Diffusion-weighted magnetic resonance imaging role in the Hepatocellular carcinoma diagnosis

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LIST OF ABBREVIATIONS

HCC = Hepatocellular Carcinoma

DWI = Diffusion-Weighted Imaging

MRI = Magnetic Resonance Imaging

CT = Computed Tomography

ADC = Apparent Diffusion Coefficient

ROI = Region of Interest

ABSTRACT

Purpose: To assess the relevance of diffusion-weighted imaging (DWI) in the hepatocellular carcinoma (HCC) detection as a stand-alone procedure or in combination to conventional magnetic resonance imaging (MRI).

Methods: Medical records from nineteen patients with pathological confirmation of HCC, who have been submitted to conventional MRI and DWI in a time frame 3 months prior and 3 months after diagnosis, were retrospectively reviewed. For each patient, apparent diffusion coefficient (ADC) values were measured in the HCC lesion, in the liver parenchyma and in the spleen. Tumor ADC and parenchyma ADC, obtained with and without normalization, were compared through paired-samples t-test. Tumor ADC was analyzed according to lobe, size category and acquisition system using the Mann-Whitney test. For sensitivity assessment of DWI and conventional MRI, individually and combined, a contingency table was made.

Results: The calculated DWI sensitivity for HCC detection (47.4%) was lower than conventional MRI sensitivity (68.4%). The highest sensitivity was obtained with the combined reading of both techniques (78.9%).

A statistically significant difference between tumor ADC and parenchymal ADC was found, both for normalized and non-normalized values, with lower values for the HCC lesions.

Comparison of tumor ADC values according to lobe, size and acquisition system did not show a statistically significant difference.

Conclusions: For HCC detection in the setting of liver cirrhosis the use of DWI increases tumor detection compared to conventional MR alone and its use is recommended. This result corroborates other literature reports regarding the added value of DWI in HCC diagnosis, irrespective of the magnetic field strength. Due to the small patient sample of the current series further investigation may be warranted.

Keywords: hepatocellular carcinoma; diagnosis; magnetic resonance imaging; diffusion weighted imaging; apparent diffusion coefficient

RESUMO

Objectivo: Determinar a relevância da ressonância magnética ponderada em difusão (DWI) no diagnóstico do carcinoma hepatocelular (CHC) a título individual e enquanto complemento à ressonância magnética (RM) convencional.

Métodos: Registos médicos de dezanove pacientes com confirmação anatomopatológica de CHC, que tinham sido submetidos a RM convencional e DWI na faixa temporal 3 meses antes e 3 meses depois do diagnóstico, foram revistos retrospectivamente.

Para cada paciente foram medidos os valores do coeficiente de difusão aparente (ADC) na lesão tumoral, no parênquima hepático e no baço. O ADC do tumor e o ADC do parênquima, com e sem normalização, foram comparados através do t-teste para amostras emparelhadas e o ADC do tumor foi analisado de acordo com lobo, categoria dimensional e sistema de aquisição utilizando o teste de Mann-Whitney. Para determinação da sensibilidade da DWI e da RM convencional, individualmente e em conjunto, foi feita uma tabela de contingência.

Resultados: A sensibilidade calculada da DWI (47.4%) foi inferior à da RM convencional (68.4%). Contudo, a sensibilidade calculada quando ambos os métodos foram combinados (78.9%) revelou-se superior.

Foi encontrada uma diferença estatisticamente significativa entre o ADC do tumor e o ADC do parênquima hepático, tanto para os valores não normalizados como para os normalizados, com valores menores registados para as lesões tumorais.

Após comparação dos ADC tumorais de acordo com lobo, categoria dimensional e sistema de aquisição, não foi encontrada uma diferença estatisticamente significativa.

Conclusões: Os resultados do nosso estudo estão em concordância com a literatura mais recente que sustenta o valor adicional da DWI no diagnóstico do CHC. No entanto, as limitações que reconhecemos ao presente trabalho sugerem a necessidade de mais investigação nesta área.

Palavras-Chave: carcinoma hepatocelular; diagnóstico; ressonância magnética; difusão; coeficiente de difusão aparente

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer[1,2] and the most common primary liver malignancy.[1,3,4] It is also the third cause of cancer-related death and a major health problem worldwide due to high rates of morbi-mortality, increasing incidence and limited curative treatment options.[2,4,5]

The probability of occurrence is higher in older male patients, with a peak around 70 years old. In most of the cases there are known risk factors such as cirrhosis, which may be caused by chronic viral hepatitis (B or C), alcohol, alcoholic or non-alcoholic steato-hepatitis (CASH and NASH) or inherited metabolic diseases such as hemochromatosis or alfa-1-antitrypsin deficiency.

High risk patients should be submitted to abdominal ultrasound surveillance with a 6-month periodicity.[6] The diagnosis can be made based on pathology or on non-invasive criteria, such as imaging hemodynamic features (arterial enhancement and delayed washout) detected per use of computed tomography (CT) or magnetic resonance imaging (MRI).

Surgery remains the most effective treatment and the only potentially curative modality;[5] however, many patients do not fulfill the stringent criteria for that option at the time of the diagnosis. Improvement in liver imaging is therefore needed.

Diffusion-weighted magnetic resonance imaging (DWI) is a functional MRI technique that provides image contrast based on differences in the motion of water molecules within tissues, that are affected by intrinsec properties (tissue cell organization, density, microstructure and microcirculation). DWI explores the random motion of water molecules in the body driven by their internal thermal energy, known as Brownian motion.[7,8]

DWI, based on a echo-planar T2-weighted sequence, applies 2 additional (motion-sensitizing) gradients, a dephasing gradient and rephasing gradient, which is known as the

Stejskal-Tanner sequence.[9,10] Tissues with low cellularity allow the free movement of water molecules between the gradient application, causing phase dispersion and a reduction in signal intensity. Tissues with high cellularity will restrict the water molecules diffusion and therefore will show a high sustained signal intensity.[4,7,9,11]

The sensitivity of a DWI sequence for lesion detection and characterization depends mostly on the programmed b-values (s/mm^2); at least 2 b-values must be obtained in order to perform this technique.[7]

The mean value of diffusion due to the movement of intracellular, extracellular and vascular water molecules within an image voxel at different b-values is called apparent diffusion coefficient (ADC, expressed in mm^2/s), the quantitative expression of DWI. ADC maps provide a physiologic estimate of water velocity within a certain tissue and so provides an indirect measure of cellularity; the ADC map, through selection of regions of interest (ROIs), allows the direct measurement of ADC values thus providing quantitative data.[12]

Originally used for the evaluation of intracranial diseases, DWI is expanding and is being applied in several abdominal applications and whole-body MRI.[7–12] There are several studies showing the potential utilization of DWI for HCC diagnosis, characterization and treatment response evaluation; [3,7,11,13,14] most authors agree that it may represent a valuable tool, particularly if associated with conventional MRI.

DWI application to liver lesions study is relatively recent and promising; therefore, it is important to address the subject and study its impact in the setting of liver cirrhosis and HCC detection.

Thus the aim of the present work is to assess the relevance of DWI for HCC diagnosis, both as an isolated technique or combined to the conventional MRI protocol.

MATERIALS AND METHODS

Study population

This retrospective study enrolled a population selected from a pool of patients with histopathological confirmation of hepatocellular carcinoma, used as the gold standard.

The initial group included patients from 11.09.2008 to 11.09.2014 whose pathological report included the expression “hepatocellular carcinoma”. From this pool, n=30 were selected by reviewing the type of imaging procedures applied and cross-linking of the pathological information with the Radiology Department records. The inclusion criteria were: (a) an MR examination containing both conventional MRI and DWI technique, (b) imaging procedures applied at the same imaging session and (c) examinations performed within a time frame of 3 months prior and 3 months after obtaining the histopathological sample that led to HCC diagnosis.

The medical records of patients were requested to the hospital’s archive to further analyse the clinical context and verify the inclusion criteria. In this process 11 patients were excluded due to: (a) previous treatment modalities susceptible of altering the results of image analysis (n=5); (b) use of the expression “hepatocellular carcinoma” in the pathological report out of the intend context (n=5) and (c) lack of data relevant to the study (n=1).

The final study group consisted of 19 patients and included 16 males and 3 females with pathological confirmation of unifocal (n=12) or multifocal (n=7) HCC through biopsy (n=6) or resection specimen analysis (n=13). The mean age at diagnosis was 64 years, ranging from46 to 76 years. In this population, 16 were cirrhotic and from those, 5 had a history of alcohol abuse, 6 had HBV and 3 had HCV.

MRI

The MR images included in this study were obtained using a 1.5T system (n=16) or a 3T system (n=3). The b-values used in the DWI study obtained with the 1.5T system (Magnetom Symphony; Siemens) were b=50 and b=700 and the b-values used in the MRI from the 3T system (Magnetom Trio, a Tim System; Siemens) were b=100 and b=800 s/mm^2.

Image analysis

MR images were analyzed with the 3D Slicer 4.4.0, an open source software platform for the analysis and visualization of medical imaging, intended for research purposes. The different MR sequences were reviewed - T1-w, T2-w, dynamic contrast-enhanced study (arterial, portal and delayed phase) and DWI – being the ADC values measured in the corresponding ADC map.

In cases of multifocal tumors, only a single representative nodule was selected per patient; in cases of unifocal HCC, that selection was made by default.

In order to measure the ADC values of the HCC lesion, of the surrounding parenchyma and of the spleen, the following method was adopted: (a) 3 circular ROIs were placed in each one of the above mentioned areas, totalizing 9 ROIs per image; (b) each circular ROI had a 5 mm radius; (c) the measurements were performed in the ADC map overlaying the DWI images fused and matched with a morphological sequence from another MRI sequence to serve as anatomical reference; (d) vessels were excluded and (e) the ROI placement on the tumor was deposited in the areas visually more hypointense and homogeneous excluding necrosis and/or hemorrhage (Fig.1).

To allow sensitivity determination of conventional MRI, of DWI and of both techniques combined, some criteria was previously defined. On conventional MRI a tumor was considered to be detected if: (a) arterial enhancement was present and (b) wash-out was

observed. Regarding DWI, a nodule was considered to represent HCC if (a) lesion ADC < surrounding parenchyma ADC, (b) hiperintensity of the lesion at high b-value and (c) hipo or isointensity in the ADC map (Fig.2). Two observers performed the readings concurrently and discrepancies were solved by consensus.

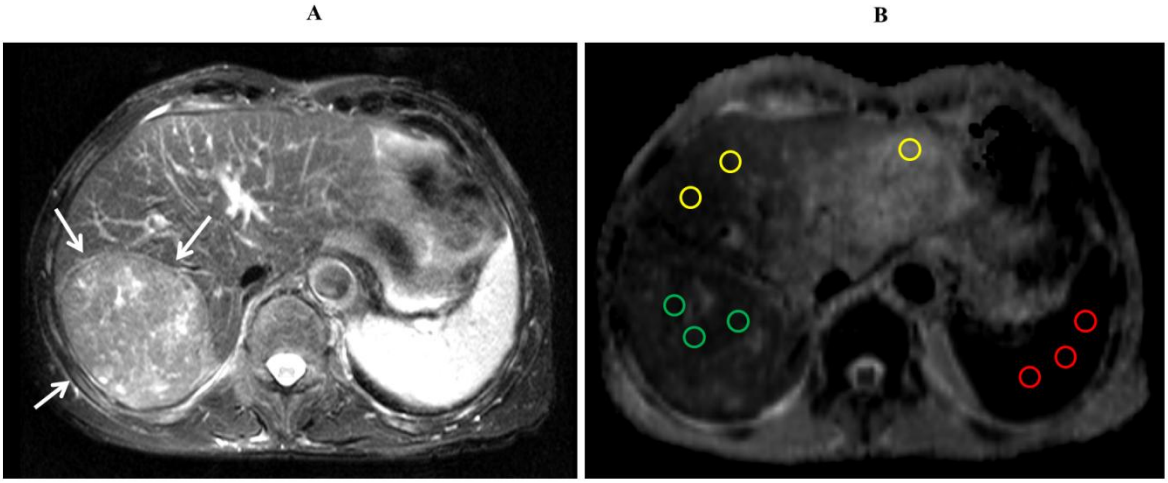

Fig. 1 Exemplification of the sampling method: (A) Conventional MRI sequence used as anatomical reference; (B) ROI placement in the HCC lesion, in the surrounding parenchyma and in the spleen.

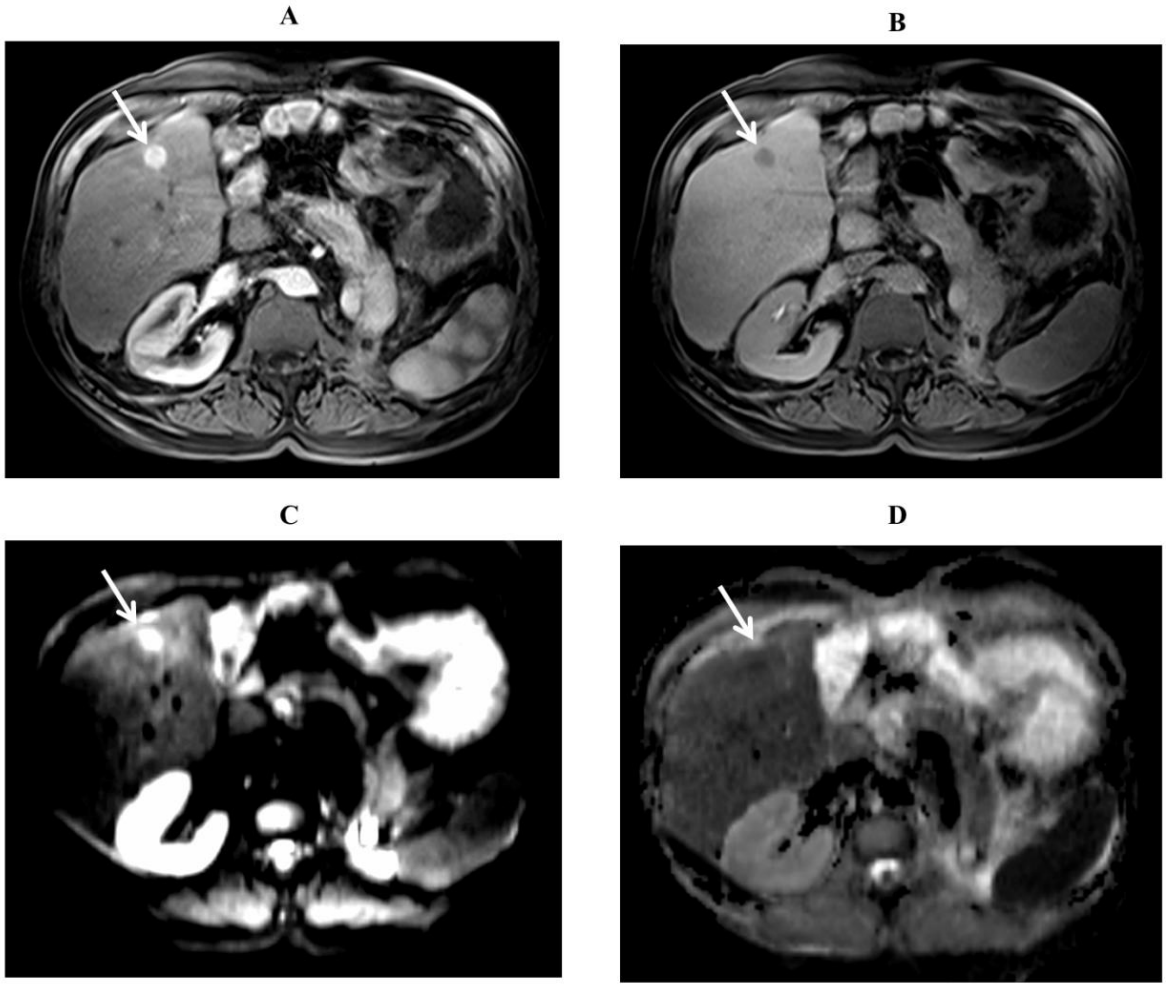

Fig. 2 Example of HCC detected by conventional MRI (A, B) and by DWI (C, D). (A) arterial enhancement ; (B) wash-out; (C) hiperintensity of the lesion at high b-value ; (D) hipo or isointensity in the ADC map.

Statistical analysis

The statistical analysis was performed using SPSS Software (version 20, SPSS).

Descriptive statistics for each variable were available and visual support of the information was also provided (boxplot graphs). To determine the sensitivity of conventional MRI, of DWI and of both methods combined, a contingency table was created.

In order to compare the tumor ADC with the parenchyma ADC, a paired-samples t-test was used. To compare tumor ADC according to lobe, size category and acquisition system non-parametric tests for 2 independent samples - Mann-Whitney test - were performed. For each test a P value of <0.05 was considered to represent a statistically significant difference.

RESULTS

From the n=19 patients of this study, n=13 were correctly diagnosed by conventional MRI, n=9 were identified by DWI and n=15 were detected by both methods combined; this results in a sensitivity of 68.4% for conventional MRI, 47.4% for DWI and 78.9% for a combination of both techniques. The summarized results can be seen in Table 1.

The mean ADC values ($x10^{-3}$ mm^2/s) obtained were: 1.159±0.032 for HCC lesions; 1.242±0.037 for the surrounding parenchyma; 0.815±0.018 for the spleen. The mean ADC values after normalization (Liver ADC / Spleen ADC) were 1.445±0.053 for the tumor lesions and 1.549±0.053 for the nearby parenchyma. The ADC measurements and results of the statistical analysis can be found in Table 2.

The results from the comparison of tumor ADC according to lobar location, largest diameter and magnetic field intensity are summarized in Table 3 and illustrated in Figure 3.

Regarding pathological differentiation of tumors, it was found that: n=1 had a well-differentiated tumor (G1), n=15 had a moderately-differentiated tumor (G2), n=1 had a moderately-undifferentiated tumor (G3) and n=1 had an undifferentiated tumor (G4).

Table 1 Comparison between Conventional MRI and DWI.

Conventional MRI	DWI	Conventional MRI + DWI
+	+	+
+	-	+
+	+	+
+	-	+
-	-	-
+	+	+
-	-	-
+	-	+
+	+	+
+	+	+
+	-	+
+	+	+
-	+	+
-	+	+
+	+	+
-	-	-
+	-	+
-	-	-
+	-	+
n=13	n=9	n=15

		Conventional MRI		
	n=19	+	-	Total:
DWI	+	n=7	n=2	n=9
	-	n=6	n=4	n=10
	Total:	n=13	n=6	

Sensitivity (Conventional MRI) =68.4%

Sensitivity (DWI) =47.4%

Sensitivity (Conventional MRI + DWI) =78.9%

Table 2 Tumor ADC vs Parenchyma ADC.

	Mean ADC ($x10^{-3}$ mm^2/s)	P-value	Liver ADC / Spleen ADC	P-value
	Mean ± SEM		Mean ± SEM	
HCC (n=19)	1.159±0.032	0.040	1.445±0.053	0.045
Parenchyma (n=19)	1.242±0.037		1.549±0.053	

SEM: Standard Error of the Mean

Table 3 Comparison of tumor ADC according to different variables.

	Mean tumor ADC ($x10^{-3}$ mm^2/s)	P-value	Mean tumor ADC / Spleen ADC	P-value
	Mean ± SEM		Mean ± SEM	
Lobe		0.486		0.336
Right lobe (n=13)	1.139±0.032		1.396±0.053	
Left lobe (n=5)	1.201±0.097		1.545±0.147	
Largest diameter		0.745		0.327
≤2 cm (n=2)	1.133±0.063		1.279±0.112	
>2 cm (n=16)	1.156±0.038		1.470±0.061	
Acquisition system		0.291		0.359
1.5T; b-values=50;700 (n=16)	1.177±0.035		1.473±0.061	
3T; b-values=100;800 (n=3)	1.065±0.069		1.292±0.004	

SEM: Standard Error of the Mean

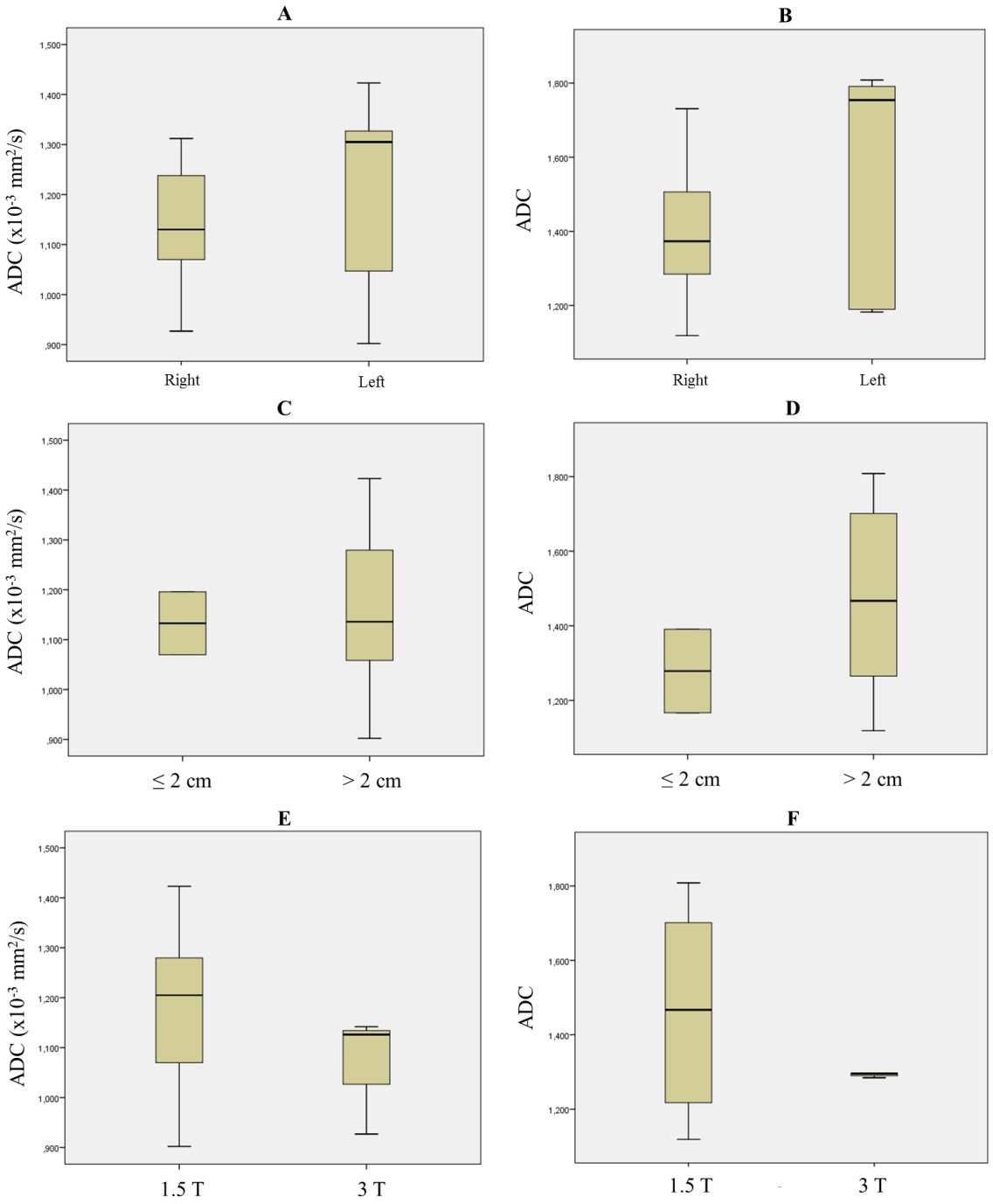

Fig. 3 (A) Boxplots comparing tumor ADC between the right and the left lobe; (B) Boxplots comparing tumor ADC between the right and the left lobe, after normalization of the measures. (C) Boxplots comparing tumor ADC between HCC with 2cm or less and HCC with more than 2 cm of largest diameter; (D) Boxplots comparing tumor ADC between HCC with 2cm or less and HCC with more than 2 cm of largest diameter, after normalization of the measures. (E) Boxplots comparing tumor ADC between the 1.5T and the 3T acquisition system; (F) Boxplots comparing tumor ADC between the 1.5T and the 3T acquisition system, after normalization of the measures.

DISCUSSION

The sensitivity of conventional MRI for HCC diagnosis calculated in this study (68.4%) was superior to the sensitivity of DWI as a stand-alone procedure (47.4%); however, it was verified that the sensitivity of both techniques combined (78.9%) was better than the sensitivity provided by conventional MRI alone. This results suggest the additional value of DWI for the HCC diagnosis, a finding that is in line with previous results published in the literature.[7,14–17]

The mean ADC values ($x10^{-3}$ mm^2/s) obtained in this study (1.159±0.032 for HCC lesions, 1.242±0.037 for the surrounding parenchyma and 0.815±0.018 for the spleen) are also in line with the ADC values reported concerning DWI application in HCC diagnosis.[13,18,19]

The mean tumor ADC was lower than the mean parenchyma ADC (both for non-normalized and for normalized values) providing a quantitative evidence of restriction in DWI in HCC lesions. The difference in mean tumor ADC to the liver parenchyma was statistically significant ($p<0.05$), both for absolute ($p=0.040$) and normalized measurements ($p=0.045$).

Our results corroborate the evidence that DWI is a valuable additional technique for the diagnosis of HCC; the technique constitutes a non-invasive method that requires no contrast media administration,[20] no extra experts and minimal additional scan time[4] so it can be incorporated in routine protocols. For HCC detection and characterization, while conventional MRI focus mostly on tumor neovascularization, DWI evaluates mainly the tumor increased cellular density;[11] the assessment of both is thus additive and may improve the chance of early HCC diagnosis and subsequent decision for earlier curative treatment options.

Kele *et al.*[7] stated that quantitative DWI proved to be helpful in characterization of focal livers lesions such as HCC, but also stated that it should always be used in combination to conventional MRI due the expressive overlap between ADC measurements of benign and malignant lesions. Lim *et al.* [11] advocated that the high efficacy of DWI in diagnosing HCC in cirrhotic patients justifies its inclusion in routine MR protocols. Nevertheless, worldwide standardization of the DWI technique regarding not only the b values but many other parameters is currently lacking, and thus investigation about the real role of DWI in the context of tumor characterization and prediction of treatment response still waits to gain worldwide acceptance.

The present study retrospectively analyzed cases from two different magnetic field systems: one of 1.5T using b-values=50 and 700; the other of 3T using and b-values=100 and 800 s/mm^2. This range of b-values is within the range of values previous described for liver DWI application and ADC measurements. There was no statistically significant difference among them, neither in terms of absolute ADC measurements (p=0.291) or normalized values (p=0.359). However, only n=3 patients had images acquired from the 3T system (b-values=100; 800), which hampers the relevance of the comparison. To better understand the influence of the technical parameters of DWI on lesion detection, a larger population should be targeted and only one variable at a time should be different - for example, to compare 1.5T with a 3T system, the b-values should have been identical. In spite of the absence of significant difference between magnets in the present study, it is known that the use of different technical parameters and b-values may explain some of the discrepancies in ADC measurements reported in the literature [21] - lower b-values may lead to overestimation of the ADC value, due to the contamination of microperfusion to the diffusion component; on the contrary, higher b-values may induce ADC underestimation, due to the increased contribution from the low ADC components and progressive reduction of the signal-to-noise ratio.[7]

Currently there is no clear consensus of which b-value should be used to optimally screen the liver for HCC detection. This factor together with the absence of other DWI parameter standardization [11] makes comparisons difficult and creates uncertainty limiting reproducibility.[8–12,14,19] The attempt to normalize the ADC values using an internal reference is that it remains relatively constant across systems or patients and thus contribute to reduce the variability in ADC measurement;[21,20] the spleen seems an adequate choice for signal intensity normalization, since it maintains a relatively stable ADC value even in case of liver disease. In this study, normalization was obtained through the ratio of liver ADC to spleen ADC. When comparing variables, the results did not differ significantly; therefore, the same conclusions can be applied after normalization, but with increased reproducibility that may allow a better study comparison.

Several publications[17,18,22] emphasize the additional DWI value to MR for the detection of small HCC lesions, both qualitatively and quantitatively. Kele *et al.*[7] reported that DWI is useful for the detection of small HCC in cirrhotic liver and that the technique has a higher sensitivity, specificity and positive predictive value compared to conventional MRI; the explanation included a better lesion to liver contrast as well the effect of background signal suppression from bile ducts and vessels. Di Martino *et al.*[18], however, reported no significant improvement in diagnostic accuracy of small HCC.

In a recent review article, Lim[11] emphasized a less consistent efficacy of conventional MRI for detecting early HCC (≤2 cm) when compared to larger tumors. This is attributable to the less well developed angiogenesis and sinusoidal capilarization seen in small HCC cases compared to larger tumors. Also the parenchymal distortion related to fibrosis and the background of regenerative nodules poses additional problems for HCC recognition.

In this study, no statistically significant difference was found between the ≤ 2 cm HCC and the >2 cm HCC, both in non-normalized (p=0.745) and in normalized (p=0.327) ADC

measures. As in this study only 2 patients had small HCC ≤2cm, no conclusions can be however derived.

Recent studies[4,21–25] point out towards a correlation between the degree of HCC differentiation and ADC values, with lower ADC values registered in poorly-differentiated tumors and higher ADC values in the well-differentiated tumors; the potential for the individual prediction of tumor histological grade remains a discussion subject, with some authors presenting high expectations while others express concerns related to inter-observer variations, lack of standardized procedures and ADC overlap between different tumor grades.[27,28] The existence of such a non-invasive information would certainly contribute to a better patient management in terms of treatment choice and prognostic information;[29] however, in the present study this factor could not be appreciated due to the low interchangeability in tumor grading of the study population.

According to literature, some limitations for the DWI detection of HCC in the left liver lobe could be expected [7,13,15] due to motion and pulsation artifacts arising from the heart, stomach and bowel with tumors located immediately below the diaphragm more prone to escape identification. In the present work, nevertheless, no statistically significant difference ($p<0.05$) could be found between tumors located at the left or right liver lobe in terms of mean ADC measurements both before ($p=0.486$) or after signal intensity normalization ($p=0.336$). We do however believe that the small sample size may not allow to derive firm conclusions concerning this particular aspect.

Our study included only patients whose MRI was assessed no longer than 3 months apart from the pathological confirmation of HCC. Given that the mean volume doubling time of the tumor ranges from 112 to 204 days,[30] the chosen interval seems to be appropriate. There is, however, a great variability of growth patterns and ideally the MR study should been obtain as close as possible to the pathological validation of the resected specimen.

This study has several limitations. The reduced number of patients narrows the chances of sustainable correlations. In fact, an increased number of patients has to be included in order to better understand the influence of each variable of the DWI technique. The retrospective type of analysis may also create a selection bias potentially overestimating the accuracy of the technique. Since all selected patients had a positive diagnosis of HCC (generating only "true positives" or "false negatives"), it was only possible to determine the sensitivity of the methods – their ability to correctly classify an individual as "diseased" - individually and combined. To fully analyze the radiologic contribute of the MR techniques under discussion, a group of " true negatives" will also need to be included in order to allow calculations of specificity, positive predictive value and negative predictive values.[31] A possible future approach to this issue could be a radiologic analysis consisting of patients submitted to liver transplantation where the pathological study of the all liver specimen is available; recognition of HCC tumors in the explanted liver not seen in conventional MR and/or DWI would also be contributive for the analysis of the techniques.

In conclusion, and despite the above mentioned limitations, we do believe that the present study provides evidence to incorporate the DWI technique in the daily MR practice for the study of HCC in the cirrhotic population.

CONCLUSION

The sensitivity of conventional MRI determined in this study was superior to the sensitivity of DWI; however, the calculated sensitivity of the combined reading of conventional MRI and DWI was superior, supporting the routine acquisition of DWI for HCC diagnosis. The major shortcomings are due to the lack of standardization of the DWI technique precluding a generalized assumption of its real clinical impact for the study of cirrhotic patients.

ACKNOWLEGMENTS

I thank Francisco Oliveira, Biomathematics professor and researcher in the Laboratory for Biostatistics and Medical Informatics, for all the help in MRI processing and statistical analysis.

REFERENCES

1. Morise Z, Kawabe N, Tomishige H, Nagata H, Kawase J, Arakawa S, et al. Recent advances in the surgical treatment of hepatocellular carcinoma. World J Gastroenterol. 2014;20(39):14381–92.

2. Daniele G, Costa N, Lorusso V, Costa-Maia J, Pache I, Pirisi M. Methodological assessment of HCC literature. Ann Oncol. 2013;24(Supplement 2):6–14.

3. Ayuso C, Rimola J, García-Criado Á. Imaging of HCC. Abdom Imaging. 2012;37(September 2011):215–30.

4. Heo SH, Jeong YY, Shin SS, Kim JW, Lim HS, Lee JH, et al. Apparent diffusion coefficient value of diffusion-weighted imaging for hepatocellular carcinoma: Correlation with the histologic differentiation and the expression of vascular endothelial growth factor. Korean J Radiol. 2010;11(2):295–303.

5. Lin S, Hoffmann K, Schemmer P. Treatment of Hepatocellular Carcinoma: A Systematic Review. Liver Cancer. 2012;1:144–58.

6. Dufour JF, Greten TF, Raymond E, Roskams T, De T, Ducreux M, et al. EASL – EORTC Clinical Practice Guidelines : Management of hepatocellular carcinoma. J Hepatol. 2012;56:908–43.

7. Kele PG, van der Jagt EJ. Diffusion weighted imaging in the liver. World J Gastroenterol. 2010;16(13):1567–76.

8. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: Applications and challenges in oncology. Am J Roentgenol. 2007;188(June):1622–35.

9. Sandrasegaran K. Functional MR imaging of the abdomen. Radiol Clin North Am. 2014;52:883–903.

10. Attariwala R, Picker W. Whole body MRI: Improved lesion detection and characterization with diffusion weighted techniques. J Magn Reson Imaging. 2013;38:253–68.

11. Lim KS. Diffusion-weighted MRI of hepatocellular carcinoma in cirrhosis. Clin Radiol. The Royal College of Radiologists; 2014;69(1):1–10.

12. Graessner J, Ing D. Frequently Asked Questions : Diffusion-Weighted Imaging (DWI). 2011;84–7.

13. Bruegel M, Holzapfel K, Gaa J, Woertler K, Waldt S, Kiefer B, 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;18:477–85.

14. Wu L-M, Xu J-R, Lu Q, Hua J, Chen J, Hu J. A pooled analysis of diffusion-weighted imaging in the diagnosis of hepatocellular carcinoma in chronic liver diseases. J Gastroenterol Hepatol. 2013;28:227–34.

15. Holzapfel K, Eiber MJ, Fingerle A a., Bruegel M, Rummeny EJ, Gaa J. Detection, classification, and characterization of focal liver lesions: Value of diffusion-weighted MR imaging, gadoxetic acid-enhanced MR imaging and the combination of both methods. Abdom Imaging. 2012;37(May 2011):74–82.

16. Vandecaveye V, De Keyzer F, Verslype C, Op de Beeck K, Komuta M, Topal B, et al. Diffusion-weighted MRI provides additional value to conventional dynamic contrast-enhanced MRI for detection of hepatocellular carcinoma. Eur Radiol. 2009;19:2456–66.

17. Park MS, Kim S, Patel J, Hajdu CH, Richard RK, Mannelli L, et al. Hepatocellular carcinoma: Detection with diffusion-weighted versus contrast-enhanced magnetic resonance imaging in pretransplant patients. Hepatology. 2012;56:140–8.

18. Di Martino M, Di Miscio R, De Filippis G, Lombardo CV, Saba L, Geiger D, et al. Detection of small (≤2 cm) HCC in cirrhotic patients: Added value of diffusion MR-imaging. Abdom Imaging. 2013;38(July):1254–62.

19. Kilickesmez O, Bayramoglu S, Inci E, Cimilli T. Value of apparent diffusion coefficient measurement for discrimination of focal benign and malignant hepatic masses. J Med Imaging Radiat Oncol. 2009;53:50–5.

20. El-Hariri M, Ali TFT, Hussien HIM. Apparent diffusion coefficient (ADC) in liver fibrosis: Usefulness of normalized ADC using the spleen as reference organ. Egypt J Radiol Nucl Med. Elsevier B.V.; 2013;44(3):441–51.

21. Do RKG, Chandanara H, Felker E, Hajdu CH, Babb JS, Kim D, et al. Diagnosis of liver fibrosis and cirrhosis with diffusion-weighted imaging: Value of normalized apparent diffusion coefficient using the spleen as reference organ. Am J Roentgenol. 2010;195(September):671–6.

22. Chen M-L, Zhang X-Y, Qi L-P, Shi Q-L, Chen B, Sun Y-S. Diffusion-weighted images (DWI) without ADC values in assessment of small focal nodules in cirrhotic liver. Chin J Cancer Res. 2014;26(1):38–47.

23. Nishie A, Tajima T, Asayama Y, Ishigami K, Kakihara D, Nakayama T, et al. Diagnostic performance of apparent diffusion coefficient for predicting histological grade of hepatocellular carcinoma. Eur J Radiol. 2011;80:29–33.

24. Nakanishi M, Chuma M, Hige S, Omatsu T, Yokoo H, Nakanishi K, et al. Relationship Between Diffusion-Weighted Magnetic Resonance Imaging and Histological Tumor Grading of Hepatocellular Carcinoma. Ann Surg Oncol. 2012;19:1302–9.

25. Saito K, Moriyasu F, Sugimoto K, Nishio R, Saguchi T, Akata S, et al. Histological grade of differentiation of hepatocellular carcinoma: Comparison of the efficacy of

diffusion-weighted MRI with T2-weighted imaging and angiography-assisted CT. J Med Imaging Radiat Oncol. 2012;56:261–9.

26. Chang WC, Chen RC, Chou C Te, Lin CY, Yu CY, Liu CH, et al. Histological grade of hepatocellular carcinoma correlates with arterial enhancement on gadoxetic acid-enhanced and diffusion-weighted MR images. Abdom Imaging. 2014;(May):1202–12.

27. Sandrasegaran K, Tahir B, Patel a., Ramaswamy R, Bertrand K, Akisik FM, et al. The usefulness of diffusion-weighted imaging in the characterization of liver lesions in patients with cirrhosis. Clin Radiol. 2013;68(7):708–15.

28. Nasu K, Kuroki Y, Tsukamoto T, Nakajima H, Mori K, Minami M. Diffusion-Weighted Imaging of Surgically Resected Hepatocellular Carcinoma : Imaging Characteristics and Relationship Among Signal Intensity, Apparent Diffusion Coefficient, and Histopathologic Grade. 2009;(August):438–44.

29. Forner A, Díaz-González Á, Liccioni A, Vilana R. Prognosis prediction and staging. Best Pract Res Clin Gastroenterol. 2014;28:855–65.

30. Trevisani F, Cantarini MC, Wands JR, Bernardi M. Recent advances in the natural history of hepatocellular carcinoma. Carcinogenesis. 2008;29(7):1299–305.

31. Parikh Rajul , Mathai Annie, Parikh Shefali, Sekhar G Chandra TR. Understanding and using sensitivity, specificity and predictive values. Indian J Ophthalmol. 2008;56(1):45–50.