

The Role of Diffusion Weighted MRI in The Differentiation between Benign and Malignant Hepatic Focal Lesion

Amr Mahmoud Abdelsamed, Remon Zaher Elia, Mohammed Uday Hatim

Department of Radiodiagnosis, Faculty of Medicine - Ain Shams University

Corresponding author: Mohammed uday hatim, Email: mohameduday100@gmail.com, Cell number: 01060560797

ABSTRACT

Background: early detection and diagnosis of hepatic focal lesions are an important step in clinical work, which would allow effective surgical or mini-invasive therapy. With the advances in magnetic resonance imaging (MR) technology, diffusion-weighted magnetic resonance imaging (DWI) is now widely used as a standard imaging sequence in clinical work and shows its potential benefit in evaluation of the focal hepatic lesions.

Aim of the work: the use of MR Diffusion imaging with both low and high B values to detect and differentiate between benign and malignant hepatic focal lesion.

Methodology: the present study included 30 patients. They were El-Demerdash hospital patients with hepatic focal lesions. Patients underwent US or CT before MR examination.

Results: thirty patients were included in this study, 20 males and 10 females. The patient's age was ranging from 33 to 60 years. There were 24 primary hepatic focal lesions, (36.7% HCC, 3.3% focal nodular hyperplasia, 3.3% cysts, 13.3% hemangiomas, 6.7% cholangiocarcinoma, 16.7% regeneration nodule) and 6 metastatic lesions.

Conclusion: we hope to use DWI to be helpful in the characterization of focal liver lesions, especially if the lesions show non classic appearance of contrast enhancement in Triphasic CT study and in patients with renal insufficiency with inability to use contrast enhancement.

Recommendations: in our opinion, DWI is a useful adjunct to routine liver imaging (i.e. used as an additional sequence to the standard protocol study and not as a unique imaging series); it is fast, requires no intravenous contrast and is non-invasive. The radiologist has to be aware of the potential pitfalls and limitations of the technique. In patients who cannot receive gadolinium-based contrast agents, DW MR imaging has the potential to be a reasonable alternative technique to contrast-enhanced imaging. We suggest the following strategy for evaluating DWI features of FLLs. We believe that most of the FLLs can be practically classified as benign or malignant by using this scheme.

Keywords: MR Diffusion imaging, Low and high B values, DWI, Malignant hepatic focal lesion.

INTRODUCTION

Early detection and diagnosis of hepatic focal lesions are an important step in clinical work, which would allow effective surgical or mini-invasive therapy^(1,2).

With the advances in magnetic resonance imaging (MR) technology, diffusion-weighted magnetic resonance imaging (DWI) is now widely used as a standard imaging sequence in clinical work and shows its potential benefit in evaluation of the focal hepatic lesions^(3,4).

DWI with low value can suppress the intra hepatic vascular signal, creating the so-called black blood effect, which improves the detection of small focal liver lesions (FLLs) especially localized near small hepatic vessels. Meanwhile, DWI with low-value has higher imaging quality compared with single shot fast spin-echo sequences^(5,6).

A substantial number of studies have compared low B-value DWI with T2-weighted imaging (T2WI) for image quality and

detection of FLLs. These studies generally showed better performance of DWI with low -value in terms of lesion detection compared with T2WI⁽²⁾.

DWI with higher b-value mainly reflects diffusion information of water molecules motion within the lesions, which help to improve the characterization of solid FLLs⁽⁴⁾.

Meanwhile, we found in practice that DWI with higher b -value also enables a better detection of lesions in liver compared with T2WI or other conventional sequences. For example, solid focal liver lesions such as focal nodular hyperplasia and hepato cellular carcinomas (HCCs) sometime can be difficult to be detected on T2WI or even DWI with low b -value due to either iso- or slightly hyper signal intensity to liver parenchyma^(7,8).

Diffusion is a physical process that results from the thermally driven, random motion of water molecules. In a container of

water, molecules undergo free, thermally agitated diffusion (with a three dimensional Gaussian distribution) ⁽⁶⁾.

The b-value represents the diffusion factor (measured in s/mm^2) and the strength of the diffusion gradients. The ideal b-value for lesion characterization is a trade-off between signal attenuation and perfusion contamination. This is generally possible using b-values between 400 and 1000 s/mm^2 for liver imaging. Pure diffusion contrast is obtained when using b-values above 1000 s/mm^2 . However, image quality can be limited by signal loss that occurs at such high b-values ⁽⁹⁾.

Two independent observers reviewed DW (b values of 0, 500, and 1000 sec/mm^2) and T2-weighted images for FLL detection and characterization. Reference standard for diagnosis was obtained from consensus review by the two observers of DW, T2-weighted, pathological data, and follow-up imaging results. Apparent diffusion coefficient (ADC) was measured for FLLs identified at consensus review. DW and T2-weighted images were compared for FLL detection and characterization by using a binary logistic regression model. Receiver operating characteristic curve analyses was conducted to evaluate the utility of ADC for diagnosis of malignancy ⁽⁹⁾.

Aim of the Work

The use of MR Diffusion imaging with both low and high B values to detect and differentiate between benign and malignant hepatic focal lesion.

PATIENT AND METHODS

Study Population:

This study included 30 patients. They were El-Demerdash hospital patients with hepatic focal lesions. Patients underwent US or CT before MR examination.

Inclusion Criteria:

Patient known to be have focal nodules detected by US and/or MSCT.

Exclusion Criteria:

Unstable clinical status, Contraindications to MR imaging; claustrophobia, patients with pace maker or metal implants.

The patients were subjected to the following:

1. Full clinical assessment including; recording of age, sex and clinical presentation.
2. Laboratory investigations {liver biochemical profile, renal function tests}.

3. Abdominal MRI (conventional MRI and diffusion-weighted imaging). The results were compared to laboratory, and other previous radiological (US&/or MSCT) findings done for all patients.

MR Examination:

Conventional MRI, diffusion MR imaging studies were performed. First; characterization and detection of focal lesions were performed; second, the diffusion images with ADC values were reviewed. MR imaging were performed on a high field system (1.5 Tesla) magnet units (Philips Intera) using a phased array coil to cover the whole liver.

MR Protocol:

A. Conventional MRI:

- T1 weighted (T1W) images: repetition time TR=10msec, echo time TE=4.58msec, matrix 179x320, slice thickness 7-8mm, slice gap 1-2 mm and FOV 355mm.
- T2 weighted (T2W) images (single shot free breathing): TR \geq 445msec, TE=26-28 msec, matrix (180-200)x240, slice thickness 7-8mm, slice gap 1- 2mm and/or 365.
- T2 SPAIR (Spectral Attenuated Inversion Recovery) fat suppression sequence: TR \geq 400msec, TE=80msec, matrix 204x384, slice thickness 7-8mm, slice gap 1- 2mm and FOV365.
- In phase and out phase gradient echo sequence (Dual/FFE): TR= 75-100msec, TE=4.6msec for in phase and 2.3msec for out phase, matrix 143x240, slice thickness 7-8mm, slice gap 0mm and FOV345.

B. Diffusion study:

Respiratory-triggered fat-suppressed single-shot echoplanar DW imaging was perform in the transverse plane with tri-directional diffusion gradients by using b values (0, 500&1000) sec/mm^2 to increase sensitivity to cellular packing. Parallel imaging with generalized auto- calibrating partially parallel acquisition (GRAPPA) with an acceleration factor of two was apply to improve image quality. The other parameters were as follows: repetition time (TR) \geq 1880 msec, echo time (TE) = 70 msec, number of excitations (NEX)=3, matrix 256x256, slice thickness 7-8mm, slice gap 1-2mm, scan time 3-4min with a field of view as small as possible with 52% rectangular field of view.

Imaging Evaluation

The morphological features of each lesion were recorded included size, shape,

margin and signal characteristics, as well as number and site of the detected focal lesions. Then, provisional diagnosis was report. Second, we reviewed the diffusion images with ADC values for final radiological detection and characterization of focal lesions.

ADC Calculation

The mean ADC of each detected focal lesion is measured by drawing a region of interest (ROI) over the lesion. The ADC was measure twice and the two measurements were averaged. To ensure that the same areas were measured, regions of interest were copied and pasted from DWMRI.

The study was done after approval of ethical board of Ain Shams university and

an informed written consent was taken from each participant in the study.

Statistical methods

IBM SPSS statistics (V. 24.0, IBM Corp., USA, 2016) was used for data analysis. Data were expressed as Mean± SD for quantitative parametric measures in addition to both number and percentage for categorized data. Diagnostic validity test was used to evaluate MRI technique versus histopathology. It includes agreement; disagreement and accuracy.

RESULT

Thirty patients were included in this study, 20 males and 10 females.

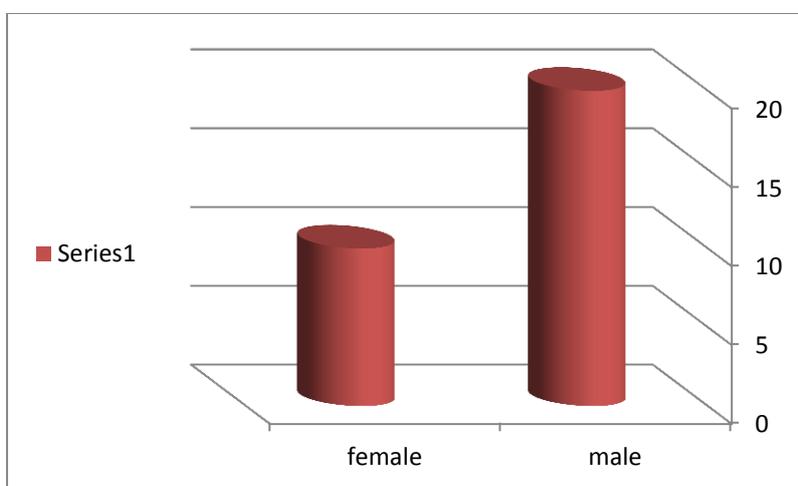


Figure 1: Sex predilection in the study.

The patient’s age was ranging from 33 to 60 years.

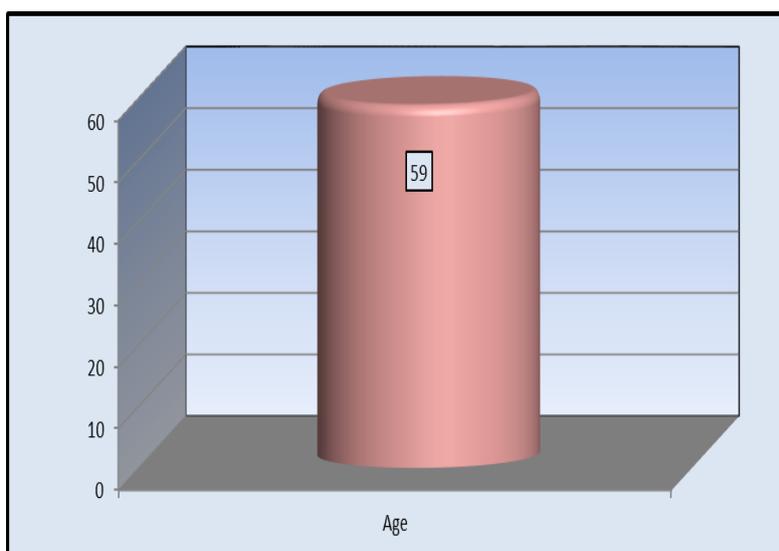


Figure 2: Age distribution of patients

There were 24 primary hepatic focal lesions, (36.7% HCC, 3.3% focal nodular hyperplasia, 3.3% cysts, 13.3% hemangiomas, 6.7% cholangiocarcinoma, 16.7% regeneration nodule) and 6 metastatic lesions.

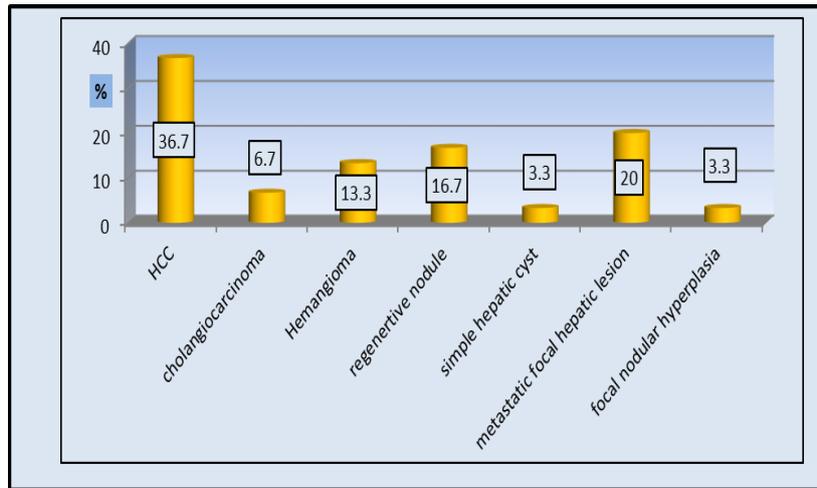


Figure 3: Number of lesions according to their types.

All cystic lesions showed facilitated diffusion, where they showed reduction of signal intensity on increasing the b-values, and those which didn't show reduction of signal showed high signal on ADC map, which also reflects facilitated diffusion. On the other hand all solid lesions showed restricted diffusion evidenced by increased signal on increasing the b-values and low signal on ADC maps.

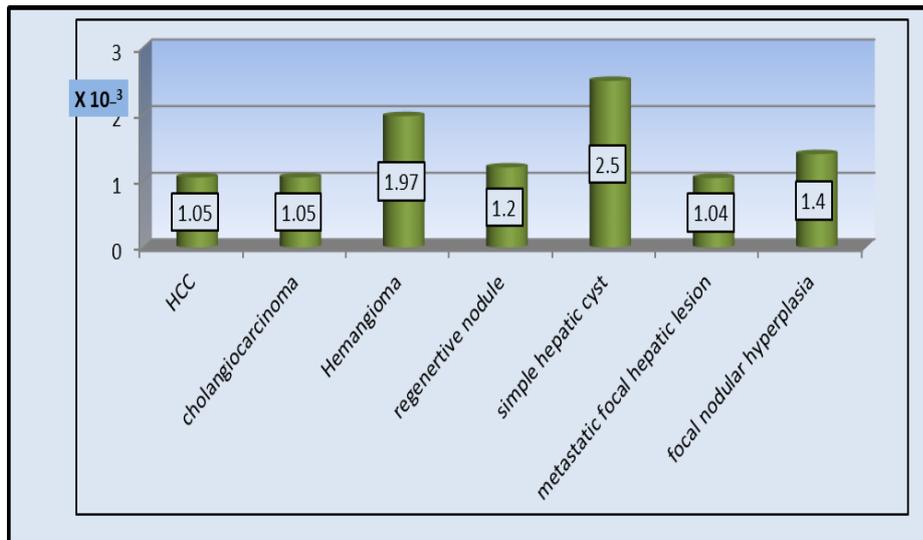


Figure 4: ADC values of lesions

The ADC value of the 11 benign lesions was $1.89 \times 10^{-3} \text{ mm}^2/\text{sec}$. ADC values of benign lesions were between 1.2×10^{-3} and $2.5 \times 10^{-3} \text{ mm}^2/\text{sec}$. The highest ADC value was for simple cysts. Among the benign lesions, regenerative nodule had the lowest ADC value.

The ADC values of the 19 malignant lesions were $1.05 \times 10^{-3} \text{ mm}^2/\text{sec}$. Among the malignant lesions, the lowest ADC value was for metastasishepatic lesion $1.04 \times 10^{-3} \text{ mm}^2/\text{sec}$. The difference between the ADC values of benign and malignant lesions was statistically significant ($P < 0.0001$). No statistically significant differences in ADC values among the different benign lesions or among the different malignant lesions.

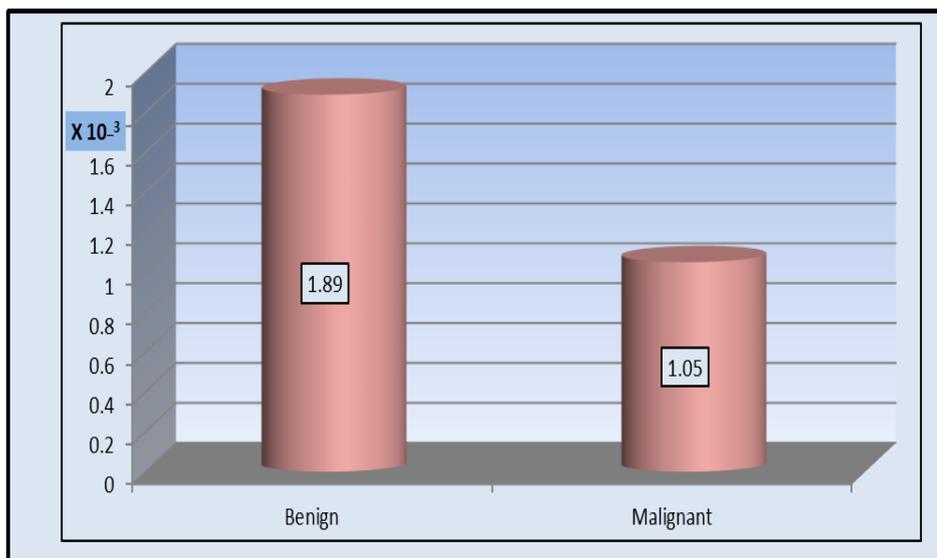


Figure 5: ADC values for all studied lesions classified according to benign or malignant

Table 1: Histopathological results in compared with MRI results

Crosstab					
			Histopathology		Total
			Confirmed	Negative	
MRI	Positive	Count	29	1	30
		%	100.0%	100.0%	100.0%
	Negative	Count	0	0	0
		%	0.0%	0.0%	0.0%
Total		Count	29	1	30
		%	100.0%	100.0%	100.0%

Agreement (%) = 29/30 = 96.7%

Disagreement (%) = 1/30 = 3.3%

Accuracy = 96.7%

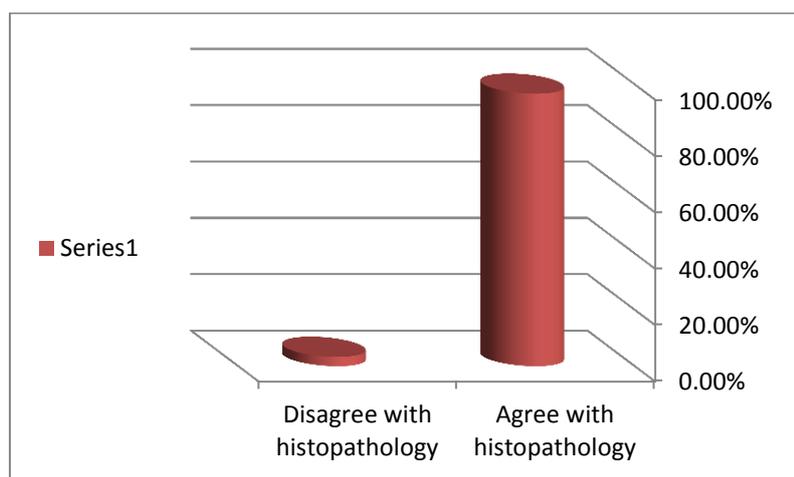


Figure 6: Histopathological results in compared with MRI results

DISCUSSION

Correct detection, classification, and characterization of hepatic focal lesions are of paramount importance as they may

significantly affect the choice of therapeutic approach in many cases ⁽¹⁰⁾.

The liver is an organ in which various benign or malignant, primary or secondary masses can be detected. Today, focal masses

are diagnosed using ultrasonography and/or computed tomography. Additionally, magnetic resonance imaging is preferred when further characterization of these masses is needed. MRI has many advantages (e.g., high contrast resolution, the ability to obtain images in any plane, lack of ionizing radiation, and the safety of using particulate contrast media rather than those containing iodine) that make it a favored modality⁽¹¹⁾.

Although dynamic contrast enhanced MR examinations have become a routine component of abdominal imaging, the high cost/benefit ratio and risk of contrast media side effects remain an issue⁽¹²⁾.

DW-MRI provides unique insight into tissue cellularity, tissue organization, integrity of cells and membranes, as well as the tortuosity of the extracellular space, which can be helpful for detecting malignant diseases, and for distinguishing tumour tissues from non-tumour tissues⁽¹³⁾.

Muller et al. first reported in 1994 on diffusion-weighted MRI of normal hepatic, splenic, and muscular tissues, as well as on focal and diffuse hepatic diseases, and obtained significant results. In the years that followed, several studies on liver, kidney, and other abdominal organs examined with diffusion weighted MRI were published. In these studies it was shown that apparent diffusion coefficient values of normal tissues and lesions can be measured using diffusion-weighted images, and the differences in ADC values can be used in the differential diagnosis⁽¹¹⁾.

The major aim of the present study was to determine the usefulness of diffusion weighted behavior in the various focal lesions of the liver, using ADC measurement, and to determine its contribution to differential diagnosis.

The current study was conducted including thirty patients 20 males and 10 females, with age ranging from 33-60 years.

In our study three different b values were conducted which was in line with the study performed by **Parikh et al.**⁽⁹⁾ and **Qayyum et al.**⁽¹⁴⁾ although the later stated that the use of only two b values (one of which is low and the other is high) can lead to ADC calculation (at least two values).

As well as the disadvantage of using multiple b values is an associated increase in

scanning time which was mentioned by **Bachir and Dow**⁽¹⁵⁾.

This study was conducted with high b value (500&1000 sec/mm²) to overcome the effect of capillary perfusion and water diffusion in extracellular extravascular space, as high b value will result in the reduction of signal from moving protons in the bile ducts, cysts, vessels, and fluid in the bowel. This will result in an increased contrast between the lesion and liver. Furthermore, the differences in the relative contrast ratio between malignant and benign lesions were increased with a high b value. This was similar to the b value used in other studies^(11,12).

In our study, small lesions were effectively detected on diffusion weighted images, where lesions as small as 0.5cm were clearly depicted, thus making DW MRI a useful tool for detection of small focal hepatic lesions even without contrast injection.

In the current study cysts and hemangiomas showed facilitated diffusion whereas solid tumoral lesions showed restricted diffusion. This data is similar to that present in literature⁽¹⁶⁾, which stated that cellular tissues, such as tumors, demonstrates restricted diffusion (high signal intensity) on higher b value (500 sec/mm²) images and by contrast, cysts and hemangiomas show a greater degree of signal attenuation on higher b value diffusion images.

As a general observation, both benign and malignant solid lesions may demonstrate residual high signal intensity on higher b value images and this makes it difficult to depend only on inspecting and reviewing the images to characterize the lesion's nature. This was also stated by Taouli and Koh⁽¹⁶⁾ and Parikh *et al.*⁽⁹⁾ that it would be difficult to characterize focal lesions with visual assessment of the DW MR images alone. Hence, once a cellular hepatic lesion is identified visually, further characterization usually relies on conventional morphologic imaging, supplemented with ADC measurements.

And since visual interpretation of images and characterization of lesions depending on diffusion appearance of lesions has its limitation, therefore the calculation of the ADC values was of importance in lesions assessment.

The absolute ADC values of the different types of lesions were not similar, which is probably due to differences in

techniques applied (b value, breath measurement methods, and mathematical technique applied). This finding was also stated by Petra and Eric ⁽¹⁷⁾ were they stated that in spite there are an increasing number of studies dealing with quantitative measurements of ADC in liver lesions, there are many discrepancies in the reported ADC values where there is no cut-off value for ADC values in normal parenchyma, benign and malignant lesions and this is often associated with many technical parameters such as the use of respiratory-triggered versus breath-hold diffusion-weighted protocol and significantly b value as high b value results in low ADC value and vice versa. Yet our findings were similar to previous studies in many aspects as follows:

The ADC measurements of benign and malignant hepatic masses were significantly different with a p value <0.0001, which supports similar previous findings where Onura MR *et al.* ⁽¹⁸⁾ stated that the mean ADC values of benign lesions were higher than malignant lesions. Miller *et al.* ⁽¹⁹⁾ stated that the ADC values of benign hepatic lesions were significantly higher than that of malignant hepatic tumors, with a P value < 0.05.

Vergara *et al.* ⁽²⁰⁾ stated that the mean ADC value obtained for benign lesions differed significantly from the average for malignant lesions with a p value <0.05 Demir *et al.* ⁽¹¹⁾ Stated that the difference between the mean ADC values of benign and malignant lesions was statistically significant ($P < 0.01$).

The lowest ADC values belonged to metastases with ADC value of 1.04×10^{-3} mm²/sec.

Robert *et al.* ⁽²¹⁾ reported that regenerative nodules demonstrate variable signal on T1-weighted images. On T2-weighted MR imaging, typical regenerative nodules are isointense to hypointense, but they are almost never hyperintense on T2-weighted imaging. In our study, the regenerative nodules were hyperintense on T1 WIs. On T2 WIs and SPAIR sequences, the regenerative nodules were hypointense, show free facilitated diffusion on DWIs with high ADC value. In dynamic MR study, all regenerative nodules were isointense to the liver parenchyma.

STUDY LIMITATIONS

Was the low number of lesions, especially the benign solid hepatocellular lesions (e.g., hepatic adenoma), thus making the comparison between solid benign and malignant masses limited.

CONCLUSION

We hope to use DWI to be helpful in the characterization of focal liver lesions, especially if the lesions show non classic appearance of contrast enhancement in Triphasic CT study and in patients with renal insufficiency with inability to use contrast enhancement.

RECOMMENDATIONS

In our opinion, DWI is a useful adjunct to routine liver imaging (i.e. used as an additional sequence to the standard protocol study and not as a unique imaging series); it is fast, requires no intravenous contrast and is non-invasive. The radiologist has to be aware of the potential pitfalls and limitations of the technique. In patients who cannot receive gadolinium-based contrast agents, DW MR imaging has the potential to be a reasonable alternative technique to contrast-enhanced imaging. We suggest the following strategy for evaluating DWI features of FLLs. We believe that most of the FLLs can be practically classified as benign or malignant by using this scheme.

REFERENCES

1. **Albiin N, Smith IC, Arnelo U *et al.* (2008):** Detection of cholangiocarcinoma with magnetic resonance spectroscopy of bile in patients with and without primary sclerosing cholangitis. *Acta Radiol.*, 49(8):855–62 .
2. **Yau T, Tang VY, Yao TJ, Fan ST, Lo CM, and Poon RT (2014):** Development of Hong Kong liver cancer staging system with treatment stratification for patients with hepatocellular carcinoma. *Gastroenterology*, 146(7): 1691–1700.
3. **Wang H, Wang XY, Jiang XX and Ye ZX (2010):** Comparison of diffusion-weighted with T2-weighted Imaging for detection of small hepatocellular carcinoma in cirrhosis: preliminary quantitative study at 3-T. *Academic Radiology*, 17(2): 239–243.
4. **Kwon GH, Kim KA, Hwang SS *et al.* (2015):** Efficiency of non-contrast-enhanced liver imaging sequences added to initial rectal MRI in rectal cancer patients. *PloS one*, 10(9):e0137320.
5. **Namimoto T, Nakagawa M, Kizaki Y *et al.* (2015):** Characterization of liver tumors by diffusion-weighted imaging: comparison of

- diagnostic performance using the mean and minimum apparent diffusion coefficient. *Journal of Computer Assisted Tomography*, 39(4):453–461.
6. **Takahara T and Kwee TC (2012):** Low b-value diffusion-weighted imaging: emerging applications in the body. *Journal of Magnetic Resonance Imaging*, 35(6): 1266–1273.
 7. **Bharwani N and Koh DM (2013):** Diffusion-weighted imaging of the liver: an update. *Cancer Imaging*, 13(2): 171–185.~~delete all lines~~
 8. **Hussain SM, Semelka RC, Mitchell DG (2002):** MR imaging of hepatocellular carcinoma. *Magnetic Resonance Imaging Clinic of North America*, 10:31–52
 9. **Chen J, Wu M, Liu R, Li S, Gao R and Song B (2016):** Preoperative evaluation of the histological grade of hepatocellular carcinoma with diffusion-weighted imaging: a meta-analysis. *PLoS ONE*, 10(2): e0117661.
 10. **Parikh T, Drew SJ, Lee VS *et al.* (2008):** Focal liver lesion detection and characterization with diffusion-weighted MR imaging: comparison with standard breath-hold T2-weighted imaging. *Radiology*, 246: 812-822.
 11. **Holzapfel K, Bruegel M, Eiber M *et al.* (2011):** Characterization of small (≤ 10 mm) focal liver lesions: Value of respiratory-triggered echo-planar diffusion-weighted MR imaging. *European Journal of Radiology*, (25): 3161-3167.
 12. **Demir OI, Obuz F, Sagol O, Dicle O (2007):** Contribution of diffusion-weighted MRI to the differential diagnosis of hepatic masses, *Diagn Interv Radiol.*, (13): 81-86.
 13. **Hosny IA (2010):** Diffusion MRI of focal liver lesions, *Pakistan Journal Of Radiology*, (20) : 01-07.
 14. **Toeny HC, De Keyzer F (2007):** Extracranial applications of diffusion-weighted magnetic resonance imaging. *Eur Radiol.*, 17:1385–1393.
 15. **Ba-Ssalamah A, Baroud S, Bastati N and Qayyum A (2010):** MR Imaging of Benign Focal Liver Lesions, *Magnetic Resonance Imaging Clinics of North America*, (18): 403-419.
 16. **Bachir T and Dow MK (2010):** Diffusion-weighted MR Imaging of the Liver, *Radiology*, (254): 47- 66.
 17. **Taouli B, Koh DM (2010):** Diffusion-weighted MR imaging of the liver. *Radiology.*, 254(1):47-66.
 18. **Petra GK and Eric J (2010):** Diffusion-weighted Imaging in the Liver, *World Journal Of Gastroenterology*, 16): 1567- 1576.
 19. **Onura MR, Cicekcia M, Kayali A *et al.* (2012):** The role of ADC measurement in differential diagnosis of focal hepatic lesions. *European Journal Of Radiology* , 81(3): 171-176.
 20. **Miller FH, Hammond N, Siddiqi AJ, Shroff S, Khatri G, Wang Y, Merrick LB, Nikolaidis P (2010):** Utility of diffusion-weighted MRI in distinguishing benign and malignant hepatic lesions. *Journal of Magnetic Resonance Imaging*, 1;32(1):138-47.
 21. **Vergara ML, Fernández M and Pereira R (2010):** Diffusion-weighted MRI characterization of solid liver lesions, *Revista Chilena De Radiología*, 16 (1): 510.
 22. **Hanna RF, Aguirre DA, Kased N, Emery SC, Peterson MR, Sirlin CB (2008):** Cirrhosis-associated hepatocellular nodules: correlation of histopathologic and MR imaging features. *Radiographics.*, 28(3):747-69.