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The Role of Diffusion Weighted Magnetic Resonance Imaging in the Differential Diagnosis of Hepatocellular Carcinomas and Regenerative-Dysplastic Nodules in Cirrhotic Liver

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objective: The differential diagnosis of hepatocellular carcinomas (HCC) and regenerative-dysplastic nodules (RDN) in cirrhotic patients is critical for patient management and can be a challenging imaging procedure. The goal of our study is to evaluate the contribution of diffusion-weighted imaging in the differential diagnosis of these lesions.
Materials and Methods: 50 patients, diagnosed as hepatocellular carcinoma and/or RDN in cirrhotic liver, were included in our study. All HCC and some of RDN lesions (5 lesions out of 25) were confirmed histopathologically. Rest RDN was called with imaging characteristics and follow-

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up images (18-27 months, mean 19.2 months follow up time). Magnetic resonance images along with Diffusion weighted images with b = 800 s/mm^2 were evaluated by 2 radiologists. All imaging examinations were performed with 1.5 Tesla MR machine. Diffusion weighted images and ADC (apparent diffusion coefficient) mapping of lesions were evaluated and ADC values were calculated. The results were compared with conventional dynamic magnetic resonance images.

Results: In our study 95% of 40 Hepatocellular carcinomas demonstrated diffusion restriction. 52% of 25 RDN were isointense on diffusion-weighted images. The difference of the signal intensity distribution was statistically significant between two lesions ($p<0.001$). On quantitative analysis, we calculated ADC values of lesions and ADC ratio of lesion-to-liver values. The mean ADC values and ADC ratio of the RDN was higher than that of the hepatocellular carcinomas, and there was a significant difference between 2 groups ($p<0.001$). When a cutoff value of 0.95 is considered for ADC ratio, on diffusion imaging with ADC mapping 97.5% sensitivity and 64% specificity can be calculated to differentiate hepatocellular carcinoma from RDN.

Conclusion: Diffusion weighted imaging can improve differential diagnosis of these two lesions in cirrhotic liver combined with contrast enhanced magnetic resonance imaging.

Keywords: Cirrhosis; diffusion weighted magnetic resonance imaging; dysplastic nodule; hepatocellular carcinoma.

1. INTRODUCTION

Hepatocellular carcinoma (HCC) of the liver is the fifth most common cancer and the third cause of cancer-related mortality worldwide [1]. Major predisposing factor for HCC is cirrhosis in that approximately 80% of HCCs develop in a cirrhotic liver [2]. Early diagnosis of HCC is crucial for the treatment management of patients. Early performed treatment options such as resection or transplantation increase the patient survival rate and bring out the opportunity of long-term survival. For this reason, imaging a cirrhotic nodule containing HCC and distinguish HCC from regenerative-dysplastic nodule (RDN) as early as possible in cirrhotic liver is essential, particularly in the selection of patients for liver transplantation who were selected with the implementation of the Milan criteria [3,4,5]. Performing biopsy for the histologic verification of HCC in cirrhotic patients, carry particularly increased risk factors such as bleeding and track seeding due to cirrhosis related coagulopathy and ascites [6]. Current guideline of AASLD (American Association for the Study of Liver Diseases) explains that the diagnosis of HCC can be made by imaging if the findings are typical for HCC therefore biopsy is not mandatory before treatment [7]. Although recent studies stated significant value of dynamic magnetic resonance imaging (MRI) in the diagnosis of HCC [8,9], it is challenging to interpret early HCC and differentiate it from RDNs in cirrhotic patients [6]. Reasons can be stated such as architectural distortion of the liver parenchyma and the development of diverse cirrhotic nodules ranging from benign regenerative nodule to overtly malignant HCC [10,11].

Diffusion is a thermodynamic term that can be defined as the arbitrary short-distance movement of water molecules. It can be measured by using apparent diffusion coefficient (ADC). ADC shows the amount of water molecules that are transported to intracellular and extracellular compartments. Diffusion is a sensitive parameter in microscopic tissue characterization. In tumorous structures, the cell density significantly rises leading to decrease in the extracellular space in that the mobility of water molecules decreases. This decrease causes diffusion restriction [12,13]. Diffusion weighted MRI (DWI) is essentially different from conventional MR imaging thus it can be exploited to acquire additional information pertinent to disease-associated histologic changes in lesions.

Studies have shown promising results that DWI can be performed to detect hepatic metastases and HCC with substantially high sensitivity [14,15]. Furthermore, DWI with quantitative ADC values can be used in the differentiation of benign and malignant liver lesions [12,13]. Nevertheless, in literature there are not too many evidence focusing on the value of implementing DWI to differentiate RDN and HCC lesions in cirrhotic liver [16]. Therefore, we carry out this study to evaluate the diagnostic feasibility of DWI and its possible contribution to conventional dynamic contrast-enhanced MRI (CE-MRI) for the differentiation of HCC versus RDN.

2. MATERIALS AND METHODS

2.1 Patient Selection

Institutional review board of our faculty has approved this study, and the requirement for informed consent was relinquished. In our study, we evaluate histologically proven HCC and RDN reports of Pathology Department of our Faculty from January 2008 to March 2011. And from our PACS we retrieve MR images of cirrhotic patients with RDN. From our search we retrieve patients that comply with the following criterions; 1) Histologically and/or clinically and radiologically proven cirrhosis 2) Cases with CE-MRI and DWI prior to biopsy and surgery 3) During follow up period (18-27 months) cases with RDN that demonstrates no change in size, signal and contrast enhancement characteristics. Among this group, cases with suboptimal MR images due to severe motion artifacts, cases that undergone trans-catheter arterial chemoembolization prior to imaging and cases with RDN but shows any change in size, signal characteristics or contrast pattern were excluded. From our search, we acquire 50 patients with 40 HCCs (size range 2-14 cm, mean size 4.5 cm) and 5 RDNs (size range 1.5 - 4.5 cm, mean size 1.9 cm) lesions that are histologically proven. And 20 RDNs are diagnosed (size range 0.5 - 4.5 cm, mean size 1.2 cm) according to imaging characteristics and follow up images. Retrospectively we evaluate the clinical, histopathologic and radiologic data of this group of 50 patients. In our cases liver cirrhosis was associated with viral hepatitis B in 84% (n=42), with viral hepatitis C in 10% (n=5) and with alcoholic hepatitis in 6% (n= 3) of patients.

2.2 Evaluation of Magnetic Resonance Images

All MR imaging examinations were performed by using 1.5-T MR imaging system (Magnetom Symphony, Siemens Medical Solutions, Germany). With this system, maximum gradient strength 30 mT/m, peak slew rate 100 mT/m/ms was implemented.

Diffusion weighted images were acquired in the axial plan by using four channel phased-array body coil and multi-slice single-shot echo planar imaging sequence without breath holding. The b values of 0, 400 and 800 were acquired. Parameters used in diffusion sequence were, parallel imaging with reduction factor 2, repetition time[TR]/ time to echo[TE]=4400/85ms, slice thickness 6mm, matrix size 128[phase] x 128 [read] field of view [FOV] 400x400 mm, partial Fourier factor 6/8, bandwidth 1370 Hz/pixel, six excitations, water excitation (b factor) 800s/mm^2. With DW images T2 weighted HASTE sequence, axial in phase and out of phase sequences and breath-holding T1 weighted sequences were acquired. All MR images were evaluated in b value of 800 s/mm^2. For the further characterization of lesions, following contrast material administration, we acquire arterial phase (delay time, 15-20 seconds), portal phase (delay time 70- 90 seconds) and equilibrium phase (delay time, 180 seconds) images.

On diffusion weighted images, signal intensities (SI) of HCC and RDN lesions relative to liver parenchyma was classified into 3 scales as 1) low SI, 2) iso-SI and 3) high SI.

ADC maps were obtained automatically on a workstation by using commercially available software (Leonardo, Siemens Medical Solutions, Germany). On ADC maps and DW images, ADCs were measured quantitatively in lesions and surrounding liver parenchyma by using operator-dependent region of interest (ROI) (Fig. 1). For all image evaluations, the oval or spherical form of ROI was used. Measurements on ADC maps were implemented on the darkest area. To ensure that the same areas were measured, the regions of interest were copied from DW images and pasted onto the ADC maps. In the surrounding liver parenchyma, regions of interest were always placed in the area to avoid vessels and bile duct as far as possible. The ADCs and the lesion-to-liver ADC ratio were each measured twice, and the measurements were averaged. All images were evaluated on a workstation by 2 radiologists (BB with 10 years of experience and RT with 5 years of experience) who were blinded to the diagnosis of the lesions.

T1 and T2 weighted MR and postcontrast dynamic imaging signal characteristics of lesions were evaluated in consensus and saved. Lesions presenting the following criteria (9, 15, 17) are called HCC; 1) nodules demonstrating arterial phase enhancement and wash-out pattern in portal phase with or without capsular enhancement (Fig. 2), 2) nodules larger than 2cm presenting predominant hypointensity in portal/equilibrium phases and no definite enhancement in arterial phase but showing mosaic pattern, peritumoral capsule or fatty metamorphosis (Fig. 3). Lesions demonstrating hyperintensity on T1 images and hypo or

isointensity on T2 images, showing no contrast enhancement and no restriction on DWI are called RDN's [18]. At follow no imaging nor size differentiation is seen in these lesions (Fig. 4).

2.3 Statistical Analysis

The statistical analyses were performed by using statistical software, SPSS for Windows 10.0. For comparison purposes Student's T test and kikare (x^2) tests were employed. ROC analyses were used to determine cut-off points and their diagnostic values were calculated. $p<0.05$ was considered statistically significant.

3. RESULTS

Table 1 depicts SI characteristics of HCC and RDN lesions on diffusion weighted MRI. Demonstrating hyperintensity in HCC group is higher than RDN group and the difference between 2 groups is statistically significant ($p<0.001$) (Table 4). In DWI, sensitivity and specificity of signal intensities are calculated 95% and 80% respectively. Table 2 shows the result of the ADC calculations. The mean ADC and ADC ratio of HCC group is lower than that of RDNs with statistically significant difference ($p< 0.01$ and $p<0.001$ respectively).

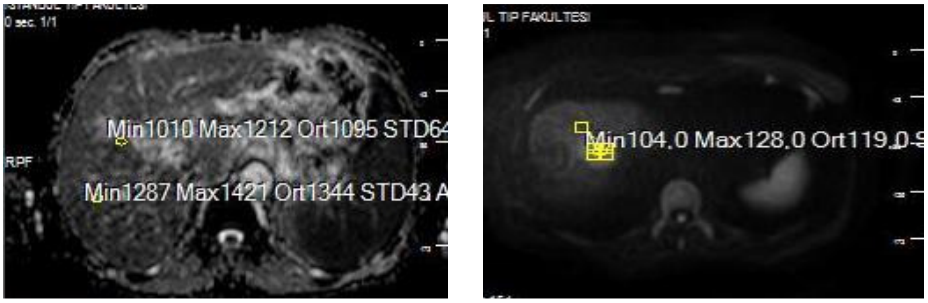

Fig. 1. 68 years old patient with HCC a) ADC measurement of the lesion and surrounding liver parenchyma b) b1000 diffusion measurement of the lesion

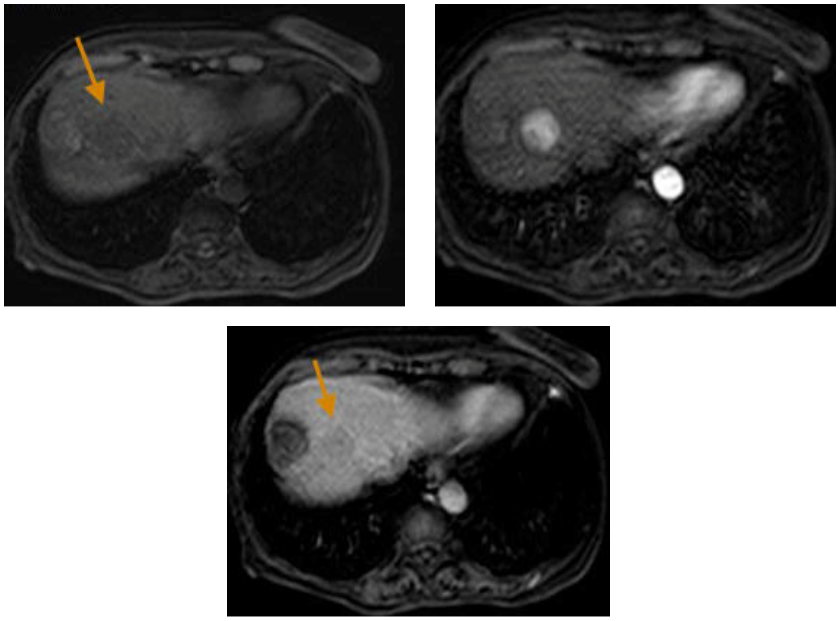

Fig. 2. A 63-year-old man with cirrhosis resulting from hepatitis C infection. Axial unenhanced T1-weighted image shows hypointense 22 mm noduler lesion. Axial contrast-enhanced MR image obtained in the hepatic arterial phase shows intense enhancement of the nodule and in the equilibrium phase shows that the nodule (arrow) demonstrates wash-out

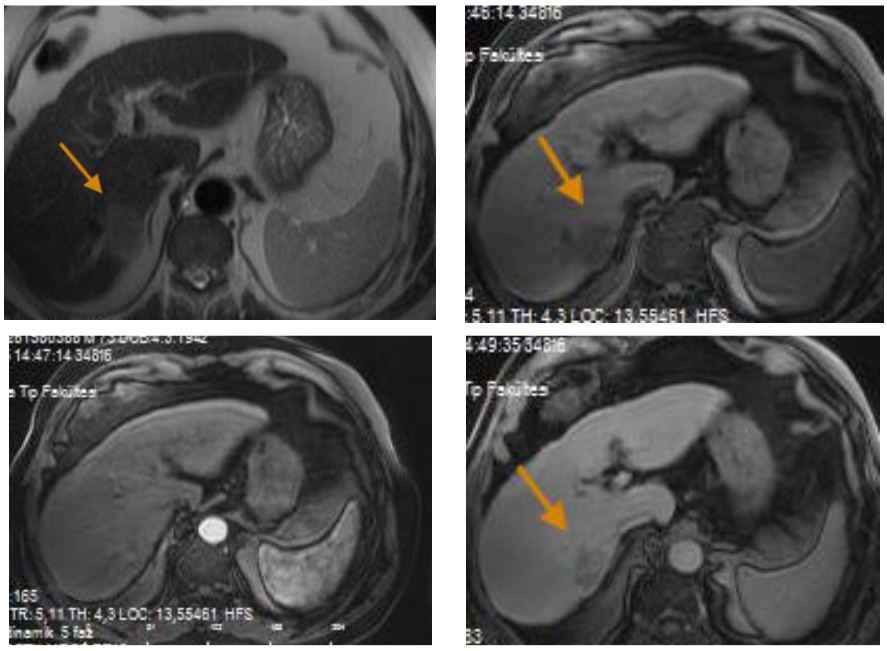

Fig. 3. A cirrhotic patient with HCC. a) T2 weighed image shows slightly hyperintense lesion larger than 2 cm b) axial unenhanced T1 weighed image shows the hypointense lesion c) the nodule doesn't show evident arterial enhancement but d) in the portal phase the lesion is predominantly hypointense and shows peritımoral capsule enhancement

ROC analyses reveal that both ADC and ADC ratio are significant to differentiate HCC from RDN. Table 3 demonstrates ADC and ADC cut-off values. 97.5% of HCC lesions have ADC ratio under 0.95 and 85% have ADC value under 1.4 $x10^{-3}$ mm2/sn. Only %36 of RDNs have ADC ratio under 0.95 and %40 ADC value under 1.4. There is statistically significant difference between these groups ($p<0.001$ for both groups). The most appropriate value for ADC is under 1.4 $x10^{-3}$ mm2/sn and for ADC ratio is under 0.95 to make differential diagnosis of HCC and RDN. The sensitivity and specificity of DWI is 97.5% and 64% respectively with the accuracy of 84.6% when ADC ratio (with cutoff value of 0.95) is used to differentiate HCC from RDN. When ADC values are used (cutoff value 1.4 $x10^{-3}$ mm2/sn) the sensitivity and specificity of DWI mildly decrease and present 85% sensitivity and 60% specificity with accuracy of 75% for the differentiation of HCC from RDN.

Table 1. SI distribution of HCC and RDN lesions on DWI

Signal intensities	RDN		HCC		p
	n	%	n	%	
Isointense	13	52,01			
Hyperintense	5	20,0	38	95,0	
Hypointense	7	28,0	2	5,0	0,000***
Signal					
Iso+hypointense	20	80,0	2	5,0	
Hyperintense	5	20,0	38	95,0	0,000***

Table 2. Comparison of ADC measurement (x 10^{-3} mm^2 /sn) Between HCC and RDN on DWI

	RDN		HCC		p
	Mean	SS	Mean	SS	
ADCs, mm2/s	1,366	,267	1,198	,210	,006**
Lesion-to-liver ADC ratio	1,038	,157	,874	,040	,000***

Table 3. Cut-off values of ADC and ADC ratio (x 10^{-3} mm^2 /sn)

ADC ratio	RDN		HCC		p
	n	%	n	%	
<0,95	9	36,0	39	97,5	
0,95 and higher	16	64,0	1	2,5	0,000***
ADC					
<1,40	10	40,0	34	85,0	
1,40 and higher	15	60,0	6	15,0	0,000***

Table 4. SI distribution of HCC and RDN lesions in DWI

SI	DN group		HCC group		p
	n	%	n	%	
Isointense	13	52,0l			
Hyperintense	5	20,0	38	95,0	
Hypointense	7	28,0	2	5,0	0,000***

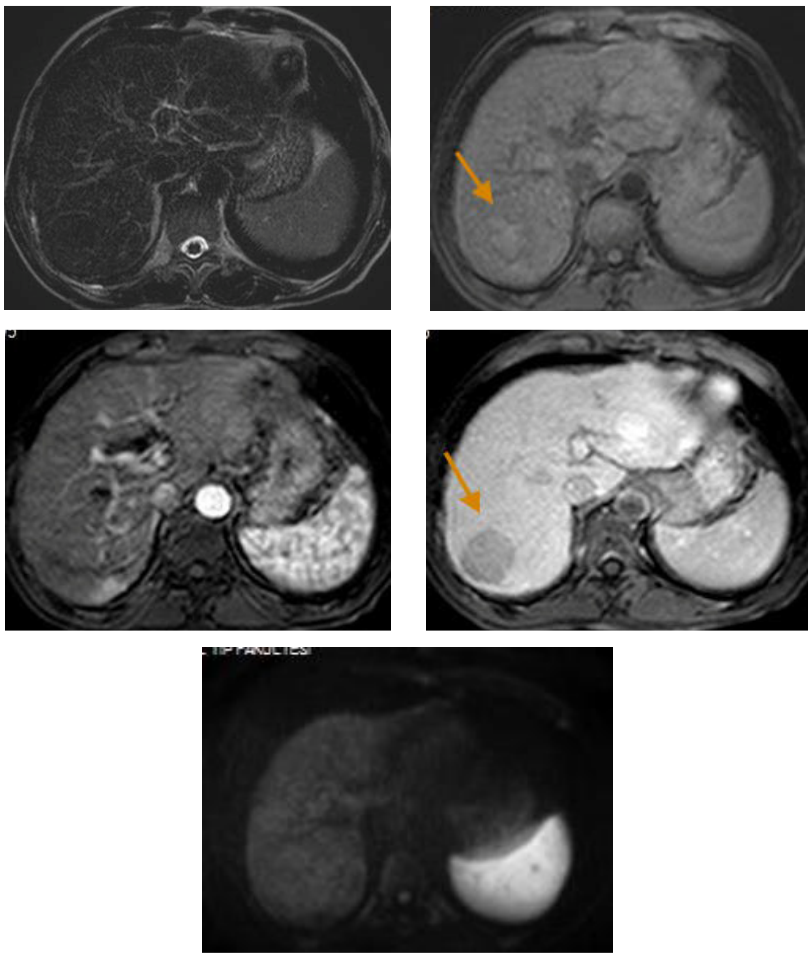

Fig. 4. A 57-year-old cirrhotic patient control MRI. a) at T2 weighed image there is no remarkable lesion. b) unenhanced T1 weighted image reveals a hyperintense noduler lesion c) that shows no enhancement in the arterial phase. d) And in the equilibrium phase the noduler lesion is hypointense e) no diffusion restriction in the lesion (Biopsy proven regenerative nodule)

4. DISCUSSION

About 80% of HCC cases develops in a cirrhotic liver in that cirrhosis is the leading predisposing factor for HCC [2]. Cirrhosis can be defined as the end stage of chronic liver disease with advanced liver fibrosis which is characterized by architectural distortion and the development of a spectrum of nodules ranging from benign regenerative nodules to dysplastic nodules to overtly malignant hepatocellular carcinoma [18,19]. HCC is the most common primary malignancy of the liver and the third cause of cancer-related mortality worldwide [1]. In a cirrhotic liver, development of HCC can be explained by de novo carcinogenesis and/or by means of multistep progression. This progression encompasses multi steps from low-grade dysplastic nodule to a high grade dysplastic nodule, to a dysplastic nodule with a focus of HCC, and finally to overt carcinoma [20]. Small HCC nodules are defined as nodules that have 2cm or smaller diameter [7]. Survival rates of HCC patients improves with early diagnosis thus the detection and making differential diagnosis of these nodules are crucial [3,4]. The combination of gadoxetic acid-enhanced MR imaging and diffusion-weighted imaging shows significantly better sensitivity in the detection of small HCCs than each MR imaging technique alone (combined 92.4%; gadoxetic acid 81.4%; DW 78.8%; p=0.01). The 5-year survival rate of patients undergoing curative therapies (such as liver transplantation, hepatic resection and percutaneus ablations) range between 40% and 75% [2]. It is crucial to detect early stage tumors to initiate curative therapies with increased survival rates.

The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver have declared imaging diagnostic criteria for HCC nodules in cirrhotic liver [21]. No biopsy is needed for nodules diameter 1 cm or larger that demonstrates hypervascularity in arterial phase and venous or delayed phase wash-out to make HCC diagnosis. For nodules smaller than 1 cm repeated follow up imaging in 3 months interval is recommended [22].

Owing to its special ability to allow differentiation of tissue by cellular density and architectural change diffusion-weighted imaging has been applied increasingly to liver imaging. DW imaging is routinely used in standard clinical protocols because it is easy to perform and needs no contrast agent.

In the literature, there are numbers of studies evaluating DWI characteristics of liver lesions. Ichikawa et al. [23] evaluate 74 focal liver lesions in 46 patients (11 hemangiomas, 15 metastases, 48 HCCs). They calculate ADCs and contrast to noise ratios (CNR) of lesions and compare with T2 fast spin echo with breath-hold images. The study reveals that the mean ADCs of every lesion are significantly different from each other (hemangioma 5.39 x 10^{-3} mm^2 /sn. metastasis 2.85 x 10^{-3} mm^2 /sn. HCC 3.84 x 10^{-3} mm^2 /sn) and significantly differs from mean liver ADC value (2.28 x 10^{-3} mm^2 /sn[$p<0.05$]). The mean values of CNRs with DW imaging are significantly higher than CNRs acquired with T2 weighted fast spin-echo images in both HCCs and metastases whereas no significant difference is noted for hemangiomas. The study highlights that DWI may be useful for increased detection of HCCs and metastases and in differentiating these entities from hemangiomas [23]. Another study by Nasu et al. [24] compare DWI and contrast MR imaging with super magnetic iron oxide (SPIO) in the detection of liver lesions. Sensitivity and specificity of SPIO is 66% and 90% respectively and DWI shows increased sensitivity and specificity rates 82% and 90% respectively. Xu et al. [6] retrospectively evaluated conventional contrast enhanced MRI and DWI of 40 HCC and 19 DNs that are histologically verified. They search for the contribution of DWI in distinguishing HCCs from DNs to contrast enhanced MRI. DWI has 97.5% sensitivity, 78.9% specificity and 91.5% accuracy for differentiating HCCs from DNs when high signal intensity of HCC lesions is proposed for diagnostic criteria. Our study reveals that HCC and RDN demonstrate particular signal intensities in DWI (Fig. 4). Pathologic process of HCCs and RDNs is responsible for this characteristic signal changes of these lesions in DWI. In the literature, it is stated that most of the HCCs show high signal intensity in DWI [6,25]. This signal characteristic can be explained by the high cellular density of the lesion [26,27]. On the other hand, there are lesions in our study that exhibit different signal intensities. 20% of RDNs show diffusion restriction in DWI. We believe that one reason can be different histopathological grades of the lesions. Another explanation can be the contribution of cirrhotic liver to the signal characteristics of lesions. In our study, calculated ADC values are parallel to the ADC values in the literature [6,12]. This outcome reveals that there

is significant difference in ADC values of HCC and RDN lesions.

There are couple of limitations in our study. First, our retrospective study was performed with histologically confirmed hepatocellular nodules therefore there might have been a potential selection bias in patient population. However, our goal was to evaluate the diagnostic performance of DWI in the differentiation of HCC from RDN by implementing our imaging criteria. Second, because of reduced image quality and overestimation of ADCs by including the perfusion fraction was possible, we did not perform high b values. On the other hand, we did not intend to measure the true diffusion coefficient so we believe that second limitation is not very critical for our study. We have a follow-up period for the RDN lesions and any change in size or MR imaging characteristics of RDN lesions were excluded from the study. This selection bias can be another limitation of our study because it has a potential that this selection bias may decrease the sensitivity and specificity of diffusion weighted imaging. Last limitation is the limited number of patients.

5. CONCLUSION

Diffusion weighted imaging can improve the sensitivity and the specificity of contrast enhanced MR imaging in distinguishing of HCCs from RDNs in cirrhotic liver.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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