

THE ROLE OF THE DIFFUSION SEQUENCE IN MAGNETIC RESONANCE IMAGING FOR THE DIFFERENTIAL DIAGNOSIS BETWEEN HEPATOCELLULAR CARCINOMA AND BENIGN LIVER LESIONS

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Abstract

Background and aim. To assess the role of diffusion weighted imaging sequence (DWI), routinely used in hepatic magnetic resonance imaging (MRI) for the differentiation of hepatocellular carcinoma (HCC) from benign liver lesions.

Methods. A number of 56 liver MRI examinations were retrospectively analyzed independently by two experienced radiologists, blinded to each other results. A total number of 70 Focal Liver Lesions (FLLs) assessed by liver MRI in 56 patients were included in the present study. All lesions were retrospectively analyzed by two experienced radiologists, independently from each other and who were not aware of the previous results given by using different imaging techniques. All included FLLs had a final histological diagnosis, or the final diagnosis was based on consensus reading by two experienced radiologists. The signal of the included FLLs 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 was calculated.

Results. The mean ADC value for benign FLLs as assessed by the two independent readers was 1.75×10^{-3} and 1.72×10^{-3} . The mean ADC value for HCC nodules was 0.92×10^{-3} for the first reader and 0.91×10^{-3} for the second reader respectively. The mean ADC ratio for benign FLLs was 1.81 and 1.84 for the two readers, respectively. The ADC ratio for HCC nodules was 0.91 and 0.91, respectively. 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 FLLs and HCC nodules. Analysis of the signal intensity on the DWI b-800 image alone is of no significance in differentiating benign FLLs from HCC nodules ($p > 0.005$).

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

Keywords: focal liver lesions, hepatocellular carcinoma, magnetic resonance imaging, diffusion weighted imaging, differential diagnosis

Introduction

Globally there is an increasing trend in the number of diagnosed malignant tumors. Each year, about 10.9 million new cases of cancer are diagnosed and there are 6.7 million deaths by cancer. Liver cancer is the third cause of death by tumors worldwide. HCC represents more than 90% of primary liver tumors [1]

The rising incidence and mortality rates of HCC require active surveillance of the patients at risk of developing the disease. The patients at risk are those known with cirrhosis caused by viral hepatitis, alcoholism, autoimmune factors or storage diseases. The surveillance is done by ultrasonography, every six months. The sensitivity of the screening ultrasonography in HCC diagnosis varies in different studies between 58% and 89% [2,3]. A study conducted in Japan, where all ultrasound examinations were performed by experts and on modern devices demonstrates a sensitivity of the ultrasonography above 90%. The nodules discovered by this study had the mean size 1.6 +/- 0.6 mm and only 2% of nodules had diameters larger than 3 cm [4]. Virtually, all nodules were discovered in this study in a therapeutically useful stage.

Magnetic Resonance Imaging (MRI) has, in HCC diagnosis, the role to confirm the results of ultrasonography, to differentiate HCC nodules from benign liver nodules and to exclude the presence of other synchronous nodules undetected at the initial ultrasound examination.

The exclusive application of the vascular criterion (hypervascularization in the arterial phase followed by portal or late washout) is not enough for the diagnosis - not all HCC nodules meet these requirements, especially those of small size. If we define HCC based only on this criterion, we will exclude many nodules that can be treated with a chance of complete cure. A study has shown that the application of the vascular criterion for nodules below 2 cm, demonstrated by two imaging techniques with injection of contrast medium, will lead to a diagnostic sensitivity of 100% but the specificity will fall to under 50% [5]

In this study the signal of HCC nodules on the diffusion sequence as compared to benign lesions was analyzed and we wanted to find out whether the additional information provided by the DWI sequence could improve the specificity of HCC diagnosis, especially in the case of small nodules.

Material and method

Patients

To carry out this study, 130 MRI examinations conducted consecutively during 2013 and 2014 were retroactively read. The total number of lesions was 225. The examinations were performed for different purposes: on the cirrhotic liver in order to specify the existence of HCC nodules, examinations for focal liver lesions discovered incidentally on ultrasound or CT (computed tomography) scans, and examinations performed for the assessment of

other organs or pathologies during which focal liver lesions were incidentally discovered.

A total 56 patients were enrolled in the study, 26 women and 30 men. The average age of patients was 59.13 years. The youngest patient was 21 and the oldest 81 years old.

Inclusion criteria

The inclusion criteria were represented by the presence of at least one focal liver lesion with diagnosis of hepatocellular carcinoma or benign liver lesion, established either by histological examination or by imaging appearance considered typical at the consensus reading of the images by two experienced radiologists with at least 5 years of experience in abdominal radiology.

Exclusion criteria

The exclusion criteria were represented by the lack of a histological diagnosis obtained by puncture biopsy or of an appearance considered typical at the consensus reading of MRI images. Furthermore, the patients who had a histological diagnosis of malignant lesion other than hepatocellular carcinoma (cholangiocarcinoma or metastases) were excluded. Patients without a definite histological diagnosis and a typical imaging appearance were excluded (12 patients with a total of 17 lesions) as well as those with a histological diagnosis / typical imaging appearance of malignant lesions other than hepatocellular carcinoma (30 lesions). Biliary cysts have also been excluded (68 lesions) - their differential diagnosis with malignant liver lesions is normally easy on both ultrasound and MRI; the lesions below 1 cm (9 focal lesions) and the patients in whom the DWI sequence was not obtained or could not be interpreted because of artefacts (30 focal lesions) were not included in this study.

MRI examination protocol

All MRI examinations were performed on the same machine (Siemens, 1.5T, Erlangen, Germany). All patients received the routine protocol that we use in the MRI examination of the upper abdomen: T2-haste in coronal and axial planes, TIRM and in- and out-of-phase T1 in axial plane, T2- Trufi in coronal and axial planes, DWI and ADC map, T1-vibe sequence before and after injecting the contrast medium. After injecting the contrast medium the liver was scanned in arterial, portal and late (parenchymal) phase. In the patients receiving the hepatocyte-specific contrast medium Gd-EOB-DTPA (Primovist, Bayer-Shering Pharma, Berlin, Germany) image acquisition during the hepatobiliary phase was also performed (20 minutes after injection).

ADC was calculated on the basis of three b values: b-0, b-400 and b-800.

Image analysis

The following data were recorded for each patient: sex, date of examination, lesion size, histological diagnosis.

MRI images were independently analyzed by two observers, experienced radiologists, unaware of the

histological diagnosis of the focal liver lesions considered. They assessed independently the features of the focal lesions at b-800 and on ADC map, the value of ADC and ADC ratio (ratio between the ADC value of the lesion and the ADC in the adjacent liver parenchyma). Table I shows the scale used to assess DWI signal at b-800 and Table II the scale according to which ADC was assessed.

Table I. Scale according to which signal intensity at b-800 was assessed.

Scale	Signal intensity
1	Hypointense
2	Isointense
3	Slightly hyperintense
4	Moderately hyperintense
5	Highly hyperintense

Table II. Scale according to which signal intensity on ADC map was assessed.

Scale	Signal intensity
1	Hypointense
2	Isointense
3	Hyperintense

The ADC value of each focal liver lesion (FLL) was calculated with a region of interest (ROI) at the centre of the assessed lesion, covering more than 50% of its surface area. In the case of necrotic lesions, the measurements were made only in the solid portion of them. ADC ratio values were calculated based on the ratio between the ADC value of the lesion and the ADC value in the remaining liver parenchyma.

Results

Distribution of lesions

Lesions in the study: 70 lesions including 44 benign lesions (63%) and 26 HCC nodules (37%) were analyzed in the study. The lesion average/patient was 1.25. 77% of HCC nodules were present in male patients (20 lesions) while only 23% were found in female patients (6 lesions).

The distribution of lesions according to patients' gender is illustrated in Figure 1.

The mean size of the lesions was 31.84 +/- 24.58 mm. The smallest lesion examined had 11 mm in diameter and the most voluminous 120 mm.

Qualitative analysis of the appearance of lesions on b-800 DWI sequence and ADC map

As regards the signal on b-800 DWI sequence for both readers, a significant degree of overlap between the signal of benign lesions and the signal of malignant lesions was noticed. There was no statistically significant relationship between the type of lesion and the type of b800 signal obtained (p -value= 0.705 >> 0.05).

Figure 2 shows the distribution of lesions according to the signal on b-800 DWI sequence in the case of the first reader.

As regards the ADC map reading, most of HCC nodules showed low signal intensity (61.5% - 16 lesions) whereas most benign lesions showed high signal intensity (79.5% -35 lesions). The relationship between the type of lesion and the intensity of ADC signal is statistically significant at the highest level of confidence of 99% (p -value = 0.000 <0.01). The correlation coefficients obtained belonged to the interval [0.7; 1], indicating that the type of lesion determines with high intensity the type of signal. Furthermore, benign lesions were characterized by higher intensity, while HCC lesions were characterized by low intensity of ADC.

Figure 3 shows the distribution of analyzed lesions according to the signal on ADC map. As can be seen, the low signal intensity prevails in HCC nodules while in benign lesions the high signal intensity prevails.

ADC value and ADC ratio

In the case of both the ADC value of lesions and the ADC ratio, the mean values for benign lesions are higher than the ones for HCC lesions, in both readings. The first reader obtained the average value 1752.61 for the ADC of benign lesions and 917.23 for HCC. The mean value of ADC ratio for malignant HCC lesions is double when compared to benign lesions.

Statistically significant differences were found in the case of the ADC value of the lesion and ADC ratio in both readers. In all four cases, p -value = 0.000, lower even than 0.01, so the differences are significant at the maximum confidence level of 99%.

ADC and ADC ratio values are shown in Table III.

Interobserver variability

Interobserver variability study did not find significant differences between the two readings. The correlation coefficients show a strong relationship between variables which means an almost similar interpretation of the data by the two readers. The correlations between the readers were performed using paired sample t-test. The result of the interobserver correlation is shown in Table IV.

The analysis of ROC curve provides statistically significant results as regards the lesion appearance on the ADC map, ADC value and ADC ratio. ADC ratio has the biggest predictive power, with an area of 0.963 under its ROC curve. This variable is followed by the ADC value of the lesion (0.957) and by the ADC signal value (0.926).

Figure 4 illustrates the sensitivity and specificity of the signs in the study, according to the ROC curve.

The specific values of ROC curve are summarized in Table V.

For the ADC ratio, which has proven to have the highest predictive power, up to a threshold of 0.9854, a false-positive rate of 0 was obtained at a sensitivity of 57.7%. The latter maintains at the same value up to a 7%

increase in the false-positive rate, when it becomes 65.4%. ADC ratio threshold value for this level is 1.0048. When the false-positive rate reaches about 10%, the sensitivity becomes 92.3% and the cut-off value of ADC ratio is 1.1977.

In second place among the parameters that we analyzed, in terms of predictive power of HCC tumors, is the ADC value of the lesion. At a false-positive rate of 0,

the sensitivity is 73.1% and the threshold value is 1024. For a false-positive rate of 5%, the sensitivity is 76.9% and the cut-off value 1040.5.

As for the ADC signal, the thresholds are much clearer. Thus, a correct classification of 92.3% of HCC lesions at a false-positive rate of 0% was obtained, when there is low or iso-signal.

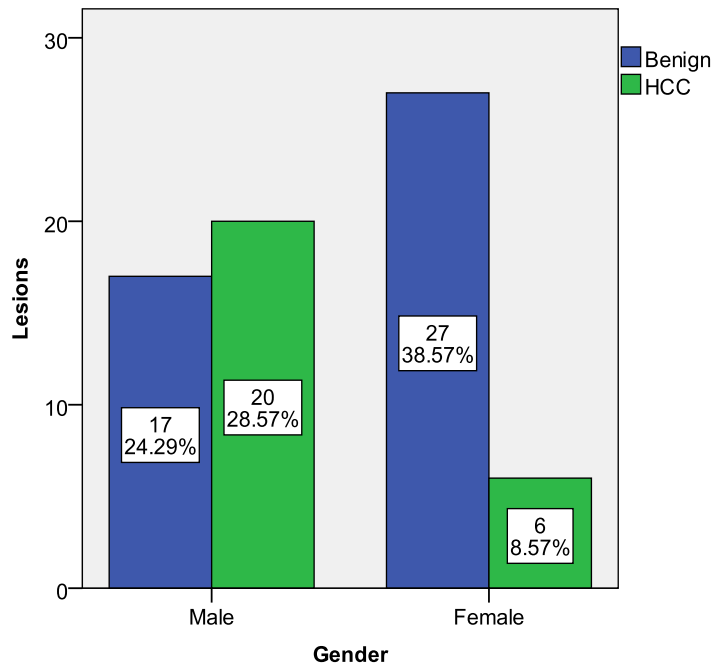


Figure 1. Distribution of lesions (HCC nodules and benign lesions) according to patients' gender.

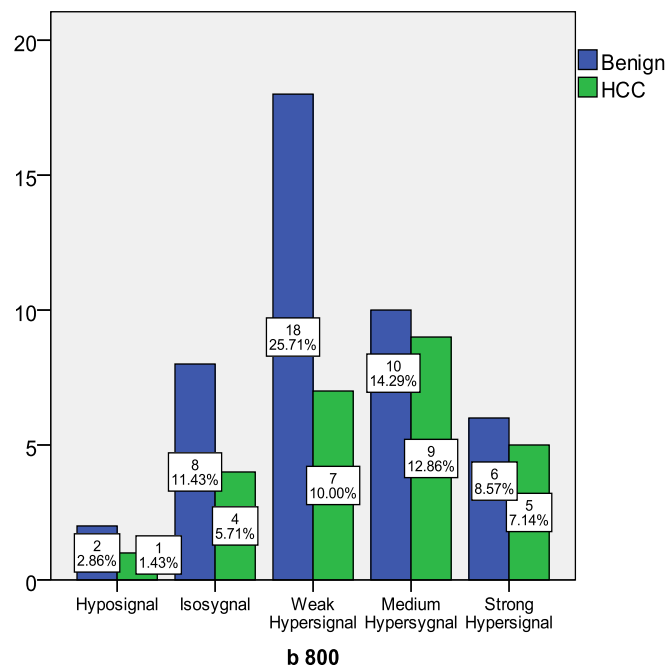


Figure 2. Sample distribution according to b800 signal and the type of lesion for the first reader.

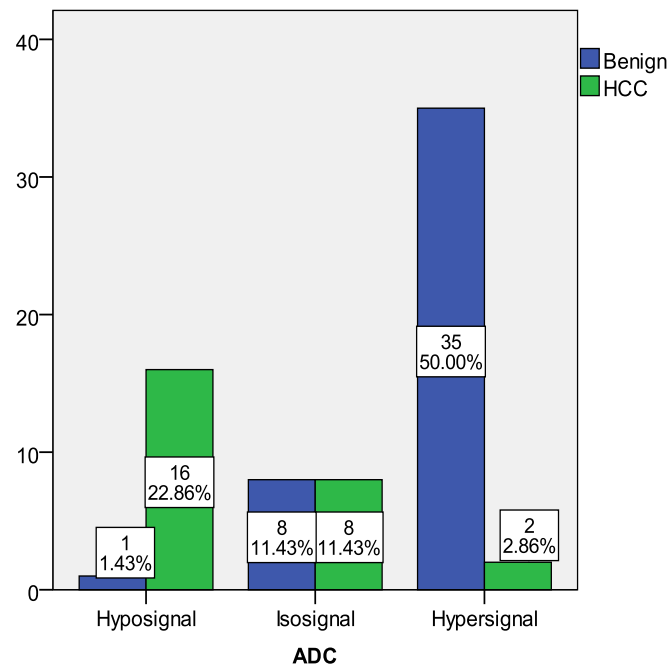


Figure 3. Distribution of lesion signal on ADC map for the first reader.

Table III. ADC and ADC ratio values calculated for the two readers.

Group Statistics					
	comparison_study 2	N	Mean	Std. Deviation	Std. Error Mean
ADC_value_lesion_R1	Benign	44	1752.6136	569.87205	85,91144
	HCC	26	917.2308	256.06113	50,21772
ADC_value_liver_R1	Benign	44	962.0682	189.58761	28,58141
	HCC	26	1009.1154	109.91936	21,55696
ADC_value_lesion_R2	Benign	43	1724.2093	515.26348	78.57694
	HCC	26	901.2692	257.65194	50.52970
ADC_value_liver_R2	Benign	43	962.2326	168.65234	25.71924
	HCC	26	992.1923	117.81579	23.10558
ADC_ratioR1	Benign	44	1.8788	.68517	.10329
	HCC	26	.9128	.23643	.04637
ADC_ratioR2	Benign	43	1.8490	.64707	.09868
	HCC	26	.9162	.24999	.04903
Maximum_size_lesion	Benign	43	24.0698	17.06486	2.60237
	HCC	26	44,6923	29.63615	5.81213

Table IV. Analysis of interobserver variability using the paired sample t-test.

Paired Samples Statistics					
		Mean	N	Std, Deviation	Std, Error Mean
Pair 1	ADC_value_lesion_R1	1460.1739	69	612.01893	73.67842
	ADC_value_lesion_R11	1414.1159	69	591.40360	71.19663
Pair 2	ADC_value_liver_R1	978.8261	69	166.33232	20.02406
	ADC_value_liver_R11	973.5217	69	151.27834	18.21177
Pair 3	ADC_ratioR1	1.5391	69	0.71827	0.08647
	ADC_ratioR11	1.4975	69	0.69923	0.08418

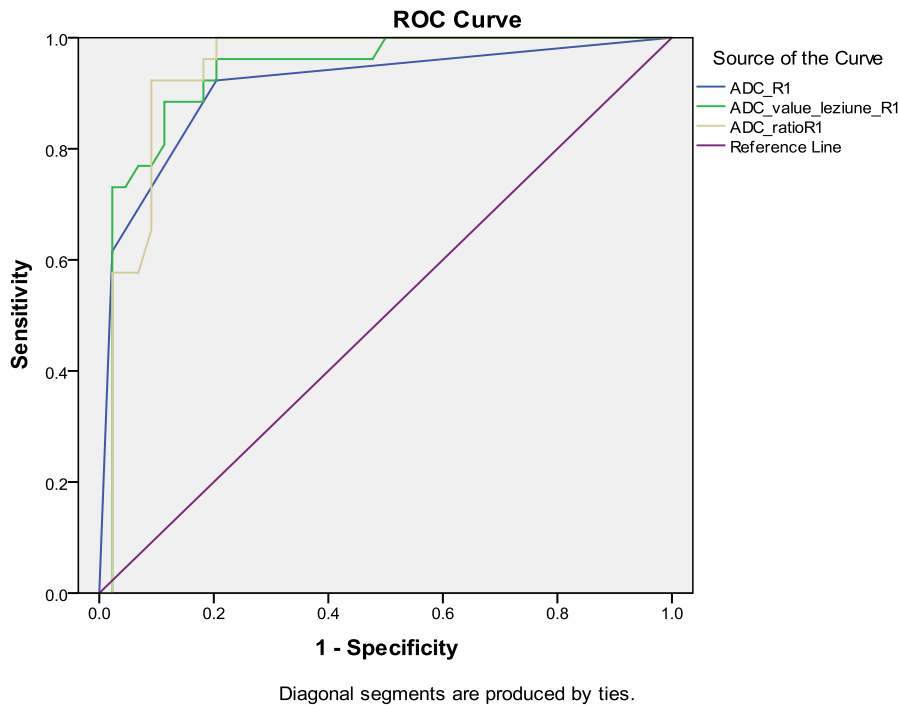


Figure 4. Sensitivity and specificity of differential diagnosis signs HCC / benign lesion studied according to ROC curve.

Table V. Area under the curve - summary.

Test Result Variable(s)	Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
b_800_R1	0.568	0.073	0.350	0.290	0.575
ADC_R1	0,926	0.036	0.000	0.854	0.997
ADC_value_lesion_R1	0,957	0.023	0.000	0.911	1.000
ADC_value_liver_R1	0,566	.069	0.363	0.299	0.569
Maximum_size_lesion	0.757	0,059	0.000	0.127	0.358
ADC_ratioR1	0.963	0.019	0.000	0.925	1.000

^a Under the nonparametric assumption

^b Null hypothesis: true area = 0.5

Discussion

Hepatocellular carcinoma (HCC) is the fifth tumor in the order of incidence worldwide. Its incidence is expected to grow in the coming years because of the hepatitis B and C epidemic and because of the growth in the number of detected cases of liver cirrhosis [6]. Its correct and early diagnosis is important because the progress in surgical and minimally invasive techniques in recent years allows complete healing to take place [7,8]. Furthermore, many masses previously considered inoperable can be operated at present due to progress in surgical technique [9]. HCC imaging aim is to provide morphological information about the lesions (number, size, location) and to provide a differential diagnosis. Failure to diagnose small lesions

leads to delays in diagnosis, delays that will influence the life expectancy of the patient [10].

Imaging has however some limitations in the diagnosis of HCC, which are mainly represented by small-size tumor masses or by masses not meeting the vascular criterion (hypervascularization in the arterial phase followed by washout in the portal or late phase).

Krinsky et al. conducted a study on 71 patients with liver cirrhosis, liver transplant candidates. The MRI examinations performed preoperatively diagnosed below 50% of lesions smaller than 2 cm. A similar study comparing imaging findings with the histopathological analysis of the explanted liver, conducted on a larger number of patients (430) and using computed tomography

as imaging technique describes a 68% sensitivity of the method in the diagnosis of HCC. Freeman conducted a study on 789 patients listed for transplantation who were evaluated prior to the surgical procedure either by CT or MRI which showed an accuracy of only 49% of imaging in the diagnosis of HCC [10,11,12].

At the moment both AASLD (American Association for the Study of Liver Diseases) and EASL (European Association for the Study of the Liver) protocols recommend using the vascular criterion (hypervascularization in the arterial phase followed by washout in the portal or late phase) [13]. These protocols take into account that not in all centers it is possible to assess the patients by MRI, therefore criteria that would be also applicable to computed tomography are also necessary.

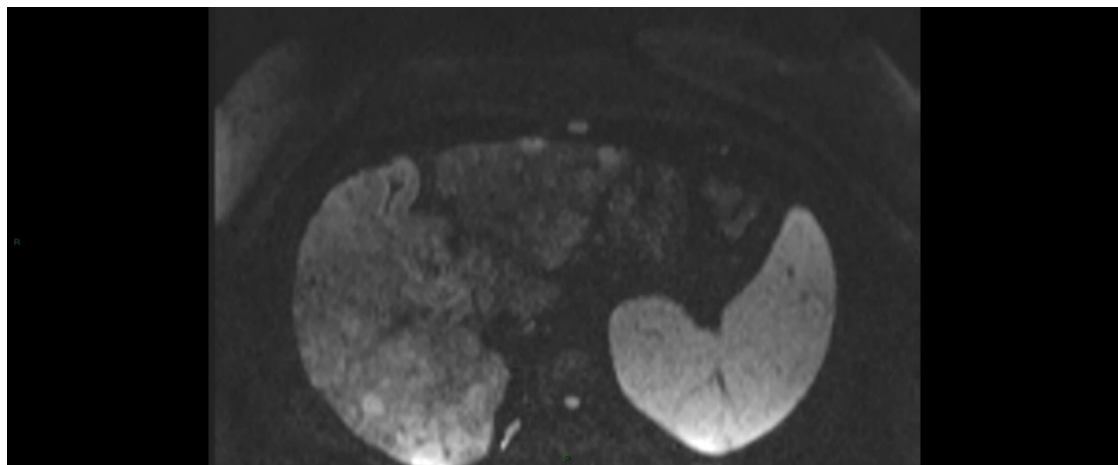
The limitations of the vascular criterion in the diagnosis of HCC are known. Thus, Yoon et al. [14] demonstrate that only 47% of nodules below 3 cm fulfill this criterion. Therefore, the application of this diagnostic criterion only for the detection of HCC will lead either to

a large number of punctures or to the failure to diagnose HCC nodules.

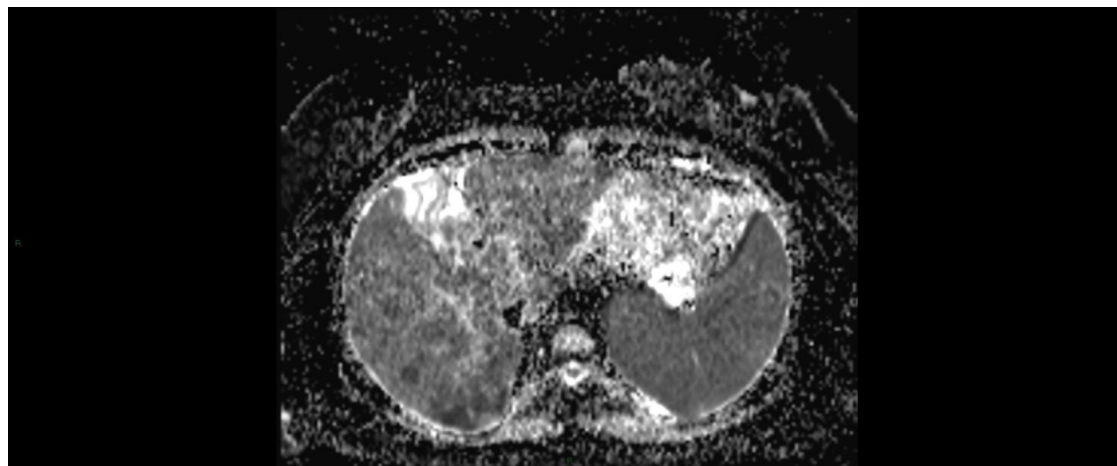
MRI, as opposed to CT, can provide further information useful in the diagnosis of HCC, also in the examination without injection of contrast medium. One of the sequences that can provide information is the diffusion sequence (DWI). It is easy to obtain (two deep breaths, blocked) and it can also be achieved in patients suffering from renal impairment. The parameter most used in abdominal pathology diffusion is ADC value (apparent diffusion coefficient) and its calculation requires at least two values of b constant (a low and a high value of b constant) [15-18]

Classically, malignant lesions will demonstrate a restricted diffusion imaging model with high signal intensity on the DWI sequence at higher b-values and low signal intensity on the ADC map [19].

The appearance of malignant lesions on DWI is shown in Figure 5.



a.



b.

Figure 5. The appearance of HCC nodules on the diffusion sequence (DWI) at b-800 (a) and on the ADC map (b). In a patient with multicentric HCC, the nodules have high signal on DWI sequence and low signal on ADC map. The confluence trend of nodules in the posterior segments of the right hepatic lobe.

The reading of images on ADC map shows a very good specificity of ADC low signal for the diagnosis of malignant lesion (HCC). In this study, besides malignant lesions, there were two lesions that had low signal intensity on the ADC map. Both lesions were regenerative nodules with a high content of iron. None of these nodules had hypervascularization in the arterial-phase examination. Thus, the association between the appearance on the ADC map and the vascular model of the lesion might increase the sensitivity of the diagnosis of HCC.

Studies conducted in the literature demonstrate that DWI is a good way to differentiate malignant and benign lesions with fluid content but there is an overlap between DWI appearance and ADC values, between malignant lesions and solid benign lesions [20-22].

The limitations of our study were:

- there was no delimitation between the types of benign lesions, considering benign lesions as a whole.
- it was conducted retrospectively which made the data liable to errors.

Conclusions

DWI can provide important information in the differential diagnosis of HCC versus benign liver lesions. Within the qualitative assessment, a low signal intensity nodule on the ADC map can be considered almost certainly HCC. The correlation between the information provided by DWI and the data obtained by imaging after injection of the contrast medium results in the improvement of the sensitivity and specificity of the diagnosis of HCC.

DWI sequences and ADC map should necessarily be obtained during the cirrhotic liver MRI examination because it allows us to gather further information on the nature of hepatic nodules.

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