer [$n = 3$]). There were 28 patients with chronic liver disease (including chronic hepatitis and cirrhosis related to hepatitis C and old bilharziasis) with suspected malignancy. Finally, there were 23 patients with no history of malignancy or chronic liver disease who underwent MR imaging for evaluation of presumably benign or indeterminate, incidentally diagnosed focal liver lesions (FLL). In patients with multiple FLL, the largest ones of each lesion type were randomly selected for further analysis by the study coordinator.

Thirty-four lesions were malignant tumors (20 hepatocellular carcinomas (HCCs), 5 cholangiocarcinomas and 9 metastases). Benign liver lesions were 26 (8 cysts, 8 hemangiomas, 5 adenomas and 5 focal nodular hyperplesia (FNH).

The standard of reference for characterizing FLL was evaluated by two radiologists (GE & MA), with experience in MR imaging of 20 and 10 years respectively. Malignant nature of lesions was confirmed by pathologic findings following biopsy or surgery for 13 HCCs, 5 cholangiocarcinomas and 5 metastases. The diagnosis of the remaining 7 HCCs lesions was confirmed by using the established imaging criteria and follow up after chemoembolization. The remaining 4 metastatic lesions were confirmed on the basis of new occurrence of a lesion compared to a prior MR study, follow up of lesion size after the start of chemotherapy in patients with known extra-hepatic primary malignancies. Three FNHs and 2 adenomas were confirmed pathologically. The remaining benign lesions were diagnosed by using established imaging criteria (13–15) in conjunction with stable appearance and size at follow-up imaging in equivocal cases with a minimum follow-up interval of 6 months (range: 6–12 months).

2.2. MR imaging and image analysis

Magnetic resonance imaging examinations were performed on 1.5 T system (Philips, Achieva) with a 16-channel body coil. Before DWI, breath-hold T1-weighted image, fat-saturated fast spin echo T2 weighted image, dual echo fast spoiled gradient-echo (FSPGR) and single shot fast spin echo (SSFSE) T2 weighted images were obtained in axial and coronal images. Diffusion weighted images were obtained before contrast administration with b values of 0, 500, and 1000 s/mm^2. Breath-hold, dynamic 3D T1 weighted sequence was performed after DWIs (bolus injection of 20 ml gadopentetate dimeglumine 1.5 ml/s). All DWIs were obtained in transverse plane using single-shot echo-planar spin echo sequences. Imaging parameters for DWIs were: TR: 1100 ms; TE: 67–91 ms; FOV: 35 cm × 35 cm (change according to body size); number of excitation: 1; matrix size: 128 × 128; section thickness: 5 mm; intersection gap: none. DW sequences required a total of 96 s to scan on MR. The array spatial sensitivity encoding technique (ASSET) was used as a parallel imaging technique.

Imaging findings were evaluated carefully, then, ADC values of different masses detected on conventional MRI sequences and DWI were measured through gray-scale ADC maps from each lesion at b 500, and b 1000 s/mm^2 gradient values by using 3 circumferential region of interests (ROIs) and the average ADC values were recorded. 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 excluded.

Mean ADC values of the benign lesion group (FNH and other benign liver masses) and the malignant lesion group (HCC, cholangiocarcinoma and metastasis) at 2 different diffusion gradients were compared. Similarly, mean ADC values of each benign and malignant lesion at 2 different gradients were also recorded and compared in order to determine whether it would be possible to define the characteristic or type of individual benign and malignant lesion.

To validate our system, ADC values of water were measured on phantoms one week before the ADC measurements. The ADC value for water was 2.21×10^{-3} mm^2/s, in agreement with other studies in the literature (16).

2.3. Statistical analysis

Statistical analysis was carried out via Statistical package for social Science (SPSS), version 17 program on windows XP. Qualitative data were represented in the form of number and frequency, while quantitative data were represented in the form of mean ± standard deviation (mean ± SD). Kolmogrov–Smirnov test was used to test normality of quantitative data. Student's *t* test, Mann–Whitney *U* and Kruskal–Wallis test were used to compare groups. Receiver operating characteristic (ROC) curve was computed to determine the cut off value for the malignancy. All tests were considered significant if *P* value equals or less than 0.05.

3. Results

Mean size of all 60 focal hepatic lesions was 2.83 ± 1.05 cm. Twenty-six of the 60 lesions were benign and 34 were malignant. Benign lesions had a mean size of 2.96 ± 0.77 cm (ranges 2–5 cm) whereas mean size of malignant lesions was 2.77 ± 1.17 cm (ranges 1–6 cm) (Table 1).

Mean ADC values of 26 benign lesions at *b* 500 and *b* 1000 gradients were $2.09 \pm 0.50 \times 10^{-3}$ and $1.55 \pm 0.43 \times 10^{-3}$ mm^2/s, respectively. Mean ADC values of malignant lesions at *b* 500 and *b* 1000 gradients were $1.20 \pm 0.18 \times 10^{-3}$ and $0.85 \pm 0.18 \times 10^{-3}$ mm^2/s, respectively. Mean ADC values of benign lesions were higher than malignant lesions and these differences were statistically significant for the 2 diffusion gradients ($P < 0.0001$ & $P < 0.0001$, respectively) (Table 1).

Mean ADC values of all lesions at *b* 500 and *b* 1000 gradients and differentiation between subtypes of benign and malignant lesions are summarized in Table 2.

An ADC cut-off value of $1.0 \times \times 10^{-3}$ mm^2/s at *b* 1000 diffusion gradient resulted in 90.3% sensitivity, 78.6% specificity and 86.7% accuracy for differentiation of benign and malignant focal hepatic lesion groups. The best result was obtained with the use of ADC cut off value of 1.5×10^{-3} mm^2/s at *b* 500 and ADC cut off value of 1.0×10^{-3} mm^2/s at *b* 1000, with 90.3% sensitivity, 92.86% specificity, and 91.1% accuracy. The results of ROC curve analyses, ADC cut off values for the differentiation between benign and malignant lesions at both *b* 500 and *b* 1000 diffusion gradients are shown in Tables 3 and 4.

Seventeen of the 26 benign lesions show low SI and 9 benign lesions show intermediate SI on DWI while 26 of the 34 malignant lesions show high SI and 8 malignant lesions show intermediate SI on DWI.

Cysts and hemangiomas showed the highest mean ADC values at *b* 500 and *b* 1000 gradients in the benign lesion group (Fig. 1). Hepatocellular carcinomas showed highest mean ADC values at *b* 500 and *b* 1000 in the malignant lesion group (Fig. 2).

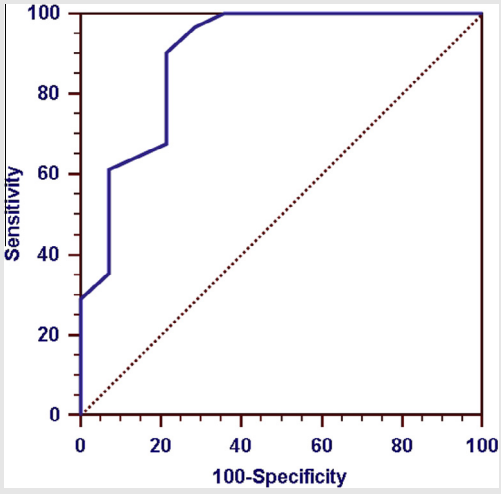
Table 1 Mean size, mean ADC values of benign and malignant lesions at both *b* 500 and *b* 1000.

Report				
Tumor		Mean size	ADC *b* 500	ADC *b* 1000
Benign	Mean	2.9643	2.0929	1.5500
	N	26	26	26
	Std. Deviation	.77122	.50909	.43456
	Minimum	2.00	1.30	.80
	Maximum	5.00	2.90	2.00
	Range	3.00	1.60	1.20
	Median	3.0000	2.2000	1.8000
Malignant	Mean	2.7774	1.2065	.8587
	N	34	34	34
	Std. Deviation	1.17266	.18246	.18335
	Minimum	1.00	.90	.50
	Maximum	6.00	1.80	1.40
	Range	5.00	.90	.90
	Median	2.5000	1.2000	.8500
Total	Mean	2.8356	1.4822	1.0738
	N	60	60	60
	Std. Deviation	1.05876	.52105	.42833
	Minimum	1.00	.90	.50
	Maximum	6.00	2.90	2.00
	Range	5.00	2.00	1.50
	Median	2.5000	1.3000	.9000

Table 2 Mean size, mean ADC values and differentiation of different subtypes of benign and malignant lesions.

Report							
Tumor Type		Mean size	ADC *b* 500	ADC *b* 1000		*P* value ADC *b* 500	ADC *b* 1000
HCC	Mean	3.1250	1.2650	.8925	HCC vs. cholangiocarcinoma	0.014	0.61
	N	20	20	20	HCC vs metastasis	0.034	0.27
	Std. Deviation	1.22512	.17554	.18806	Cholangiocarcima vs metastasis	0.44	0.51
	Minimum	1.50	1.00	.50			
	Maximum	6.00	1.80	1.40			
	Range	4.50	.80	.90			
	Median	2.8500	1.2000	.8900	Adenoma vs HCC	< 0.001	0.008
Metastases	Mean	1.9000	1.1111	.8078	Adenoma vs metastases	< 0.001	0.014
	N	9	9	9	Adenoma vs cholangiocarcinoma	< 0.001	0.023
	Std. Deviation	.59372	.16159	.18089	FNH vs HCC	< 0.001	< 0.001
	Minimum	1.00	.90	.55	FNH vs metastases	< 0.001	0.004
	Maximum	3.00	1.40	1.20	FNH vs cholangiocarcinoma	0.005	0.015
	Range	2.00	.50	.65			
	Median	2.0000	1.1000	.8000			
Cholangiocarcinoma	Mean	3.2500	1.0500	.7500			
	N	5	5	5			
	Std. Deviation	.35355	.07071	.07071			
	Minimum	3.00	1.00	.70			
	Maximum	3.50	1.10	.80			
	Range	.50	.10	.10			
	Median	3.2500	1.0500	.7500			
FNH	Mean	3.2000	1.8600	1.4600	FNH vs Hemangioma	0.16	0.27
	N	5	5	5	FNH vs adenoma	0.98	0.45
	Std. Deviation	1.15109	.47223	.51284	FNH vs cysts	0.001	0.05
	Minimum	2.00	1.30	.90	Hemangioma vs adenoma	0.22	0.06
	Maximum	5.00	2.30	1.90	Hemangioma vs cysts	0.15	0.47
	Range	3.00	1.00	1.00	Adenoma vs cysts	0.002	< 0.001
	Median	3.0000	2.1000	1.8000			
Hemangioma	Mean	2.7500	2.3000	1.7500			
	N	8	8	8			
	Std. Deviation	.64550	.53541	.37859			
	Minimum	2.00	1.60	1.20			
	Maximum	3.50	2.90	2.00			
	Range	1.50	1.30	.80			
	Median	2.7500	2.3500	1.9000			
Adenoma	Mean	3.0000	1.8667	1.2333			
	N	5	5	5			
	Std. Deviation	.50000	.49329	.37859			
	Minimum	2.50	1.30	.80			
	Maximum	3.50	2.20	1.50			
	Range	1.00	.90	.70			
	Median	3.0000	2.1000	1.4000			
Cysts	Mean	2.7500	2.6000	1.8500			
	N	8	8	8			
	Std. Deviation	.35355	.14142	.07071			
	Minimum	2.50	2.50	1.80			
	Maximum	3.00	2.70	1.90			
	Range	.50	.20	.10			
	Median	2.7500	2.6000	1.8500			
Total	Mean	2.8356	1.4822	1.0738			
	N	60	60	60			
	Std. Deviation	1.05876	.52105	.42833			
	Minimum	1.00	.90	.50			
	Maximum	6.00	2.90	2.00			
	Range	5.00	2.00	1.50			
	Median	2.5000	1.3000	.9000			

Table 3 Mean ADC cut off value for the differentiation between benign and malignant liver lesions at *b* 1000 diffusion gradient:



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Cutoff	AUC ± SE	95%CI	Sensitivity (95%CI)	Specificity (95%CI)	Accuracy (95%CI)	PPV (95%CI)	NPV (95%CI)
ADC′ 1000 ⩽ 1.0	0.895 ± 0.059	0.767–0.967	90.32% (74.2–98%)	78.57 (49.2–95.3)	86.7 (72–95.1)	90.3 (79.7–96.5)	78.6 (55–92.2)

Comparison of ADC values revealed that mean ADC value of all benign hepatic focal lesions were significantly higher than all malignant focal lesions at *b* 500 and *b* 1000 gradients ($P < 0.0001$) (Figs. 3 and 4).

Differentiation of benign and malignant subtype lesions from each other in their groups shows some promising results. There was a statistically significant difference between: the mean ADC values of cysts and adenoma at both *b* 500 and *b* 1000 (P value = 0.002, <0.001), the mean ADC values of cysts and FNH at *b* 500 (P value = 0.001). However, there was no significant difference between mean ADC values of other benign focal lesions from each other.

At *b* 500 gradient, HCCs had significant high ADC value than metastases and cholangiocarcinoma (P value = 0.034, 0.014 respectively) with difficult differentiation between metastases and cholangiocarcinoma. At *b* 1000 gradient, there was no significant difference between HCCs, metastases and cholangiocarcinomas.

There was a statistically significant difference between ADC values of solid benign (adenoma, FNH) and solid malignant subtype lesions, as there was a significant difference between: mean ADC values of FNH and HCC at both *b* 500 and *b* 1000 (P value $\leqslant 0.001$, <0.001) (Figs. 5 and 6), mean ADC values of FNH and metastases at both *b* 500 and *b* 1000 (P value $\leqslant 0.001$, 0.004) and mean ADC values of FNH and cholangiocarcinoma at both *b* 500 and *b* 1000 (P value = 0.005, 0.015) respectively. Also, a significant difference was found between: mean ADC values of adenoma and HCC at both *b* 500 and *b* 1000 (P value $\leqslant 0.001$, 0.008), mean ADC values of adenoma and metastases at both *b* 500 and *b* 1000(P value $\leqslant 0.001$, 0.014) and mean ADC values of adenoma and cholangiocarcinoma at both *b* 500 and *b* 1000 (P value $\leqslant 0.001$, 0.023) respectively.

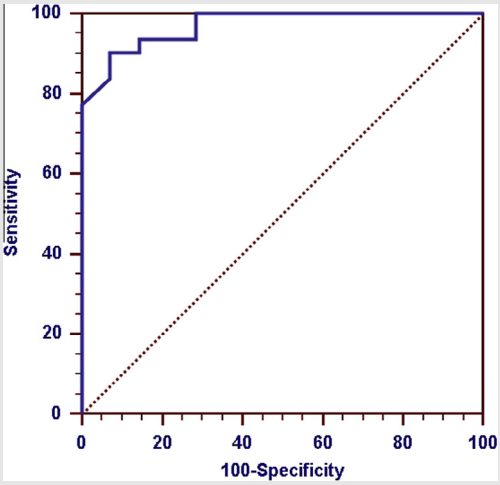
4. Discussion

Reliable detection and characterization of focal liver lesions are critical for optimal patient management. Magnetic resonance imaging (MRI) has an established role in focal liver lesion detection and characterization and traditionally includes a combination of unenhanced T1- and T2-weighted sequences, in and out-of-phase T1-weighted sequences, and enhanced T1-weighted sequences after gadolinium administration or other liver-specific contrast agents. There is good evidence that diffusion-weighted (DW) MRI has the potential to improve hepatic lesion detection rates and contribute to the differentiation of benign from malignant hepatic lesions (12).

Appearance of focal hepatic lesions on DWI especially at high *b* values was reported to be diagnostic in several studies due to restricted diffusion and increased signal intensity on DW images (8,17). However this measurement was a qualitative assessment and represented a subjective interpretation. On the contrary, ADC value is a quantitative parameter of water diffusion. There are several studies in the literature emphasizing diagnostic utility of ADC measurement in the differentiation of benign and malignant focal hepatic lesions. According to these studies malignant lesions had lower ADC values compared to benign lesions which was attributed to high cellularity of malignant masses (7).

Chandarana and Taouli (18) said that, there is no consensus in the scientific community about which *b*-values are optimal for liver imaging and when performing DW-MRI in the liver, it is advantageous to perform imaging with at least 3 *b*-values including both lower and higher *b*-values (e.g. using $b = 0$, $b \leqslant 100$, and $b \geqslant 500$ s/mm^2). Goshima et al. (19) recommended DW-EPIs with low and high *b* values as supplementary sequences in the detection and characterization of benign and malignant hepatic lesions. In our study, DWI was done with 3 diffusion gradients at *b* 0, *b* 500 and *b* 1000.

Table 4 Mean ADC cut off values for the differentiation between benign and malignant liver lesions at both *b* 500 and *b* 1000 diffusion gradients:



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Cutoff	AUC ± SE	95%CI	Sensitivity (95%CI)	Specificity (95%CI)	Accuracy (95%CI)	PPV (95%CI)	NPV (95%CI)
ADC′1000 ⩽ 1.0 + ADC500 ⩽ 1.5	0.97 ± 0.02	0.87–0.998	90.32% (74.2–98%)	92.86% (66.1–99.8%)	91.1 (77.1–95.3	96.6 (85.7–99.8)	81.3 (61.5–87.2)

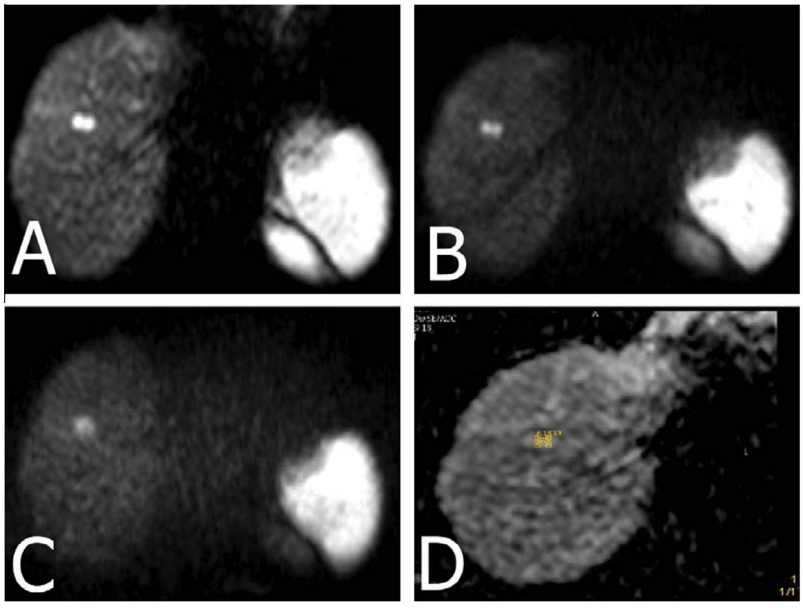

Fig. 1 Diffusion weighted MR images of female patient, aged 35 years with small focal hemangioma, DWI at b0 (A), *b* 500 (B), *b* 1000 (C). ADC map at *b* 1000 (D) shows relative high SI with high mean ADC value = 1.7×10^{-3} mm^2/s.

Most of the studies (1,20,10) indicated that a region of interest (ROI) should be placed within the confines of the lesion in image analysis and put away from prominent vascular structures to avoid motion artifact. However, some authors (1,20) placed ROI that covered entire lesions without separating component with various signal intensities for analysis of heterogeneous lesions, whereas Gourtsoyianni et al. (10) put the ROI in both sites in a lesion with different signal behavior in the periphery and center. In the current study, ROI was placed within the confines of the lesion and put away from vascular and necrotic portions of the lesion.

Kandpal et al. (21) found that respiratory-triggered DWI was superior to breath-hold DWI for hepatic imaging because it provides higher SNR. In our study, DWI was done with the respiratory triggered technique.

Most of the studies included hemangiomas and cysts in the benign lesion group (7,22,23). Thus it was concluded that

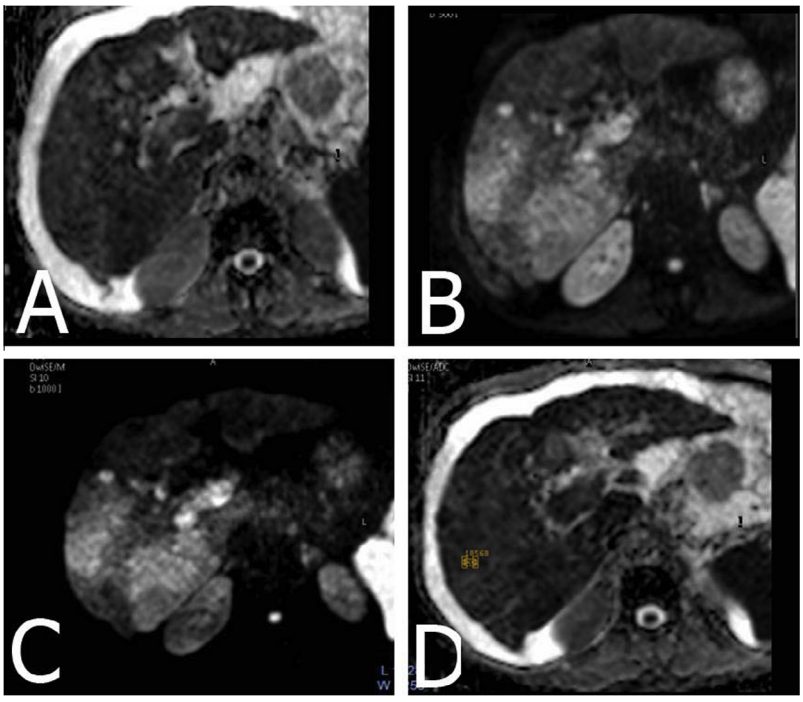

Fig. 2 Diffusion weighted MR images of 60 year old male patient with HCC, DWI at b0 (A), DWI at *b* 500 (B), DWI at *b* 1000 (C) and ADC map (D) shows restricted diffusion with mean ADC value at *b* 1000 = 0.85×10^{-3} mm^2/s.

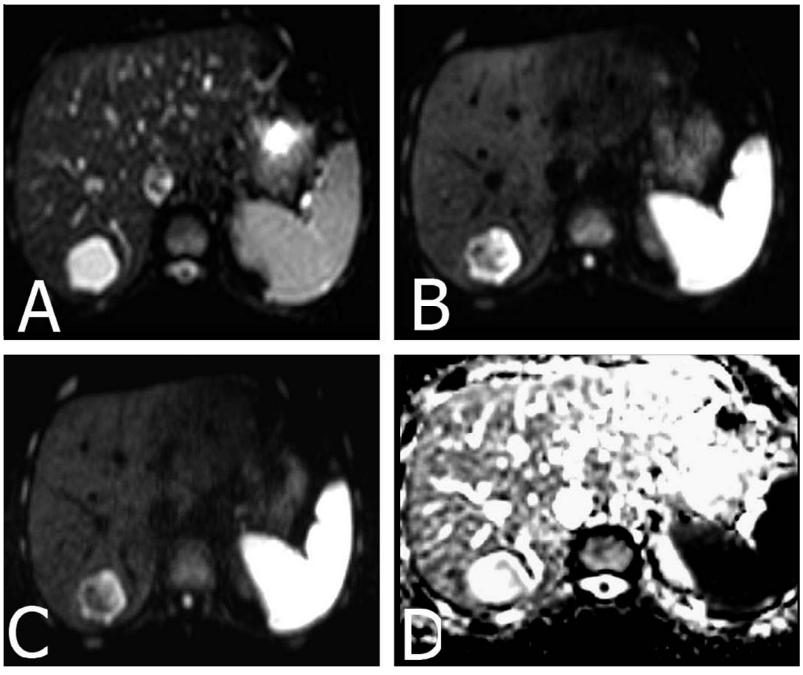

Fig. 3 Diffusion weighted MR images of 42 year old male patient with hemangioma, DWI at b0 (A), DWI at *b* 500 (B), DWI at *b* 1000 (C) and ADC map (D) shows mixed high SI with high mean ADC value at *b* 1000 = 2×10^{-3} mm^2/s.

hypercellular benign lesions like FNH should also be studied in order to discriminate benign and malignant hepatic lesions more reliably (10). While in the study of Onur et al. (11), solid (high cellular) benign liver lesions were included with exclusion of cystic benign lesions. In our study, cystic benign lesions as hemangiomas and cysts and solid benign lesions as FNH and adenoma were included in the benign lesion group.

Our results revealed that ADC measurements at *b* 500 and *b* 1000 diffusion gradients were useful in differential diagnosis of benign and malignant lesions and adding ADC cut off

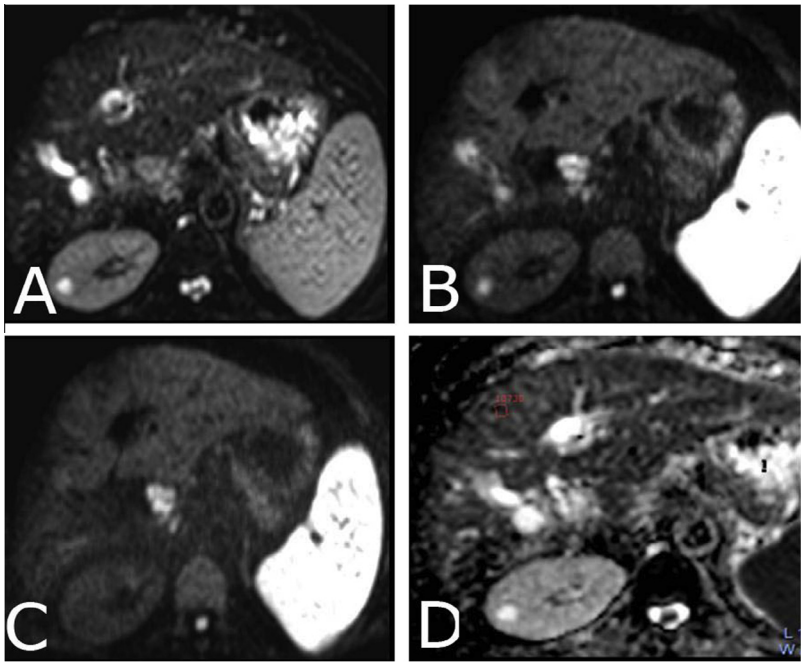

Fig. 4 Diffusion weighted MR images of 55 year old male patient with small HCC, DWI at b0 (A), DWI at *b* 500 (B), DWI at *b* 1000 (C) and ADC map (D) shows isointense SI with restricted diffusion with mean ADC value at *b* 1000 = 0.9×10^{-3} mm^2/s.

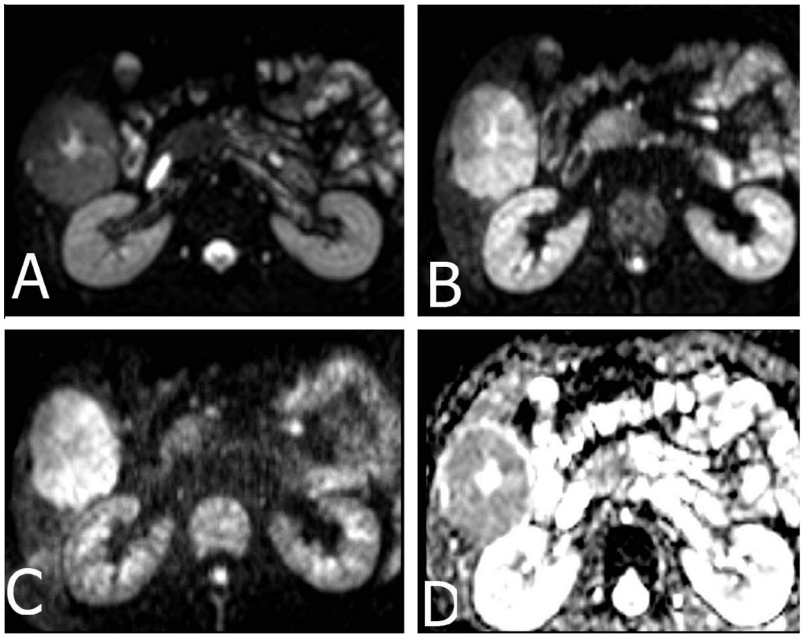

Fig. 5 Diffusion weighted MR images of 40 year old female patient with FNH, DWI at b0 (A), DWI at *b* 500 (B), DWI at *b* 1000 (C). ROI is located peripherally in the lesion since central part represents vascular scar tissue. Mean ADC value at *b* 1000 (D) = 1.3×10^{-3} mm^2/s. Though lesion is hyperintense at DWMRI, it shows high ADC value.

values at *b* 500 and *b* 1000 diffusion gradients increases sensitivity and specificity for differentiation.

In the present study, comparison of ADC values for individual benign and malignant lesions showed that there were statistically significant differences between lesions at different gradients. Mean ADC values at *b* 500 and *b* 1000 of different benign lesions are as follows: FNH (1.86 and 1.46×10^{-3} mm^2/s), adenoma (1.86 and 1.23×10^{-3} mm^2/s), hemangioma (2.30 x10^{-3} mm^2 and $1.75 \times \times 10^{-3}$ mm^2/s) and cysts (2.60×10^{-3} mm^2/s and 1.85×10^{-3} mm^2/s). While, mean ADC values at *b* 500 and *b* 1000 of different malignant lesions are: HCC (1.26 and 0.89×10^{-3} mm^2), metastases (1.11 and 0.80×10^{-3} mm^2) and cholangiocarcinoma (1.05 and 0.75×10^{-3} mm^2).

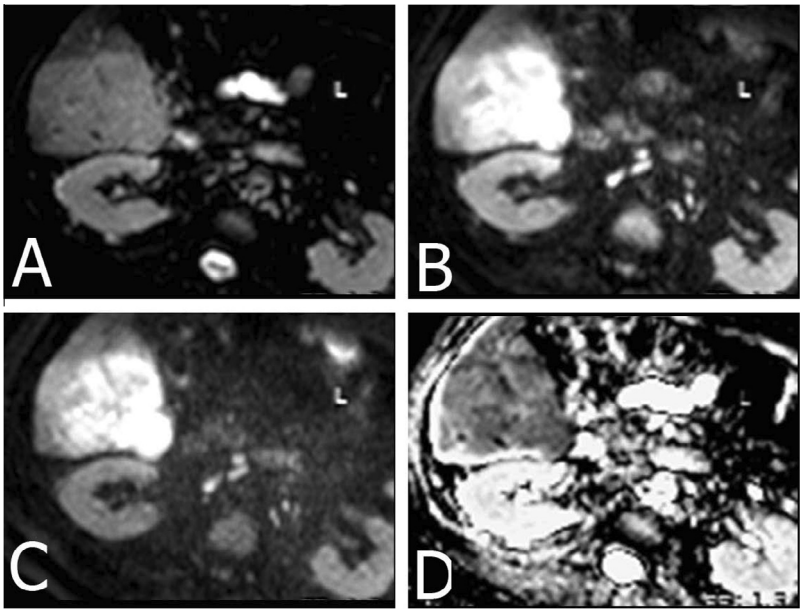

Fig. 6 Diffusion weighted MR images of 57 year old male patient with HCC, DWI at b0 (A), DWI at *b* 500 (B), DWI at *b* 1000 (C). The lesion shows low SI on ADC map (D) with restricted diffusion and mean ADC value at *b* 1000 = 0.8×10^{-3} mm^2/s .

In the study of Onur et al. (11), FNH was easily differentiated from malignant lesions except HCC at *b* 100 gradient. Other benign solid liver lesions also could be differentiated from metastases and cholangiocarcinomas at all gradients. They concluded that solid benign liver lesions did not show a significant difference from HCCs at all gradients. Also, Parikh et al. (8) and Demir et al. (9) said that the ADC values of these solid benign lesions were similar to ADC values of malignant lesions. Yet, in our study, FNH and other benign lesions could be differentiated from malignant lesions including HCC at both *b* 500 and *b* 1000 diffusion gradients.

Taouli et al. (7) concluded that some overlap is present between metastatic lesions and FNHs, however, in our study, metastatic lesions had lower ADC values than FNH at both *b* 500 and *b* 1000 diffusion gradients. This matches with the results of Onur et al. (11) who observed that ADC measurements were successful in differentiating these lesions. This may be due to exclusion of necrotic components of metastases at ADC measurement which may increase the ADC values of metastases.

In the current study, the differentiation between different subtypes of malignant lesions with mean ADC values showed some difficulty at both gradients. At *b* 500 gradient, HCCs had significant high ADC value than metastases and cholangiocarcinoma with difficult differentiation between metastases and cholangiocarcinoma. At *b* 1000 gradient, a significant difference was only found between HCCs and cholangiocarcinomas. This is similar to the results of Gourtsoyianni et al. (10), Kilickesmez et al. (24) and Onur et al. (11) who concluded that the differentiation of malignant lesions with mean ADC values was difficult at all gradients and similarity of ADC values was found between malignant hepatic lesions. Onur et al. (11) said that, the reason for highest mean ADC values measured in HCCs among all malignant lesions may be due to relatively increased perfusion of HCCs than hypovascular metastases and cholangiocarcinomas and we agree with that explanation.

Results of our study showed that cysts and hemangiomas have high ADC value than adenoma and FNH, however, cysts and hemangiomas and also adenoma and FNH could not be differentiated well from each other at both diffusion gradients, This is similar to the results of Onur et al. (11), as ADC measurements were not helpful in differential diagnosis of different types of solid benign lesions.

Sandrasegaran et al. (25) and Miller et al. (26) suggested that ADC values of solid benign lesions (FNH and adenoma) are similar to malignant lesions (metastasis and HCC) and DW imaging is not helpful in differentiating solid benign lesions from solid malignant lesions. However, in our study, there was a significant difference between solid benign (adenoma, FNH) and solid malignant lesions. This may be due to diminished perfusion effect due to high diffusion gradient as we used *b* 0, *b* 500 and *b* 1000 and previous studies used *b* 0, *b* 50 and *b* 500 as diffusion gradients.

Different studies reported variable ADC cut-off values for differentiation of benign and malignant focal hepatic lesions. Taouli et al. (7) offered a threshold value as 1.5×10^{-3} at *b* 500 gradient with sensitivity of 84% and specificity of 89%. Parikh et al. (8) reported an ADC value of 1.6×10^{-3} as a cut off value with sensitivity of 74.2% and specificity of 77.3% at *b* 500 gradient. Onur et al. (11) concluded a cut-off value of 1.23×10^{-3} at *b* 1000 with sensitivity of 83% and specificity of 76% for differentiation between benign and malignant lesions. In our study, using 1.0×10^{-3} mm^2/s as an ADC cut-off value at *b* 1000 diffusion gradient resulted in 90.3% sensitivity, 78.6% specificity and 86.7% accuracy for differentiation of benign and malignant focal hepatic lesion groups. The best result was obtained with the use of ADC

cut off value (at *b* 500) of 1.5×10^{-3}mm^2/s and ADC cut off value (at *b* 1000) of 1.0×10^{-3}mm^2/s, with 90.3% sensitivity, 92.86% specificity, and 91.1% accuracy.

To best of our knowledge, there are only few studies in the literature measuring ADC values of different subtypes of either benign or malignant lesions. Our results showed that HCC had high ADC value than metastases and cholangiocarcinima in the malignant group liver masses. Cysts and hemangiomas had high ADC values than adenoma and FNH in the benign group liver masses.

5. Limitation of the study

There was a small number of cases with FNHs and other benign liver masses and as well as cholangiocarcinoma. However, these lesions were not seen usually as metastases or HCC and most of these lesions (FNH, other benign liver masses and cholangiocarcinoma) were rarely compared with each other via ADC values in the literature.

6. Conclusion

So, adding DWI to routine abdominal MRI and ADC measurements at least at 2 different gradients is a useful tool in differential diagnosis of malignant from benign liver lesions and may be useful for differentiation of different subtypes of either benign and malignant lesions, further investigation in this point is recommended.

Conflict of interest

There is no conflict of interest.

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