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Diffusion Weighted Magnetic Resonance Imaging for the Classification of Focal Liver Lesions as Benign or Malignant

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ABSTRACT

Background & Aims: To assess the role of diffusion weighted imaging sequence (DWI), routinely used in hepatic magnetic resonance imaging (MRI) for the differentiation of focal liver lesions (FLLs) as benign or malignant.

Method: 99 FLLs assessed by liver MRI in 80 patients were included in the present study. All lesions were retrospectively analyzed by two experienced radiologists, independent from each other, who were not aware of the previous results obtained by using different imaging techniques. All included FLLs had a final histological diagnosis or a final diagnosis based on consensus reading by two experienced radiologists and follow-up at 6 months. The FLLs signal was qualitatively appreciated on the b-800 sequences and on the apparent diffusion coefficient (ADC) map. The ADC value of each FLL was measured and the ADC ratio between the ADC value of the assessed FLL and that of the surrounding liver parenchyma were calculated.

Results: The mean ADC value for benign FLLs as assessed by the two independent readers was 1.78 x 10^{-3} and 1.72 x 10^{-3}, respectively. The mean ADC value for malignant FLLs was 0.92 x 10^{-3} for the first reader and 0.95 x 10^{-3} for the second reader. The mean ADC ratio for benign FLLs was 1.91 and 1.85 for the two readers and for malignant FLLs was 0.91 and 0.94, respectively. Using an ADC value lower than 1.024 x 10^{-3} offers a specificity of 100% and a sensitivity of 62.5% for the diagnosis of malignant FLLs. The ADC value is an indicator which is less prone to interobserver variability (correlation of 0.919→1). The ADC ratio has, as the analysis of the ROC curve shows, the best predictive value for differentiation between benign and malignant FLLs. Analysis of the signal intensity on the DWI b-800 image alone is of no significance in differentiating benign from malignant FLLs ($p>0.05$).

Conclusions: The ADC value and the ADC ratio assessed on liver DWI are useful diagnostic tools in the differential diagnosis of benign vs. malignant FLLs. Quantitative methods such as calculating the ADC value or ADC ratio have better diagnostic value than the qualitative techniques.

Key words: focal liver lesions – benign – malignant – magnetic resonance imaging – diffusion weighted imaging – differential diagnosis.

Abbreviations: CCC: cholangiocarcinoma; FLL: focal liver lesion; FNH: focal nodular hyperplasia; HCA: hepatocellular adenoma; HCC: hepatocellular carcinoma; MRI: magnetic resonance imaging; DWI: diffusion weighted imaging; ADC: apparent diffusion coefficient; CT: computed tomography; US: ultrasound; CEUS: contrast-enhanced ultrasound.

INTRODUCTION

The accurate diagnosis of focal liver lesions (FLLs) is important in oncological patients for an accurate staging and in patients without known oncological pathology for avoiding unnecessary liver biopsies. The widespread use of imaging techniques, such as ultrasound (US), computed-tomography (CT) and magnetic resonance imaging (MRI) has led to a constantly increasing detection and diagnosis of FLLs in completely asymptomatic patients [1-4]. The frequency of incidentally detected FLLs varies in the literature between 7.2% and 33% for CT, 10.2% and 34.5% for MRI, and between 2.3% and 6.2% for screening US [5].

Imaging is an important decision-making tool in the diagnosis of FLLs as it can accurately differentiate benign from malignant lesions in most of the cases. The majority of FLLs have a characteristic imaging aspect allowing a confident final diagnosis. In atypical FLLs, follow-up and/or biopsy might be required. In this kind of FLLs, the usage of an

additional imaging tool to differentiate benign from malignant lesions would be helpful. It is worth noting that a fortuitously discovered FLL in a patient without known oncological pathology has over a 95% chance of being benign [3].

Ultrasound has a high sensitivity (Se) for FLLs detection but a low specificity (Sp) for discriminating between different entities (30-60%) [6-8]. By means of contrast-enhanced ultrasound (CEUS), the Sp for benign-malignant differentiation and the final diagnosis of a FLL has significantly increased [9-11]. The accuracy of CEUS for the final diagnosis of FLL is similar to that of contrast-enhanced CT (90.3% CEUS vs. 87.8% for contrast-enhanced CT) [11, 12] and of contrast-enhanced MRI [11, 13].

CT is recommended in patients with known malignancy for staging, and in patients with chronic liver disease or even in otherwise healthy persons for confirmation of a suspected liver tumor detected on US [14]. The limits of CT are represented by small hypovascular FLLs, such as small metastases, difficult to differentiate from simple liver cysts or from small hemangiomas.

MRI is considered the imaging technique with the best Se and Sp for FLL diagnosis [15]. When compared to US and CT, MRI has a better Se and Sp for the diagnosis of hepatocellular carcinoma (HCC); the detection of HCC in the cirrhotic liver is better by means of MRI (72%) as compared to both CT (65%) and US (48%) examinations [16]. For liver metastases, the detection rate of contrast-enhanced imaging techniques (CEUS, CT, and MRI) has offered comparable results [2].

Diffusion weighted imaging (DWI) is a relatively recent non-contrast imaging tool. It has a high contrast resolution allowing accurate FLLs detection and characterization [4]. Its principle is based upon measuring the random motion of water into a voxel of tissue. It provides quantitative information about tissue cellularity, depicting between normal parenchyma and malignant tissues [17]. A recent application of MRI and of DWI in particular, the apparent diffusion coefficient (ADC) value is a measure of the magnitude of diffusion within a tissue. The ADC values are automatically calculated by software and displayed as a parametric map. The ADC measurements are possible for a given region by drawing the regions of interest (ROI) on the ADC map [19, 20]. Usually, malignant FLLs are characterized by a restricted diffusion defined by hyperintensity on the b-800 image and hypointensity on the ADC map. Benign FLLs with fluid content (such as hemangioma or biliary cysts) are characterized by hyperintensity both on the DWI at high b-values, and on the ADC map, behavior known as "T2-shine through" [4]. DWI is an excellent method for the detection and the differential diagnoses of liver metastasis (Se 87% and Sp 97%) compared with triphasic CT (Se 53% and Sp 78%) [18].

The aim of this study was to assess the role of DWI, routinely used in hepatic MRI for the differentiation of FLLs as benign or malignant.

MATERIAL AND METHODS

Patients

One hundred and thirty consecutive liver MRI examinations realized between June 2013 and May 2014 were retrospectively analyzed and a total number of 225 FLLs were detected. The patients had different pathologies: hepatic nodules in a cirrhotic liver, malignancy elsewhere in the body, accidentally discovered FLLS on MRI or US.

Inclusion criteria: the presence of at least one FLL with a histological analysis or consensus MRI reading by two experienced radiologists and a six months follow-up scan, confirming that the lesion has the same aspect and the same size.

Exclusion criteria: the patients without histological proof and without a typical aspect on MRI as defined above (12 patients with 17 FLLs). Also excluded were patients with DWI sequence not done or non-interpretable DWI sequences due to artifacts (18 patients with 27 FLLs). Also, 68 cystic FLLs (most of them simple cysts), lesions smaller than 1 cm (9 FLLs) and FLLs located in the upper left liver lobe (potential artifacts given by the proximity of the heart: 3 FLLs) were excluded (i.e., a total number of 18 patients). Two more patients were excluded because they were outliers - very low ADC value, due to the rich iron content (benign regenerative nodules in cirrhotic livers).

MRI

Protocol

All liver MRI examinations were done using the same machine (Siemens, 1,5T, Erlangen, Germany) and the ADC values were calculated based on three b-values (b-50, b-400 and b-800). A routine MRI protocol was used: T2-haste in coronal and axial planes, TIRM and T1-in and out of phase in axial plane, T2-Trufi in the axial and coronal planes, DWI and ADC map, T1 vibe before and after the injection on contrast media. After injection of contrast media, the liver was scanned in the arterial, portal and late phases; in some examinations, the liver specific contrast media-Gd-EOB-DTPA-(Primovist, Bayer-Shering Pharma, Berlin, Germany) was used: for these cases, a hepatobiliary phase was also obtained.

Image analysis

The following data were recorded for each patient: sex, age, size of the lesion, histologic diagnosis of the assessed FLL. The MRI images were read by two independent readers, experienced radiologists, blinded to each other's results and to the histological diagnosis. They assessed independently the FLLs aspect on DWI at b-800 and on the ADC map, the ADC value and the ADC ratio as described above. A 5-level scale was used to assess the signal at b-800 with 1 meaning hypointensity and 5 strong hyperintensity and a 3-level scale to assess the ADC aspect with 1- hypointensity, 2- isointensity to the liver parenchyma and 3- hyperintensity.

The ADC value of each FLL was calculated within a region of interest (ROI) placed in the center of the assessed FLL, covering more than 50% of its surface. In cases of necrotic FLLs (metastases or HCC), measurements were taken only in the solid part, trying to avoid inclusion within the ROI of any necrotic part. In order to avoid variations of the ADC value in the surrounding liver, measurements were taken approximately at the level of the assessed FLL. The ADC ratio was calculated using the obtained ADC values, the one for the assessed FLL, and the other one for the surrounding liver parenchyma.

For patients with multiple FLLs, each lesion was individually analyzed.

Statistical analysis

The data were first descriptively analyzed. As the normality of the distribution was accepted, the *t* test (Student) was applied either in the Independent Samples (benign vs. malignant), or in the Paired Samples version (inter-observer variability), depending on the features assessed. For ordinal data, comparisons were made using the Spearman correlation coefficient, while for scale data the Pearson coefficient was employed. In the case of ordinal data, comparisons between the two types of FLLs were made, based on nonparametric tests – the median. When qualitative data were analyzed, the Chi-square test, along with the contingency and the uncertainty coefficients were applied (with group proportion comparisons and adjusted p-value – Bonferroni method).

In order to assess the predictability power of the analyzed measures, the ROC curve was constructed and its parameters were estimated: Se, Sp, positive predictive value (PPV), and NPV (negative predictive value).

In all cases, the standard significance level of 5% was used as a starting point (Sig. = p-value < 0.05). However, due to effective values obtained, confidence level was either augmented at 99%, or diminished at 90%.

RESULTS

Patients' characteristics

A total number of 80 patients were finally included in the study: 42 men (52.5%) and 38 women (47.5%). The average age of the patients was of 59.84 ± 11.48 (age range: 21-81 years), being significantly lower (p = 0.038) in women (57.05 ± 12.20) than in men (62.36 ± 10.29).

Analyzed focal liver lesions

A total number of 99 FLLs were finally included in the study, an average of 1.237 FLLs/patient. The number of malignant FLLs in women (23) was significantly lower than that in men (33) (p = 0.025).

The distribution of the 99 analyzed FLLs was: 39 hemangiomas, 4 focal nodular hyperplasias (FNHs), 26 hepatocellular carcinomas (HCCs), 23 liver metastases, and 7 cholangiocarcinomas (CCCs).

The mean size of the assessed FLLs was 32.32 ± 2.01 mm (11-120). The mean size of the benign FLLs was 24.07 ± 17.06 mm and of the malignant FLLs 38.67 ± 28.2 5mm.

Signal qualitative analysis on the b-800 DWI and on the ADC map

The statistical analysis of the qualitative assessment of signal intensity on the b-800 showed a p value of 0.695 (not significant) proving an important overlap in signal intensities of benign and malignant FLLs. Results are summarized in Table I.

The qualitative analysis of signal intensity on the ADC map showed that these parameters can be confidently used in order to diagnose malignant FLLs when they are hypointense on the ADC map. A lesion with lower ADC value than the ADC value measured in the surrounding liver parenchyma is 100% malignant as our results have proved. The Sp of hyperintensity on the ADC map for benign FLLs was 92.1% (Table II).

Table I. Signal intensity of/for benign and malignant focal liver lesions at b-800

Signal intensity	Benign (Coded diagnosis/%)	Malignant (Coded diagnosis/%)	Total/%
Hypo [1]	1a/1.0	2a/2.0	3/3.0
Iso [2]	8a/8.1	6a/6.1	14/14.2
Slightly hyper [3]	18a/18.2	22a/22.2	40/40.4
Moderately hyper [4]	10a/10.1	19a/19.2	29/29.3
Strongly hyper [5]	6a/6.1	7a/7.1	13/13.2
TOTAL /%	43/43.4	56/ 56.6	99/100

Table II. Signal intensity of/for benign and malignant focal liver lesions on the ADC map

Signal intensity	Benign (Coded diagnosis/%)	Malignant (Coded diagnosis/%)	Total/%
Hypo	0a/.0	31b/31.3	31/31.3
Iso	8a/8.1	22b/22.2	30/30.3
Hyper	35a/35.4	3b/3.0	38/38.4
TOTAL/%	43/43.4	56/ 56.6	99/100

ADC value and ADC ratio

The mean ADC value was of 1301.71 ± 578.39 for Reader 1 and 1288.24 ± 554.36 for Reader 2 (Fig. 1). The values of ADC for benign and malignant FLLs, as well as the ADC ratios for benign and malignant FLLs are reflected in Table III. Figure 2 illustrates the ADC-ratio for benign and malignant FLLs.

The ADC values as well as the ADC ratios for benign FLLs proved to be significantly higher than those for malignant FLLs. The mean value of the ADC ratio for malignant FLLs was, for both readers, lower than 1. We can conclude that both the ADC value and the ADC ratio are significantly lower for malignant FLLs, at a confidence level of 99% (p = 0.000). The differences between the ADC value and the ADC ratio for benign and malignant FLLs are shown in Table III.

Inter-observer variability

The study of the inter-observer variability demonstrated a good correlation between the two independent readers. The

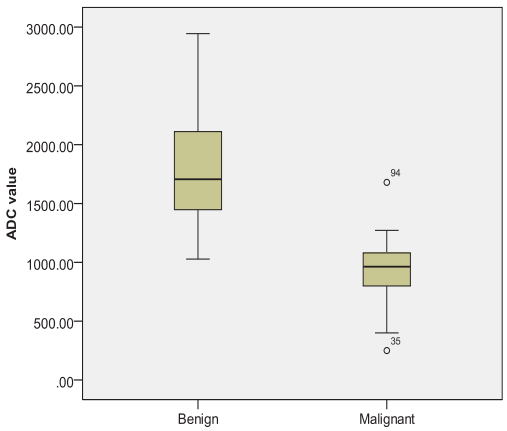

Fig. 1. Box plot illustrating ADC values for benign and malignant lesions.

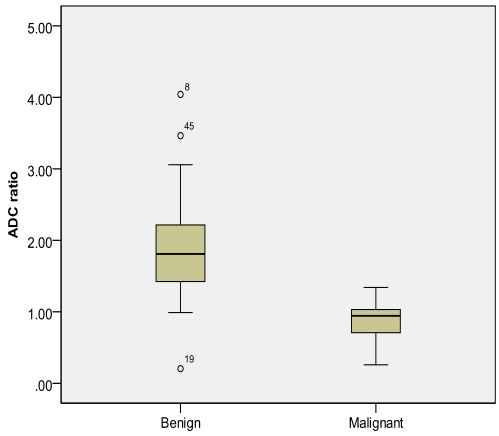

Fig. 2. Box plot illustrating ADC ratios for benign and malignant lesions

correlation coefficients showed a very strong link between the variables, which means nearly similar data interpretation by the two readers. Their value are significant at a significance level of 1% (Sig = p-value = 0.000). The value which was less prone to variations between readers was the ADC value (0.919 → 1). The correlation between readers is illustrated in Table IV. Inter-observer variability was also assessed by using the paired-samples *t* test. The analysis of the ROC curve offered statistically significant results for the qualitative assessment of the signal on the ADC map, for the ADC value and for the ADC ratio. The area under the curve showed high values for all the three variables: 0.932, 0.951, and 0.967, respectively. The ADC ratio had the best predictive value for discriminating between benign and malignant FLLs. The signal analysis of b-800 sequence alone is not a significant diagnostic factor in the prediction of malignancy (AUROC = 0.454, Sig. = 0.433).

The diagnostic value of the qualitative assessment of lesion signal on the ADC map is important for malignant FLLs. If a FLL could be confidently classified as hyposignal on the ADC map, there was a Se of 55.4% and a Sp of 100% for malignancy. When we included both iso- and hyposignal of a FLL, there was a Se of 94.6% for malignancy at a false positive rate of 18.6%.

For the ADC value/FLL, a threshold of 1024 led to a Se for malignancy of 62.5% and a rate of false-positive results of 0%. Using a higher threshold, such as 1040, the Se for malignancy was 66.1%, at a false-positive rate of 5%. The obtained Se, Sp, NPV, and PPV for the ADC values, ADC ratios and for the lesion aspect on the ADC map are illustrated in Table V.

For the ADC ratio we had a false-positive rate of 0 for a cut-off of 0.9854 (every lesion with a lower ADC ratio than 0.9854 was malignant). The Se for malignancy for this cut-off was 57.1%. If we used a cut-off value of 1.22, the Se was 94.6% for a Sp of 95%.

Table IV. The linkage analysis of variables on the regard of correlations (Pearson coefficient for quantitative variables and Spearman for ordinary variables- b-800 and ADC_R)

		N	Correlation	Sig.
Pair 1	B 800 R1 & b 800 R11	99	0.880	0.000
Pair 2	ADC R1 & ADC R11	99	0.857	0.000
Pair 3	ADC value lesion R1 & ADC value lesion R11	99	0.919	0.000
Pair 4	ADC value liver R1 & ADC value liver R11	99	0.766	0.000
Pair 5	ADC ratioR1 & ADC ratio R11	99	0.877	0.000

Table V. Sensitivity, specificity, positive predictive value, and negative predictive value for ADC values

ADC value	Threshold	Se	Sp	PPV	NPV
ADC map	hyposignal	55.4%	100%	100%	63.26%
ADC map	hypo & isosignal	94.6%	81.4	86.88%	92.05%
ADC value/ lesion	1024	62.5%	100%	100%	67.19%
	1040	66.1%	95%	94.51%	68.27%
	1142	84%	90%	91.62%	81.2%
ADC ratio	0.9854	57.1%	100%	100%	64.16%
	1.22	94.6%	95%	96.1%	93.1%

DISCUSSION

In most cases, the differential diagnosis of FLLs is straightforward, as most lesions have a typical imaging aspect. The imaging diagnosis of atypical FLL is difficult, a biopsy being often required. DWI, a recently introduced technique shows promising results for FLLs characterization, being relatively quickly to be performed (two breath hold acquisitions). It does not require contrast agent administration, being performed

Table III. ADC values per lesion and ADC ratio for benign and malignant focal liver lesions

	Diagnosis			
	Total	Benign	Malignant	p-value
	$X \pm \sigma_x$	$X \pm \sigma_x$	$X \pm \sigma_x$	
ADC value lesion R1	1301.71 ± 578.39	1788.47 ± 524.01	927.95 ± 242.74	0.000
ADC value liver_R1	997.55 ± 152.51	960.5116 ± 191.55	1025.98 ± 107.38	0.049
ADC ratio R1	1.35 ± 0.68	1.92 ± 0.64	0.91 ± 0.22	0.000
ADC value lesion R2	1288.24 ± 554.36	1724.21 ± 515.26	953.48 ± 286.58	0.000
ADC value liver_R2	991.84 ± 141.5	962.23 ± 168.65	1014.57 ± 112.9	0.084
ADC ratio R2	1.34 ± 0.65	1.85 ± 0.65	0.94 ± 0.27	0.000
Median size of lesions	32.32 ± 2.01	24.07 ± 17.06	38.67 ± 28.25	0.002

R1: Reader 1; R2: Reader 2.

also in patients with severe renal insufficiency [4]. The most used parameter for quantification in DWI for abdomen assessment is the ADC value requiring at least two b-values (a low and a high b value) [21-24].

Benign fluid FLLs (hemangiomas and biliary cysts) show hyperintensity on the DWI image and also hyperintensity on the ADC map, the pattern known as "T2 shine through". Benign solid FLLs are not or only slightly distinguishable from the liver parenchyma on the DWI at higher b-value and are iso/slightly hyperintense compared to the surrounding liver on the ADC map. Malignant FLLs, such as HCC nodules or metastases, present a pattern known as "restricted diffusion", i.e. hyperintensity on the DWI image and hypointensity on the ADC map [4].

Hemangioma is typically strongly hyperintense on a T2-weighted sequence and enhances in a centripetal way (Fig. 3). The signal intensity of hemangiomas on the ADC map is slightly lower than the signal of biliary cysts [25, 26].

Focal nodular hyperplasia (FNH) is hypervascular in the arterial phase and does not show wash-out on portal or delayed phases. Also it shows a central scar which is typically hyperintense on T2 weighted images (Fig. 4). But as the presence of the central scar is an inconstant finding and some malignant lesions can present similar

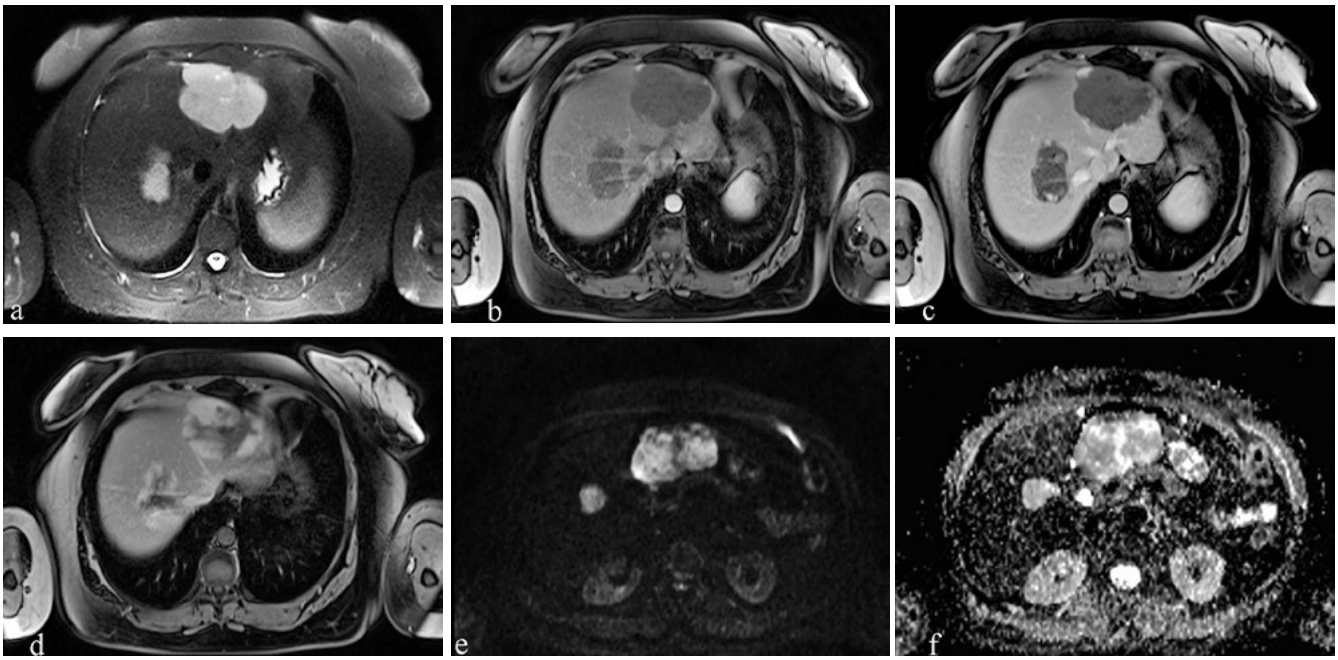

Fig. 3. Liver hemangiomas appearing as strongly hyperintense FLL on the T2 image (malignant lesions have only a slightly higher signal than the surrounding liver on the T2 weighted image) (a) and showing progressive, centripetal fill in on consecutive arterial, portal and late phases (b, c, d). Images of a different patient showing the behavior of two liver hemangiomas on DWI at b-800 (strong hyperintensity) and on the ADC map (hyperintense to the surrounding liver: T2-shine through) (e, f).

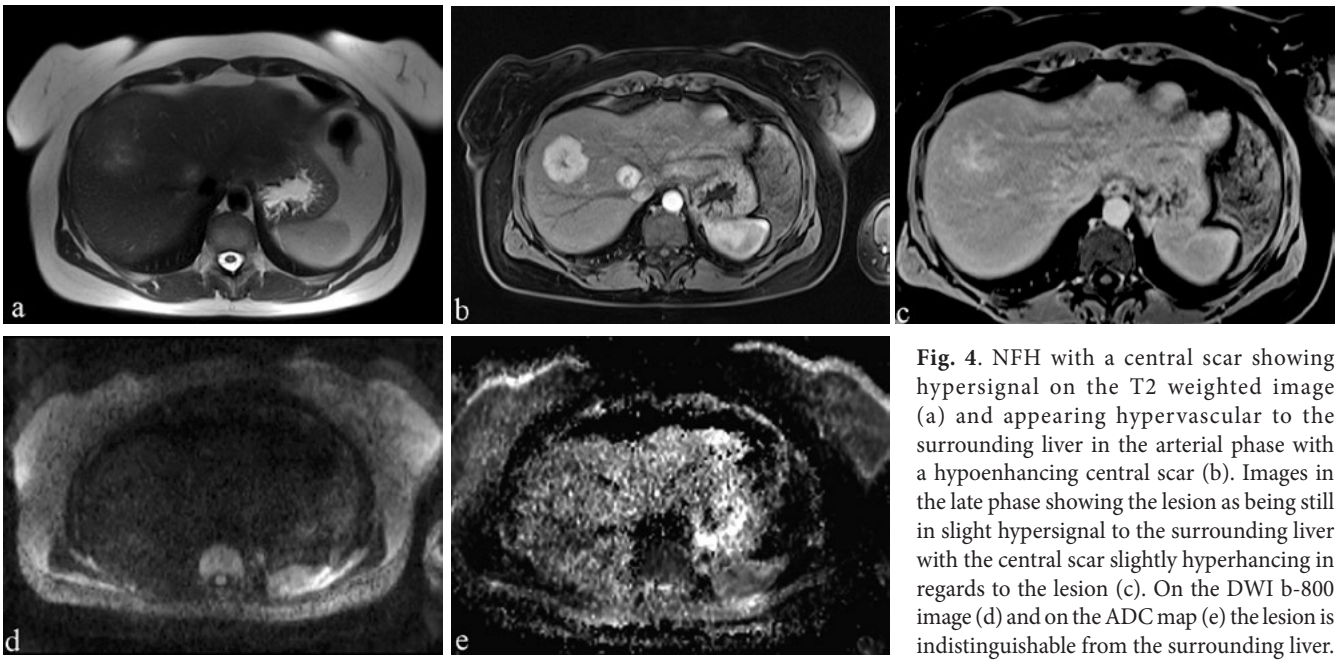

Fig. 4. NFH with a central scar showing hypersignal on the T2 weighted image (a) and appearing hypervascular to the surrounding liver in the arterial phase with a hypoenhancing central scar (b). Images in the late phase showing the lesion as being still in slight hypersignal to the surrounding liver with the central scar slightly hyperhancing in regards to the lesion (c). On the DWI b-800 image (d) and on the ADC map (e) the lesion is indistinguishable from the surrounding liver.

enhancing pattern, e.g. hypervascularity in the arterial phase associated with absence of wash-out in later phases, the use of another diagnostic tool such as DWI can be of great help in differentiating FNHs from malignant FLLs.

Hepatocellular adenomas (HCAs) are infrequent FLLs which in most cases appear in a specifical clinical context: young woman taking oral contraceptives. Hepatocellular adenoma mimics the vascular aspect of FNH.

Previous papers highlighted a significant overlap between the ADC value of benign solid FLLs (such as FNH and HCA) and malignant FLLs [26, 27]. Our series shows a slight difference between the mean ADC values for NFHs (1036), not significantly higher than the mean ADC value for malignant FLLs (953). Our conclusions are limited by the low number of NFHs taken into account (n=4). Regarding HCAs, a recent study sustained that their mean ADC value is significantly higher than that of malignant FLLs [28]. The result needs to be proved by further studies, but additional research is difficult due to the fact that HCAs are rare lesions and obtaining statistically relevant series will be difficult. The meta-analysis by Chen et al. [26] reports no significant differences between ADC values of FNHs and adenomas. There is a possibility that the variations of the ADC values and of the DWI b-800 aspects of liver HCAs are due to different histological subtypes.

Metastases are usually multiple, hypovascular in both arterial and portal phases and have an enhancing peripheral ring, which rapidly washes out. They show restricted diffusion and are hypointense in the hepatobiliary phase after the injection of liver-specific contrast media (Fig. 5). Every FLL with arterial hyperenhancement and portal or late phase wash-out appearing in a cirrhotic liver is considered to be an HCC nodule until proved otherwise [29] (Fig. 6).

DWI is considered to be more useful in the diagnosis of liver metastases than of HCC because metastases have a lower ADC value: they are clearly in hyposignal as compared to the surrounding liver [30]. The HCC diagnosis is even more difficult because the cirrhotic liver shows restricted diffusion itself making HCC lesions difficult to spot on the ADC map. In our series, the mean ADC values of HCC and of metastases were relatively similar, without significant differences in the behavior of HCCs and metastases on the ADC map. Kim et al. [31] showed that hyperintensity on DWI at b-800 can accurately differentiate HCC from the benign hepatic nodules which are hypoattenuating in the hepatobiliary phase. Parsai et al. [32] reported an increased ADC value for CCCs as compared to other malignant FLLs, but further research is required because the number of CCCs in their study was low (n=4). In our series, the mean ADC value (1080) of CCCs (n=7) was also higher than the mean ADC value of malignant FLLs.

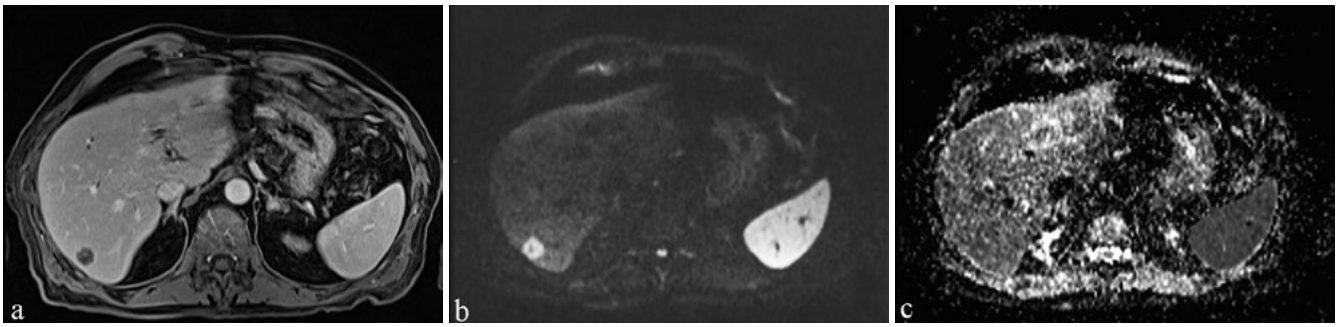

Fig. 5. Liver metastasis from a digestive tumor appearing as hypoenhancing on the portal venous phase after contrast administration (a). The lesion shows restricted diffusion with hyperintensity on the b-800 image (b) and slight hypointensity on the ADC map (c).

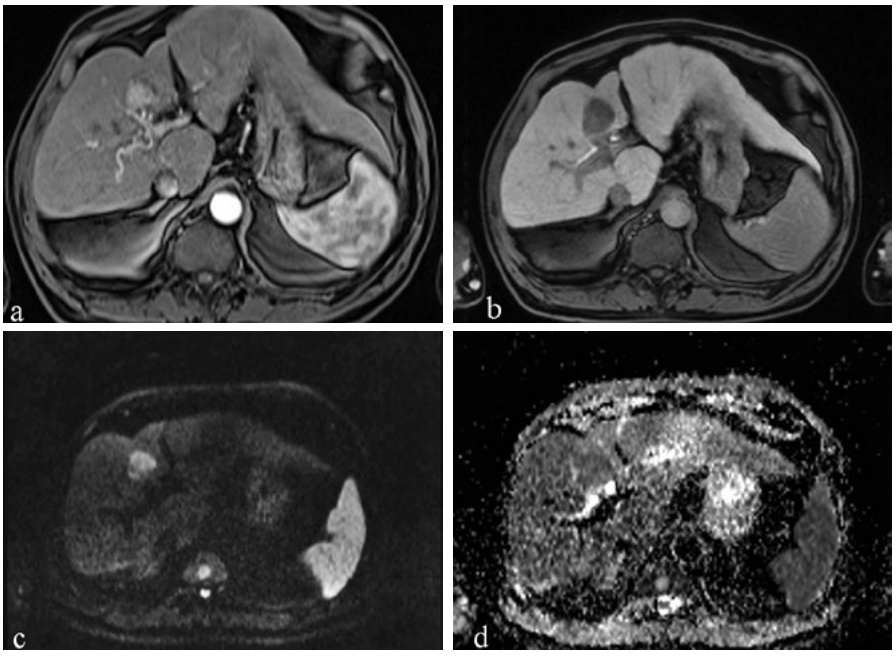

Fig. 6. MRI aspect of an HCC. The lesion is hyperenhancing in the arterial phase (a) and hypointense in regard to the liver parenchyma in the hepatobiliary phase after administration of hepatocyte-specific contrast media (Primovist) (b). The lesion shows restricted diffusion with hyperintensity on the b-800 image (c) and slight hypointensity on the ADC map (d).

Table VI. Sensitivity and specificity for different ADC values used as cut-off in the literature for the diagnosis of malignant focal liver lesions (from reference [21], modified).

	Kim, AJR 2009 [36]	Taouli, Radiology 2003 [22]	Bruegel, Eur Radiol 2008 [34]	Gourtsoyiani, Eur Radiol 2008 [35]	Parikh, Radiology 2008 [37]	Caraiani, (present study)
ADC threshold	1600	1500	1630	1470	1600	1142
Sensitivity	98	84	90	100	74	84
Specificity	80	89	86	100	77	90

Our study proves that the correct qualitative and quantitative analysis of DWI b-800 and ADC maps can improve the differential diagnosis of FLLs differentiating benign from malignant lesions; a lesion with a distinct lower signal on the ADC map than the surrounding liver can be classified as malignant. However, a study by Miller et al. [33] suggests that solid benign FLLs may show restricted diffusion and be hypointense on the ADC map. In our series there were no FNH nodules with either strong hyperintensity on the DWI or with hypointensity on the ADC map. But the small number of FNH nodules included (4) does not allow us to make conclusions about the behavior of FNH nodules on DWI.

The present study shows, in accordance with other published studies, that interpreting the DWI b-800 signal alone is not helpful in differentiating benign from malignant FLLs [4, 21-24, 34]. The quantitative assessment of the ADC value and the ADC ratio has better diagnostic value than the qualitative evaluation of restricted diffusion, i.e. hyperintensity of the FLL on b-800 and hypointensity on the ADC map.

Mean ADC values of the liver and ADC thresholds used in order to separate benign from malignant FLLs vary largely in different papers [22, 34-37]. The great variability in calculating ADC values is due to different acquisition schemes of MRI machines, gradient performances and artifacts reduction methods [21]. In order to avoid these variations we introduced the ADC ratio. The ADC ratio is not so prone to variations related to the machine used or to acquisition technique. The AUROC proves that the ADC ratio has the best predictive power for discriminating between malignant and benign FLLs. As far as we know, our paper is the first to use the ADC ratio for discriminating between benign and malignant lesions in liver pathology. Previously, the ADC ratio was proved to be a good diagnostic tool for malignancy in prostatic cancers [38]. On the other hand, the ADC value is less prone to variations between readers. The ADC ratio might be a better and more objective discriminator between benign and malignant FLLs but this has to be proved by further research.

By comparing our data with the literature (Table VI), differences in Se and Sp are small and mostly due to the usage of different MRI machines, different imaging techniques, and also different b-values used in clinical practice.

The only study with significantly different results from ours is that of Gourtsoyianni et al. [35]. In their series of 39 patients with 37 FLLs the benign lesions were mainly biliary cysts (15 out of 22 FLL) with significantly higher ADC than any other FLL.

Our study has as limitation the retrospective analysis and the fact that not all of the included patients had a histological analysis of the assessed FLL. However, as the vast majority of hemangiomas do not require biopsy for a correct diagnosis, by restricting the FLLs included in the study to lesions confirmed by histology, we would virtually exclude hemangiomas from the study. Also, we excluded from the study iron containing FLLs (regenerative nodules) because of their very low ADC value which would have biased our data.

CONCLUSIONS

The ADC value, the ratio between the ADC value of the lesion and the ADC value of the surrounding liver parenchyma have very good accuracy in differentiating benign from malignant FLLs. Quantitative methods (such as ADC value and ADC ratio) offer better diagnostic accuracy than the qualitative appreciation of signal intensity on the DWI b-800 and on the ADC map. Nevertheless, a FLL clearly hypointense as compared to the surrounding liver on the ADC map is almost certain to be malignant. The ADC ratio has a better sensitivity and specificity for the diagnosis of malignant FLLs than the ADC value.

Conflicts of interest: No conflict to declare.

Authors' contribution: C.C. performed the study concept and design, acquisition and interpretation of data and drafted the manuscript. L.C. had a substantial role in drafting and organizing the manuscript. R.B. supervised the study concept and design. A.L. helped drafting the manuscript and data acquisition. D.I.F. performed data acquisition. D.F. was the second reader, also involved in the statistical analysis. M.G., A.C. and M.D. helped in data acquisition and in creating the database. C.M. performed the statistical analysis.

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REFERENCES

1. Marrero JA, Ahn J, Rajender Reddy K; Americal College of Gastroenterology. ACG clinical guideline: the diagnosis and management of focal liver lesions. Am J Gastroenterol 2014; 109: 1328-1347. doi: 10.1038/ajg.2014.213
2. Dietrich CF, Kratzer W, Strobe D, et al. Assessment of metastatic liver disease in patients with primary extrahepatic tumors by contrast-enhanced sonography versus CT and MRI. World J Gastroenterol 2006; 12: 1699-1705. doi: 10.3748/wjg.v12.i11.1699
3. Dietrich CF, Sharma M, Gibson RN, Schreiber-Dietrich D, Jenssen C. Fortuitously discovered liver lesions. World J Gastroenterol 2013; 19: 3173-3188. doi: 10.3748/wjg.v19.i21.3173

4. Galea N, Cantisani V, Taouli B. Liver lesion detection and characterization: role of diffusion-weighted imaging. J Magn Reson Imaging 2013; 37: 1260-1276. doi: 10.1002/jmri.23947
5. Chiorean L, Cantisani V, Jenssen C, Sidhu PS, Baum U, Dietrich CF. Focal masses in a non-cirrhotic liver: The additional benefit of CEUS over baseline imaging. Eur J Radiol 2015. doi: 10.1016/j.ejrad.2015.05.007
6. Strobel D, Hahn EG, Becker D. Harmonic imaging for improving diagnosis of liver tumors--preliminary report. Z Gastroenterol 2001; 39: 287-289, 292-284. doi: 10.1055/s-2001-12863
7. Hohmann J, Skrok J, Puls R, Albrecht T. Characterization of focal liver lesions with contrast-enhanced low MI real time ultrasound and SonoVue. Rofo 2003; 175: 835-843. doi: 10.1055/s-2003-39923
8. von Herbay A, Vogt C, Haussinger D. Late-phase pulse-inversion sonography using the contrast agent levovist: differentiation between benign and malignant focal lesions of the liver. AJR Am J Roentgenol 2002; 179: 1273-1279. doi: 10.2214/ajr.179.5.1791273
9. Konopke R, Bunk A, Kersting S. The role of contrast-enhanced ultrasound for focal liver lesion detection: an overview. Ultrasound Med Biol 2007; 33: 1515-1526. doi: 10.1016/j.ultrasmedbio.2007.04.009
10. Dietrich CF. Characterisation of focal liver lesions with contrast enhanced ultrasonography. Eur J Radiol 2004; 51 Suppl: S9-S17. doi: 10.1016/j.ejrad.2004.03.034
11. Strobel D, Seitz K, Blank W, et al. Contrast-enhanced ultrasound for the characterization of focal liver lesions--diagnostic accuracy in clinical practice (DEGUM multicenter trial). Ultraschall Med 2008; 29: 499-505. doi: 10.1055/s-2008-1027806
12. Seitz K, Strobel D, Bernatik T, et al. Contrast-Enhanced Ultrasound (CEUS) for the characterization of focal liver lesions - prospective comparison in clinical practice: CEUS vs. CT (DEGUM multicenter trial). Parts of this manuscript were presented at the Ultrasound Dreilandertreffen 2008, Davos. Ultraschall Med 2009; 30: 383-389. doi: 10.1055/s-0028-1109673
13. Seitz K, Bernatik T, Strobel D, et al. Contrast-enhanced ultrasound (CEUS) for the characterization of focal liver lesions in clinical practice (DEGUM Multicenter Trial): CEUS vs. MRI--a prospective comparison in 269 patients. Ultraschall Med 2010; 31: 492-499. doi: 10.1055/s-0029-1245591
14. Winterer JT, Kotter E, Ghanem N, Langer M. Detection and characterization of benign focal liver lesions with multislice CT. Eur Radiol 2006; 16: 2427-2443. doi: 10.1007/s00330-006-0247-9
15. Francisco FA, de Araújo ALE, Oliveira Neto JA, Parente DB. Contraste hepatobiliar: diagnóstico diferencial das lesões hepáticas focais, armadilhas e outras indicações. Radiol Bras 2014; 47: 301-309. doi: 10.1590/0100-3984.2013.1867
16. Yu NC, Chaudhari V, Raman SS, et al. CT and MRI improve detection of hepatocellular carcinoma, compared with ultrasound alone, in patients with cirrhosis. Clin Gastroenterol Hepatol 2011; 9: 161-167. doi: 10.1016/j.cgh.2010.09.017
17. Sinha R, Rajiah P, Ramachandran I, Sanders S, Murphy PD. Diffusion-weighted MR imaging of the gastrointestinal tract: technique, indications, and imaging findings. Radiographics 2013; 33: 655-676. doi: 10.1148/rg.333125042
18. Holzapfel K, Reiser-Erkan C, Fingerle AA, et al. Comparison of diffusion-weighted MR imaging and multidetector-row CT in the detection of liver metastases in patients operated for pancreatic cancer. Abdom Imaging 2011; 36: 179-184. doi: 10.1007/s00261-010-9633-5
19. Mascalchi M, Filippi M, Floris R, Fonda C, Gasparotti R, Villari N. Diffusion-weighted MR of the brain: methodology and clinical application. Radiol Med 2005; 109: 155-197.
20. Kang Y, Choi SH, Kim YJ, et al. Gliomas: Histogram analysis of apparent diffusion coefficient maps with standard- or high-b-value diffusion-weighted MR imaging--correlation with tumor grade. Radiology 2011; 261: 882-890. doi: 10.1148/radiol.11110686
21. Taouli B, Koh DM. Diffusion-weighted MR imaging of the liver. Radiology 2010; 254: 47-66. doi: 10.1148/radiol.09090021
22. Taouli B, Vilgrain V, Dumont E, Daire JL, Fan B, Menu Y. Evaluation of liver diffusion isotropy and characterization of focal hepatic lesions with two single-shot echo-planar MR imaging sequences: prospective study in 66 patients. Radiology 2003; 226: 71-78. doi: 10.1148/radiol.2261011904
23. Koh DM, Padhani AR. Diffusion-weighted MRI: a new functional clinical technique for tumour imaging. Br J Radiol 2006; 79: 633-635. doi: 10.1259/bjr/29739265
24. Papanikolaou N, Gourtsoyianni S, Yarmenitis S, Maris T, Gourtsoyiannis N. Comparison between two-point and four-point methods for quantification of apparent diffusion coefficient of normal liver parenchyma and focal lesions. Value of normalization with spleen. Eur J Radiol 2010; 73: 305-309. doi: 10.1016/j.ejrad.2008.10.023
25. Goshima S, Kanematsu M, Kondo H, et al. Diffusion-weighted imaging of the liver: optimizing b value for the detection and characterization of benign and malignant hepatic lesions. J Magn Reson Imaging 2008; 28: 691-697. doi: 10.1002/jmri.21467
26. Chen ZG, Xu L, Zhang SW, Huang Y, Pan RH. Lesion discrimination with breath-hold hepatic diffusion-weighted imaging: a meta-analysis. World J Gastroenterol 2015; 21: 1621-1627. doi: 10.3748/wjg.v21.i5.1621
27. Wei C, Tan J, Xu L, et al. Differential diagnosis between hepatic metastases and benign focal lesions using DWI with parallel acquisition technique: a meta-analysis. Tumour Biol 2015; 36: 983-990. doi: 10.1007/s13277-014-2663-9
28. Hennedige TP, Hallinan JT, Leung FP, et al. Comparison of magnetic resonance elastography and diffusion-weighted imaging for differentiating benign and malignant liver lesions. Eur Radiol 2015. doi: 10.1007/s00330-015-3835-8
29. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022. doi: 10.1002/hep.24199
30. Kanematsu M, Goshima S, Watanabe H, et al. Detection and characterization of focal hepatic lesions with diffusion-weighted MR imaging: a pictorial review. Abdom Imaging 2013; 38: 297-308. doi: 10.1007/s00261-012-9940-0
31. Kim YK, Lee WJ, Park MJ, Kim SH, Rhim H, Choi D. Hypovascular hypointense nodules on hepatobiliary phase gadoxetic acid-enhanced MR images in patients with cirrhosis: potential of DW imaging in predicting progression to hypervascular HCC. Radiology 2012; 265: 104-114. doi: 10.1148/radiol.12112649
32. Parsai A, Zerizer I, Roche O, Gkoutzios P, Miquel ME. Assessment of diffusion-weighted imaging for characterizing focal liver lesions. Clin Imaging 2015; 39: 278-284. doi: 10.1016/j.clinimag.2014.09.016
33. Miller FH, Hammond N, Siddiqi AJ, et al. Utility of diffusion-weighted MRI in distinguishing benign and malignant hepatic lesions. J Magn Reson Imaging 2010; 32: 138-147. doi: 10.1002/jmri.22235
34. Bruegel M, Holzapfel K, Gaa J, et al. Characterization of focal liver lesions by ADC measurements using a respiratory triggered diffusion-weighted single-shot echo-planar MR imaging technique. Eur Radiol 2008; 18: 477-485. doi: 10.1007/s00330-007-0785-9

35. Gourtsoyianni S, Papanikolaou N, Yarmenitis S, Maris T, Karantanas A, Gourtsoyiannis N. Respiratory gated diffusion-weighted imaging of the liver: value of apparent diffusion coefficient measurements in the differentiation between most commonly encountered benign and malignant focal liver lesions. Eur Radiol 2008; 18: 486-492. doi: 10.1007/s00330-007-0798-4
36. Kim T, Murakami T, Takahashi S, Hori M, Tsuda K, Nakamura H. Diffusion-weighted single-shot echoplanar MR imaging for liver disease. AJR Am J Roentgenol 1999; 173: 393-398. doi: 10.2214/ajr.173.2.10430143
37. Parikh T, Drew SJ, Lee VS, et al. Focal liver lesion detection and characterization with diffusion-weighted MR imaging: comparison with standard breath-hold T2-weighted imaging. Radiology 2008; 246: 812-822. doi: 10.1148/radiol.2463070432
38. Lebovici A, Sfrangeu SA, Feier D, et al. Evaluation of the normal-to-diseased apparent diffusion coefficient ratio as an indicator of prostate cancer aggressiveness. BMC Med Imaging 2014; 14: 15. doi: 10.1186/1471-2342-14-15