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Original Research

Relative Contribution of Apparent Diffusion Coefficient (ADC) Values and ADC Ratios of Focal Hepatic Lesions in the Characterization of Benign and Malignant Lesions

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ABSTRACT
Objective: The aim of the present study was to compare relative contribution of apparent diffusion coefficient (ADC) values and ADC ratios (ADC of the lesion/ADC of the neighboring hepatic parenchyma) in the differential diagnosis of benign and malignant focal hepatic lesions.
Methods: A total of 80 patients with 94 focal hepatic mass lesions (mean size, 5.3 cm; range, 1–12 cm) were evaluated retrospectively using 3 Tesla magnetic resonance imaging (MRI). The ADC values and ADC ratios were compared for different types of lesions to obtain ideal cut-off values.
Results: Mean ADC values (±SD) were 0.93±0.15, 0.95±0.48, 1.44±0.39, 1.88±0.50, and 2.94±0.75×10^{-3} mm^2/sec respectively for hepatocellular carcinoma (HCC), metastasis, focal nodular hyperplasia (FNH), hemangioma, and cysts with a mean ADC value of 1.97±0.68 for benign lesions and 0.94±0.29×10^{-3} mm^2/sec for malignant lesions. The ADC ratios of benign and malignant lesions were 1.50±0.53 and 0.80±0.20×10^{-3} mm^2/sec, respectively, and the ADC values and ratios were found to differ significantly between benign and malignant lesions. Assuming a cut-off ADC value of 1.26×10^{-3} mm^2/sec for discrimination of benign and malignant lesions provided 94% sensitivity and 92% specificity. Sensitivity of 85% and specificity of 92% were found when a cut-off ADC ratio of 0.90×10^{-3} mm^2/sec was used for discrimination of benign and malignant lesions. Compared to ADC values, ADC ratios were found to have lower sensitivity and higher specificity for discriminating between benign and malignant lesions.
Conclusion: Diffusion weighted imaging is used in combination with conventional MRI, and it enhances the diagnostic accuracy of MRI in the characterization of benign and malignant lesions.
Keywords: Diffusion weighted imaging, hepatic mass, echo-planar imaging

INTRODUCTION

Diffusion is the random microscopic motion of water molecules within the tissue. Diffusion weighted imaging (DWI) measures the movements of water molecules in extracellular, intracellular, and intravascular spaces (1). DWI is extremely sensitive to motion, and respiratory, cardiac, and peristaltic physiological movements impair the image quality considerably and make the evaluation more difficult. For this reason, DWI has been limited to brain imaging for many years. The development of echo-planar imaging (fast gradient echo sequence), a fast magnetic resonance imaging (MRI) method, eliminated prolonged imaging time and associated artifacts observed with conventional sequences and allowed use of DWI for evaluation of abdominal organs (2). The apparent diffusion coefficient (ADC) value is a mathematical representation of diffusion obtained by mapping signals lost after applying a diffusion gradient (3). ADC values are often calculated automatically by clinical MR systems. While lower ADC values indicate malignancy (hypointense with ADC, hyperintense with DWI), higher ADC values favor benignancy (hyperintense with ADC, hypointense or hyperintense with DWI). On the other hand, the ADC ratio is calculated by dividing the ADC value of a lesion by the ADC value of the adjacent liver parenchyma, and it provides more comprehensive results by eliminating differences in devices, technical approaches, and variability resulting from using different b values.

The aim of our study was to assess relative contributions of ADC values and ADC ratios to the characterization of benign and malignant hepatic lesions.

METHODS

From January 2016 to November 2016, the DWI was included in routine MRI scans. The retrospective study was performed after obtaining the approval from Gaziantep University Medical Ethics Committee with a decision number 2017/43. Patients were informed of the procedures to be used in the study, and they signed an informed consent statement.

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Ninety-four lesions detected using the combined method in a total of 80 patients (37 males, 43 females) with primary or metastatic hepatic tumor or benign lesions were studied. The mean age of patients was 53 years (range, 11–89 years). Nine patients had simple hepatic cysts diagnosed with typical ultrasound (US) and MRI findings. Hemangioma (n=41) was confirmed by MRI and/or archived computed tomography (CT) image characteristics and typical patterns of contrast enhancement. Cases of focal nodular hyperplasia (n=10) were diagnosed on the basis of iso-hyperintense appearance obtained with a liver-specific contrast agent following the administration of 0.25 mmol/mL gadoxetic acid disodium (Primovist; Bayer) in the late phases compared to the liver parenchyma and typical dynamic images. Eleven metastatic masses were lesions diagnosed as metastatic, showing growth during routine follow-up in patients with known primary malignancy (4 cases of breast cancer, 4 cases of colon cancer, 1 cervical cancer, 1 endometrial cancer, 1 renal cell carcinoma). Out of 23 cases with lesions associated with primary hepatocellular tumors, 10 were diagnosed by histopathological features and by typical dynamic CT–MRI image characteristics in others. Overall, the diameter of 94 mass lesions ranged between 1 and 12 cm with a mean diameter of 5.3 cm. Eighty patients underwent upper abdominal MRI and DWI with 3 Tesla MR (Ingenia 3.0T; Philips Healthcare, Best, The Netherlands) using phased-array coils. Routine examination protocol consisted of axial T2-weighted TSE (Turbo Spin Echo) with fat suppression, gradient echo mode in in-phase and in opposed phase with T1-weighting, contrast-enhanced dynamic T1-weighted imaging. Diffusion weighted MR examination was performed before obtaining slices with contrast material. Diffusion weighted sequence (Repetition Time [TR]/Echo Time [TE], 1121/57; flip angle, 90°; slice thickness, 5 mm; Field of View [FOV], 250–202–230) was obtained by applying diffusion-sensitive gradients in all three directions (x,y,z) at two different b values (b=0 and b=600 mm^2/s) to single-shot echo-planar sequence in axial plane. The first series of the sequential image set consisted of echo-planar spin echo T2-weighted images (b=0); the next three series contained images with diffusion-sensitive gradients applied on the first series in x, y, and z directions with a b value of 600 mm^2/sec, and the final series consisted of isotropic images calculated from projection of diffusion vectors in three directions. Isotropic images were images created by the device by calculating the cube root of the product of signal intensities obtained in x, y, and z directions by excluding directionally sensitive signal changes. ADC maps for isotropic images were automatically constructed by the device, and average ADC values of all lesions were measured from these maps. Measurements were obtained by positioning a circular region of interest (ROI) with an approximate diameter of 1 cm on the lesions. For greater lesions, three separate ROI measurements on the same cross-section were averaged. For lesions with a heterogeneous internal structure, measurements were obtained from solid parts that showed contrast enhancement in conventional sequences and contrast-enhanced sections. The ADC value of lesions with a diameter of 1 cm was calculated using a single ROI. ADC values of normal hepatic parenchyma were also measured for 80 patients. An average ADC value was calculated from three sequential sections with measurements from the posterior segments of the right lobe of the liver by establishing 1 cm ROIs at three different locations for each section. ADC values were hepatic focal masses determined and compared between benign and malignant lesions.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Version 22.0, IBM Corp.; New York, USA) software package. Since the number of patients was sufficient in both groups (benign and malignant), comparison between the groups was done using the independent two-sample t-test. A p-value below 0.05 was considered significant. The Mann–Whitney U test was used to compare lesions because the number of cysts, hemangiomas, focal nodular hyperplasia (FNH), hepatocellular carcinoma (HCC), and metastatic lesions was insufficient and/or did not show normal distribution within groups. Additionally, for discrimination between benign and malignant lesions, cut-off values for ADC values and ADC ratios were evaluated by the Receiver operating characteristic ROC analysis, and sensitivity, specificity, and cut-off values were estimated.

RESULTS

The ADC values were 0.94±0.15, 0.95±0.48, 1.44±0.39, 1.88±0.50, and 2.94±0.75×10^{-3} mm^2/sec, respectively, for HCC, metastases, FNH, hemangiomas, and cysts, and the average ADC values were 1.96±0.68×10^{-3} mm^2/sec for benign lesions and 0.94±0.29×10^{-3} mm^2/sec for malignant lesions (Table 1).

Table 1. The number of lesions, average ADC of the mass, parenchymal ADC, and ADC ratios by the type of mass lesion

Type of mass lesion	Number of lesions	Average ADC value of the lesion mass (×10^{-3} mm^2/s)	Average parenchymal ADC value (×10^{-3} mm^2/s)	Average ADC ratio (×10^{-3} mm^2/s)
Benign	60	1.96±0.68	1.32±0.19	1.50±0.53
Simple cyst	9	2.94±0.74	1.38±0.29	2.17±0.48
Hemangioma	41	1.88±0.50	1.28±0.14	1.47±0.45
FNH	10	1.44±0.39	1.41±0.23	1.02±0.24
MALIGN	34	0.94±0.29	1.21±0.18	0.80±0.20
HCC	23	0.94±0.15	1.22±0.19	0.78±0.13
Metastasis	11	0.95±0.48	1.18±0.17	0.84±0.30

ADC: apparent diffusion coefficient; FNH: focal nodular hyperplasia; HCC: hepatocellular carcinoma

Figure 1. a-c. Boxplots for comparison between benign and malign groups: (a) mass ADC values; (b) adjacent hepatic parenchyma ADC values; (c) ADC ratio

ADC: apparent diffusion coefficient

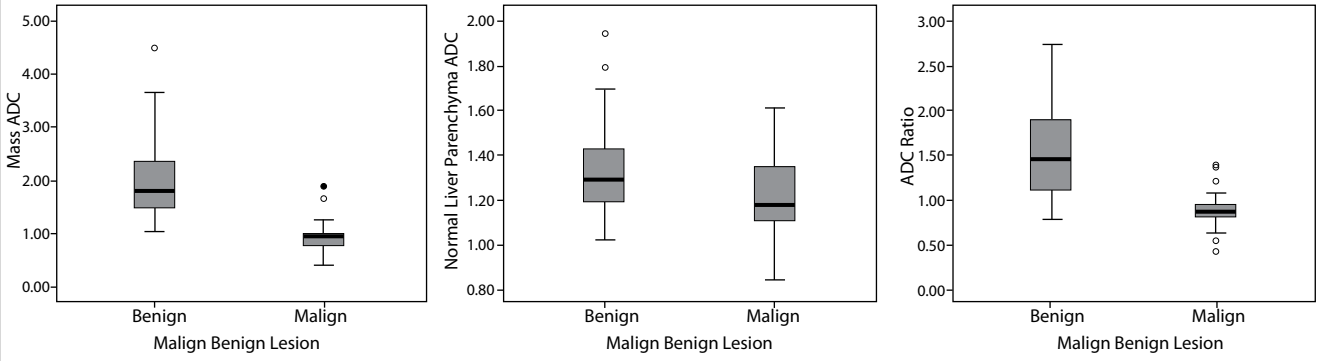


Figure 2. a, b. (a) ROC curve of the mass ADC value; (b) ROC curve of the ADC ratio

ADC: apparent diffusion coefficient

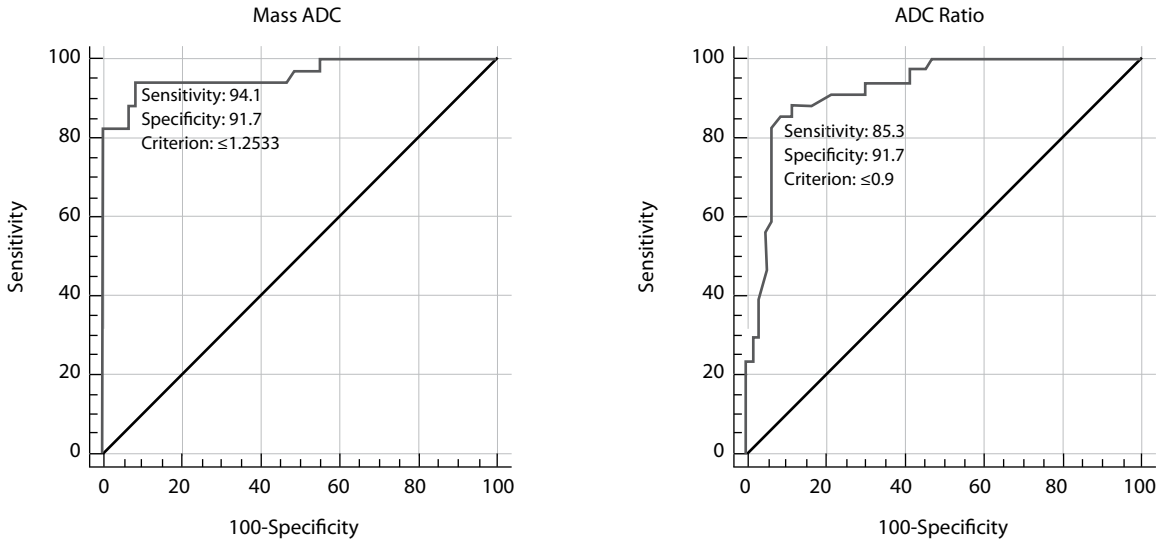


Table 2. Between-group comparison by the type of lesion. ADC measurements of mass and mass/parenchyma ratios showed a significant difference between lesion groups (p=0.001)

	Lesion		
	Malign (n=34)	**Benign (n=60)**	**p**
MASS ADC value	0.94±0.29	1.96±0.68	0.001
Normal parenchymal ADC	1.21±0.18	1.32±0.19	0.007
ADC ratio (mass/parenchyma)	0.80±0.20	1.50±0.53	0.001

ADC: apparent diffusion coefficient

The mean ADC values of adjacent hepatic parenchyma were 1.32±0.19×10^{-3} mm^2/sec for cases with benign lesions and 1.21±0.18×10^{-3} mm^2/sec for cases with malignant lesions (Table 1). The mean ADC values of cirrhotic and normal livers were 1.22±0.19 and 1.29±0.19×10^{-3} mm^2/sec, respectively.

The mean ADC ratios of benign and malignant lesions were 1.50±0.53×10^{-3} mm^2/sec and 0.80±0.20×10^{-3} mm^2/sec, respectively (Table 2) (Figure 1). Differences in the average ADC measurements, parenchymal ADC values, and ADC ratios between benign and malignant lesions were statistically significant (p<0.001) (Table 2).

The ADC values for focal hepatic masses were significant, except for metastasis–HCC, and ADC ratios were significant, except for metastasis–HCC, and metastasis–FNH (Table 3).

Sensitivity and specificity of optimal ADC and ADC ratio cut-off values for characterization of the lesions are shown in Figure

Figure 3. a-h. Hemangioma in the right lobe of the liver in a 36-year-old female patient: (a) shine-through pattern observed in DWI with b=600 s/mm2; (b) no restricted diffusion on the ADC image; (c) typical hyperintensity on T2-weighted axial image; (d) non-contrast; (e) arterial; (f) portal; (g) venous phase (h) late venous phase T1-weighted imaging after injection of contrast agent, showing typical peripheral nodular contrast-enhancement pattern

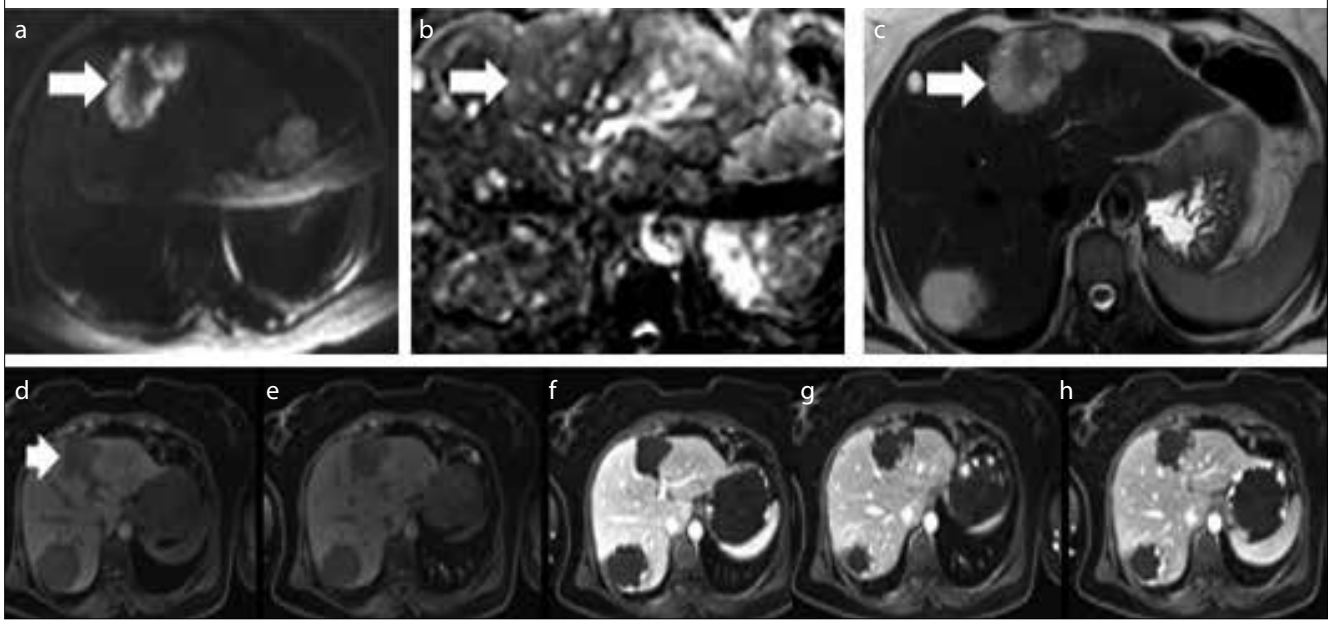
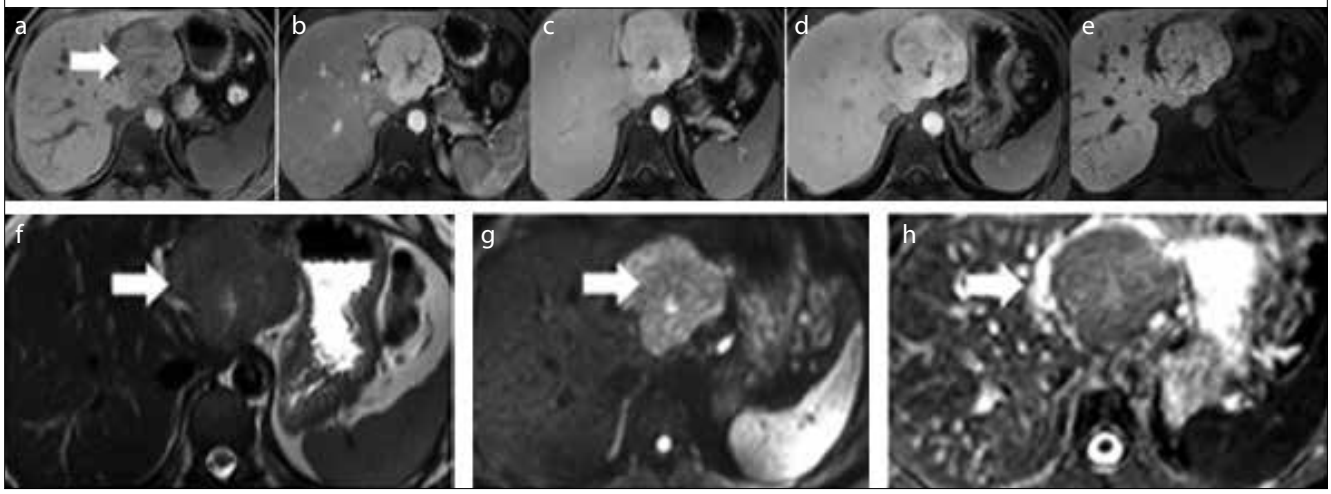


Figure 4. a-h. FNH in the left lobe of the liver of a 30-year-old male patient: (a) non-contrast; (b) arterial T1-weighted image showing marked contrast enhancement; (c) portal venous; (d) hepatic venous; (e) slight hyperintensity in T1-weighted imaging liver-specific phase at 20 minutes after injection of contrast agent; (f) typical central scar on T2-weighted axial image; (g) shine-through pattern on DWI, b=600 sn/mm^2; (h) slight restricted diffusion on the ADC image

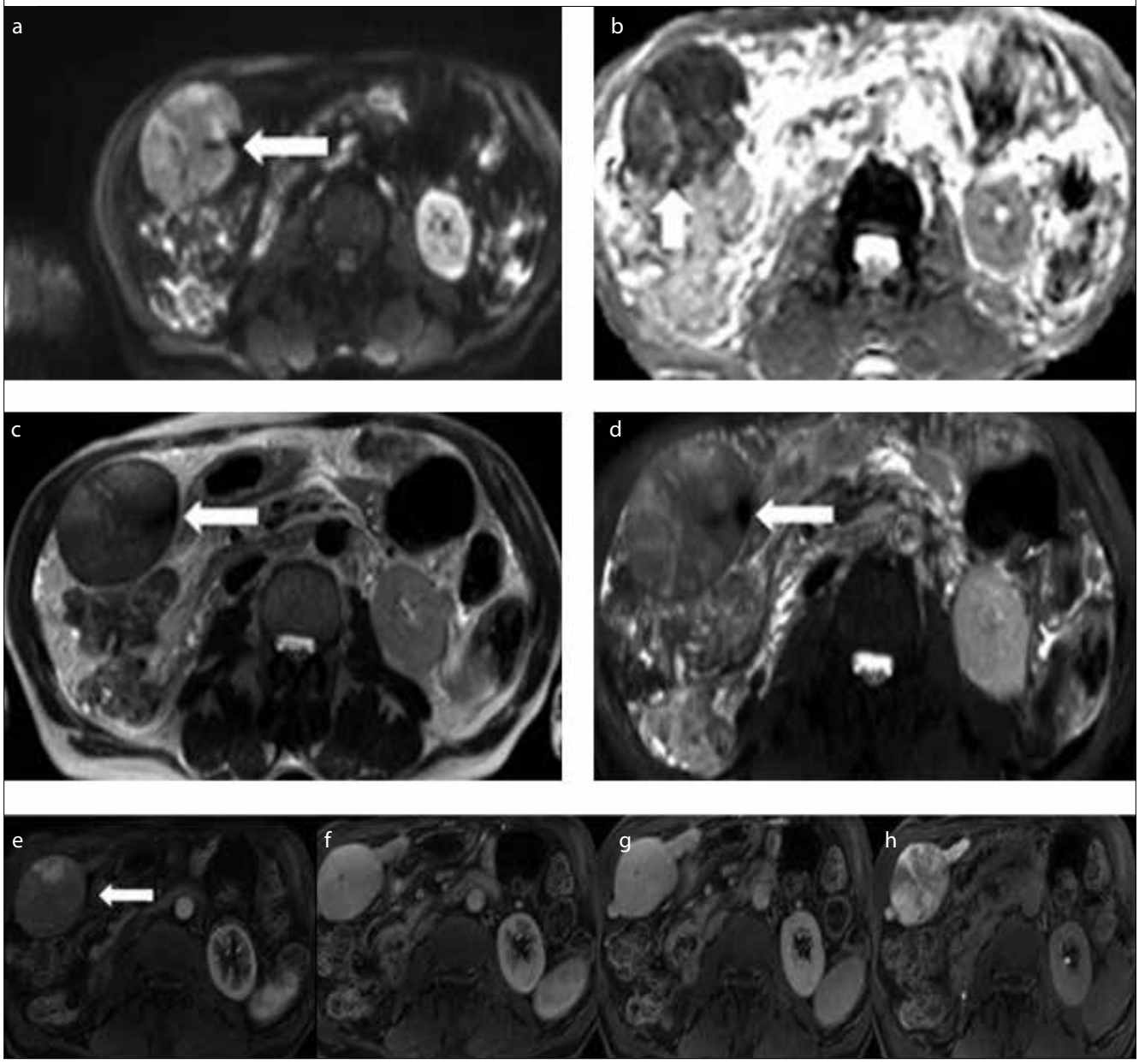


2. Lesions were accurately categorized as benign or malignant when an ADC cut-off value less than or equal to 1.26 was applied, as shown in Figure 2a. Similarly, using an ADC ratio cut-off value ≤0.9 allowed accurate classification of benign and malignant lesions, as shown in Figure 2b.

DISCUSSION

The differential diagnosis of focal hepatic masses is broad, and while most lesions show typical imaging characteristics, differential diagnosis of atypical lesions is challenging, and biopsy is often recommended. DWI has promising results in the characterization of typical lesions. Its advantages include faster acquisition of images compared to routine MR sequences and no requirement for contrast agents (4). DWI should include at least two b values when it is used to examine the abdominal region (low and high b values) (5–8). Benign hepatic lesions with fluid content (hemangioma, cyst, hydatid cyst) appear hyperintense on DWI images and ADC maps, and this pattern is called "T2 shine-through." On the other

Figure 5. a-h. HCC in the left lobe of the liver in a 49-year-old male patient; (a) shine-through pattern on DWI b=600 s/mm2; (b) periferally restricted diffusion on the ADC image; (c, d) slight hyperintensity on T2- and fat-suppressed T2-weigted axial image; (e) non-contrast; (f) arterial; (g) portal; (h) liver-specific phase in T1-weighted imaging after injection of contrast agent on dynamic imaging and hypointensity in liver-specific phase-washout in portal phase



hand, benign solid lesions cannot be differentiated clearly on DWI images with higher b values compared to adjacent liver parenchyma or they appear slightly iso-hyperintense. Malignant hepatic masses (e.g., HCC, metastasis) show restricted diffusion and appear hyperintense on DWI and hypointense on ADC maps (4).

Hemangiomas typically appear hyperintense on a T2-weighted sequence, and contrast enhancement is peripheral and nodular in early phase and usually becomes isointense to the liver in delayed phase (Figure 3). Hemangiomas have slightly lower signal intensities than cysts on ADC maps, and reduced signals are observed with increasing b values in cysts (9, 10). Cysts have significantly higher ADC values and ratios compared to other lesions, and they can be easily differentiated (10). However, some hemangiomas should be evaluated in combination with T2-weighted sequences and contrast-enhanced MRI since there is overlapping with malignant lesions when only the ADC value is used for assessment (9, 10). Similarly, highest ADC values and ratios were observed in cysts in our study, and although there were overlaps in the ADC values of hemangiomas and malignant lesions, they differed statistically significantly from all malignant and benign lesions.

Focal nodular hyperplasia is hyperintense in the arterial phase secondary to hypervascularization, and it does not show washout in portal venous or late venous phases. A typical FNH has a

Figure 6. a-g. Breast carcinoma metastasis in the right lobe of the liver in a 55-year-old female patient: (a) non-contrast; (b) arterial; (c) portal; (d) venous; (e) late venous phase T1-weighted image showing typical circular contrast enhancement on dynamic imaging after contrast injection; (f) shine-through pattern on DWI, b=600 s /mm2; (g) restricted diffusion on the ADC image

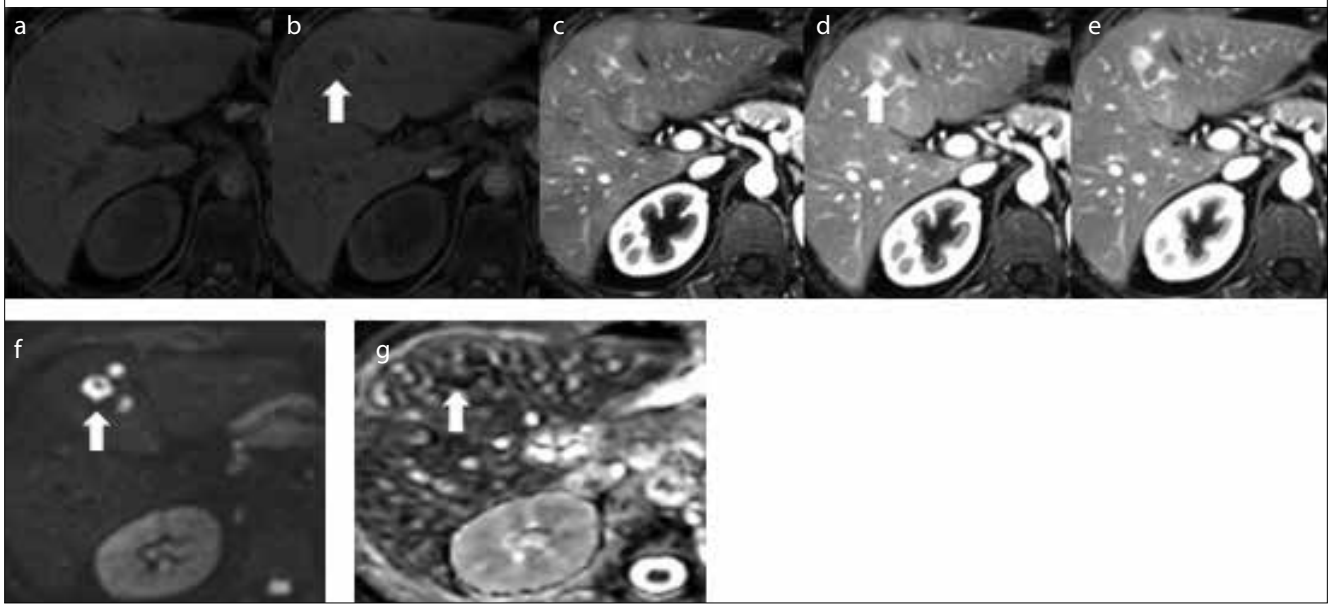


Table 3. Comparisons between lesions. Significant differences were found between lesion groups with respect to ADC values and ADC ratios (p<0.001)

Diagnosis	Type of Diagnosis	p (ADC value)	p (ADC ratio)
Cyst	Hemangioma	.001	.001
	FNH	.001	.001
	HCC	.001	.001
	Metastasis	.001	.001
Hemangioma	FNH	.006	.002
	HCC	.001	.001
	Metastasis	.001	.001
FNH	HCC	.001	.001
	Metastasis	.001	.114
HCC	Metastasis	.561	.424

ADC: apparent diffusion coefficient; FNH: focal nodular hyperplasia; HCC: hepatocellular carcinoma

central scar that is hyperintense on T2-weighted sequence and shows contrast enhancement in late venous phase. Recently, liver-specific contrast agents were introduced and iso-hyperintensity observed in the sequences obtained at least 20 minutes after injection of such a contrast agent contributes significantly to differential diagnosis (Figure 4) (11). Hepatic adenomas are frequently confused with HCC due to their atypical enhancement patterns and washout sign (12). Adenomas are rare lesions, and statistical power could not be achieved in studies due to small number of cases. However, no significant differences were found between the ADC values of FNH and adenomas in a meta-analysis, and as a group, adenomas showed variations in ADC values within different subtypes (10, 13). In our study, adenomas did not contribute to the differential diagnosis due to insufficient number of adenomas and a low ADC value. Considerable overlaps in ADC values were reported between benign solid focal liver masses including FNH and adenoma and malignant lesions (10, 14). Consistent with this finding, no statistically significant difference was found between ADC ratios of FNH and metastases. This lack of difference was considered to be due to heterogeneous nature of metastases. However, there was a statistically significant difference between the ADC values and ratios of FNH and HCC. In differential diagnosis, DWI with ADC mapping provides additional information for discrimination of FNH and HCC lesions.

In a cirrhotic liver, lesions that show contrast enhancement in the arterial phase and washout in the portal or late phase should be considered as HCC until proven otherwise (Figure 5) (15). Metastases are multiple lesions that are hypovascular and usually show peripheral "ring-like" contrast enhancement in arterial and portal phases (Figure 6). Both metastases and HCC are hypointense in hepatobiliary phase following injection of liver-specific contrast material and show restricted diffusion. DWI provides more useful data for liver metastases than for HCC because metastases have low ADC values, and signal can be more clearly observed compared to surrounding liver parenchyma (16). However, since HCC lesions often develop on a cirrhosis background and since cirrhotic hepatic parenchyma shows areas of restricted diffusion, their diagnosis and demonstration of the lesion in an ADC map is more difficult compared to metastases. Similarly, HCC lesions with a cirrhotic background could be less well discriminated by the

ADC mapping in our study. However, there were no statistically significant differences in ADC values and ratios between metastases and HCC. Metastases are a more heterogeneous group and may show lower or higher ADC values than HCC depending on the nature of the primary lesion (hypovascular or hypervascular). In a study on hypovascular and hypervascular metastases, lower ADC values were measured for hypervascular metastases, and higher ADC values were demonstrated for hypovascular metastases (17). We believe that statistically non-significant metastasis-HCC ADC values observed in our study resulted from heterogeneous nature and small sample size of the metastasis group.

Overall, benign hepatic lesions showed higher ADC values compared to malignant lesions, although a variable degree of overlapping was observed (12, 14, 16). Several cut-off values ($1.4–1.6\times10^{-3}$ mm^2/sec) are described for ADC in the literature with a reported sensitivity of 74%–100% and specificity of 77%–100% for the diagnosis of malignant lesions. Significantly high diagnostic accuracy was reported for ADC values and ADC ratios in malignant/benign lesions. Consistently, they showed high sensitivity and specificity in our study. Differential results have been reported in the literature due to the use of different MRI devices, imaging techniques, and b values. Several different cut-off values of the ADC value have been used for discrimination of malignant and benign lesions in studies, which may be explained by differences in calculation, the use of different gradients in MRI devices, and various artifact reduction methods (9). The ADC ratio is used to avoid such variations. In recent years, ADC ratios were shown to have a good diagnostic performance for prostate cancer (18). Studies have demonstrated that ADC ratios could also be used for differentiation of benign and malignant hepatic lesions (19). However, given the age-related variations in ADC values and HCCs that developed in a background of cirrhosis, ADC ratios did not provide additional information for discrimination of benign and malignant lesions beyond that provided by the ADC value in our study. It is our belief that by excluding cirrhotic liver diseases, future studies with age-matched groups may better discriminate metastases and solid/benign lesions using the ADC ratio based on the fact that metastasis is associated with parenchymal changes and systemic manifestations.

CONCLUSION

When added to conventional MRI, the ADC value and ADC ratio assessed on DWI improve the accuracy of MRI in the characterization of benign and malignant lesions. Using the ADC ratio (the ADC value of the lesion/hepatic parenchyma ADC value), higher diagnostic accuracy may be achieved for the discrimination of metastasis and benign solid lesion versus the ADC value by excluding differences in technical parameters.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.
Peer-review: Externally peer-reviewed.

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