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Can Liver Imaging for Focal Lesions be Limited with Only Diffusion-Weighted Sequences in Patients without Known Malignancy?

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BACKGROUND/AIMS

Our purpose is to investigate whether the diffusion-weighted imaging (DWI) can be used as an initial and decisive sequence to shorten liver magnetic resonance imaging (MRI) study, rather than being complementary to conventional sequences especially in patients without known malignancy.

MATERIAL and METHODS

The MRI characteristics of 105 focal liver lesions (FLLs) were classified as benign or malignant by visually assessing the DWI features, and the lesions were compared with a complete liver MRI protocol. Hyperintensity or isointensity of a lesion in apparent diffusion coefficient map by visual assessment was accepted as unrestricted diffusion and benignity, while hypointensity in any part of a lesion was accepted as restricted diffusion and malignancy. Specificity, sensitivity, positive predictive value, negative predictive value, and accuracy of DWI were calculated.

RESULTS

The visual assessment of DWI alone had 74.29% sensitivity, 94.29% specificity, 86.67% positive predictive value, 88.00% negative predictive value, and 87.62% accuracy in differentiating malignant lesions from the benign ones. In 28 of 32 patients without malignancy, DWI results were in concordance with the final diagnosis of benign lesions. The misinterpreted lesions in these patients were three abscesses and a hemorrhagic adenoma.

CONCLUSION

Visual DWI characteristics of FLLs in patients without known malignancy can accurately classify the lesions as benign or malignant. In appropriately selected patients, a liver MRI examination can be completed with only DWI, resulting decrease in time and cost related to intravenous contrast media usage.

Keywords: MRI, diffusion-weighted imaging, liver, tumor, intravenous contrast, abdomen

INTRODUCTION

Characterizing focal liver lesions (FLLs) is an important part of the radiology practice. Ultrasonography (US), computed-tomography (CT), and magnetic resonance imaging (MRI) can be used for this; however, intravenous (iv) contrast-enhanced liver MRI has the highest accuracy. Relatively costly and time-consuming conventional abdomen MRI requires the use of iv contrast agents. Diffusion-weighted imaging (DWI) has long been used as a complementary sequence in abdominal MRI. DWI is a noninvasive imaging method based on the Brownian motion of water molecules. Diffusion of water molecules is quantitatively expressed by apparent diffusion coefficient (ADC). Low ADC values are associated with high cellularity and viscosity suggesting malignancy or abscess, respectively (1). DWI has begun to play an important role in the detection and characterization of FLLs in conjunction with evolving hardware and software technologies (2). Many studies investigate the role of DWI in discrimination of malignant abdominal tumors from the benign ones. Most of these studies compare quantitative ADC values (3-9). A systematic database review study conducted by Vermoolen et al. (10) reported that mean ADC values of malignant lesions and benign lesions ranged from 0.86±0.11 to 1.52±0.55×10^{-3} mm^2/s and 1.94–2.86×10^{-3} mm^2/s, respectively. Bharwani et al. (11) reported that the threshold of 1.7×10^{-3} mm^2/s ADC value had a significantly higher diagnostic sensitivity and specificity in differen-

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tiation of malignant and benign FLLs. In an another study that examined 215 FLLs, the optimal ADC threshold value generating 79% sensitivity and 82.6% specificity was found to be 1.25×10^{-3} mm^2/s (4). As shown in the abovementioned studies, the wide range of ADC values can be because of scanners and the b-values. A group of researchers compared visual evaluation of the DWI and ADC maps with measured ADC values in FLLs, and they found high sensitivity and accuracy rates of visual assessment in both adult and pediatric abdominal tumors (12, 13). We hypothesized that beginning the liver imaging with DWI and visual assessment of its results eliminates an iv contrast-enhanced abdominal MRI protocol and decreases time and cost. Our purpose is to investigate whether the DWI can be used as an initial and decisive sequence to shorten liver MRI study, rather than being complementary to conventional sequences especially in patients without known malignancy.

MATERIAL and METHODS

Patients

Ethics committee approval was received for this study from Near East University Ethics Committee for Scientific Researches (Approval Date: 04.26.2018). In total, 213 upper abdominal MRI studies performed in our department between January 2016 and February 2018 were retrospectively evaluated. FLLs were found in 65 patients. Patients without known primary malignancy were referred to MRI examination for lesions determined in US or in CT examination, while patients with known primary malignancy were referred for screening or follow-up. Institutional review board approval was obtained for this retrospective study. FLLs smaller than 1 cm, non-iv contrast studies, ADC map with motion or pulsation artifacts, and cases with nine or more liver lesions were excluded. Twelve of these patients were excluded because of lack of a contrast-enhanced study or an artifact-free ADC map. Three patients were excluded for having nine or more lesions. Only the first MRI study of a patient was included if they had multiple. Finally, 105 FLLs of 50 patients were included in the statistical analysis.

MRI Protocol

The MRI studies were carried out with a 1.5-T MR scanner (Magnetom Aera, Siemens Healthcare, Erlangen, Germany). The standard imaging protocol included axial and coronal T2-weighted half-Fourier acquisition single-shot turbo spin echo (HASTE) sequences [repetition time (TR)/echo time (TE), 1200/91 ms; flip angle (FA), 169°; slice thickness (THK), 6 mm; and number of excitations (NEX), 1], axial fat-saturated T2-weighted HASTE sequence (TR/TE, 1200/94 ms; FA, 160°; THK, 6 mm; and NEX, 1), axial fat-saturated T1-weighted fast low-angle shot (FLASH) sequence (TR/TE, 126/2.38 ms; FA, 70°; THK, 6 mm; and NEX, 1), axial in-phase and opposed-phase T1-weighted FLASH sequences (TR/TE, 119/4.76 and 2.38 ms, respectively; FA, 70°; THK, 6 mm; and NEX, 1), axial T2 and heavily T2-weighted HASTE sequence (TR/TE, 1600/118 and 445 ms, respectively; FA, 157°; THK, 6 mm; and NEX, 1), pre-contrast axial, fat-saturated T1-weighted volumetric interpolated breath-hold examination (VIBE) sequence (TR/TE, 4.36/1.91 ms; FA, 10°; THK, 4 mm; and NEX, 1) and contrast-enhanced fat-saturated T1 weighted VIBE sequences with same parameters at 30 s (arterial phase), 60 s (portal phase), and 150 s (venous phase) after injection of 0.1 mmol/kg of gadoterate meglumine (Dotarem; Guerbet Group, France) bolus tracked visually by a real-time sequence, and a post-contrast axial T1-weighted fat-saturated FLASH sequence at 300 s (late venous phase) after the injection. Diffusion-weighted images were obtained in axial plane with b-values of 50, 400, and 800 s/mm^2. Respiratory-triggered single-shot echo-planar images had these parameters: TR/TE, 8000/61 ms; FA, 90°; THK, 6 mm; NEX, 3. The ADC maps were automatically created.

MRI Analysis

Histopathologic results or clinical and radiographic follow-up and typical imaging findings were accepted as reference standard. A radiologist with more than 10 years of experience in abdominal imaging read the whole data for each patient including physical examination findings, medical history, all MRI sequences, findings in other modalities (CT, US), pathology reports, and follow-up imaging findings to classify the lesions as malignant or benign. Lesions with peripheral globular contrast enhancement in the arterial phases and being hyperintense in the late venous phases compared to the normal liver parenchyma were evaluated as hemangioma (14). Lesions with peripheral rim-type contrast enhancement and having different enhancement pattern from normal liver parenchyma in patients with known primary tumors were evaluated as typical metastasis (15, 16). The diagnoses of metastases were also confirmed by decrease in size in patients receiving chemotherapy and increase in size in untreated patients who have follow-up imaging. Lesions being hyperintense on T2-weighted images and showing no contrast enhancement were evaluated as cysts (16). Lesions being mildly hypointense to moderately hyperintense on T1-weighted images, mildly hyperintense on T2-weighted images, showing homogeneous enhancement in the arterial phases, and becoming nearly isointense in venous phases were evaluated as adenomas (16, 17). Lesions with heterogeneous internal structure and rapid contrast enhancement in the arterial phases and wash-out in venous phases were interpreted as hepatocellular carcinoma (HCC) (16-18). Pathological diagnoses of HCCs were also present. The abscesses showed peripheral enhancement of capsules and central restriction of diffusion in the ADC maps (19). Abscess material was evacuated with percutaneous drainage from two lesions. Transient hepatic attenuation differences (THAD) were found in a patient who showed wedge-shaped focal areas of hyperintensity in arterial phase and isointensity to normal liver in other phases and sequences and did not have mass effect (20). A lesion without a mass effect, showing signal drop-out in opposed-phase T1-weighted sequence and similar contrast enhancement compared to normal liver parenchyma was diagnosed as focal fatty infiltration (21, 22).

An another radiologist with six years of experience in general radiology interpreted only the diffusion-weighted and ADC images of the patients who were included in the study, and

classified the lesions as being benign or malignant. He was blinded to the data and images other than DWIs and ADC maps. As in previous studies, hyperintensity or isointensity of a lesion in ADC map by visual assessment was accepted as unrestricted diffusion and benignity, whereas hypointensity in any part of a lesion was accepted as restricted diffusion and malignancy (13, 23).

Statistical Analysis

Diagnostic performance of DWI-alone interpretation was made by identifying true benign, false benign, true malignant, and false malignant lesions. Specificity, sensitivity, positive predictive value, negative predictive value, and accuracy were calculated from these results.

RESULTS

Eighteen of the patients included into the study had at least one known primary malignancy. Thirty-two of the patients did not have any known history of malignancy. Among the patients included in statistical analysis, 13 had malignant and

TABLE I. Distribution of the lesions and patients according to the diagnosis and counts of total lesions and patients

Type of lesion	Number of lesions	Number of patients	Number of patients with known malignancy	Number of patients without known malignancy
Hemangioma	47	23	4	19
Metastasis	32	11	11	0
Cyst	10	7	1	6
Adenoma	7	3	1	2
HCC	3	2	1	1
Abscess	3	2	0	2
THAD	2	1	0	1
Focal fatty infiltration	1	1	0	1
Total	105	50	18	32

HCC: hepatocellular carcinoma; THAD: Transient hepatic attenuation differences

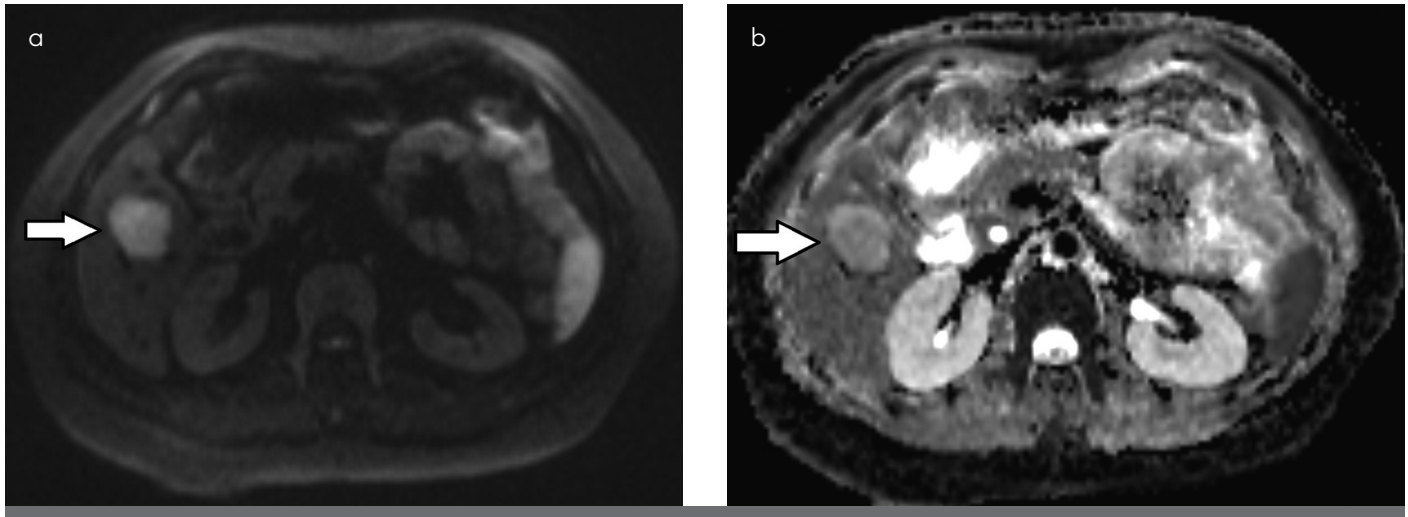

FIGURE 1. a, b. A hemangioma in the right liver lobe. The lesion is hyperintense both on the diffusion-weighted image (a) with b value of 800 s/mm² and on the ADC map (b)

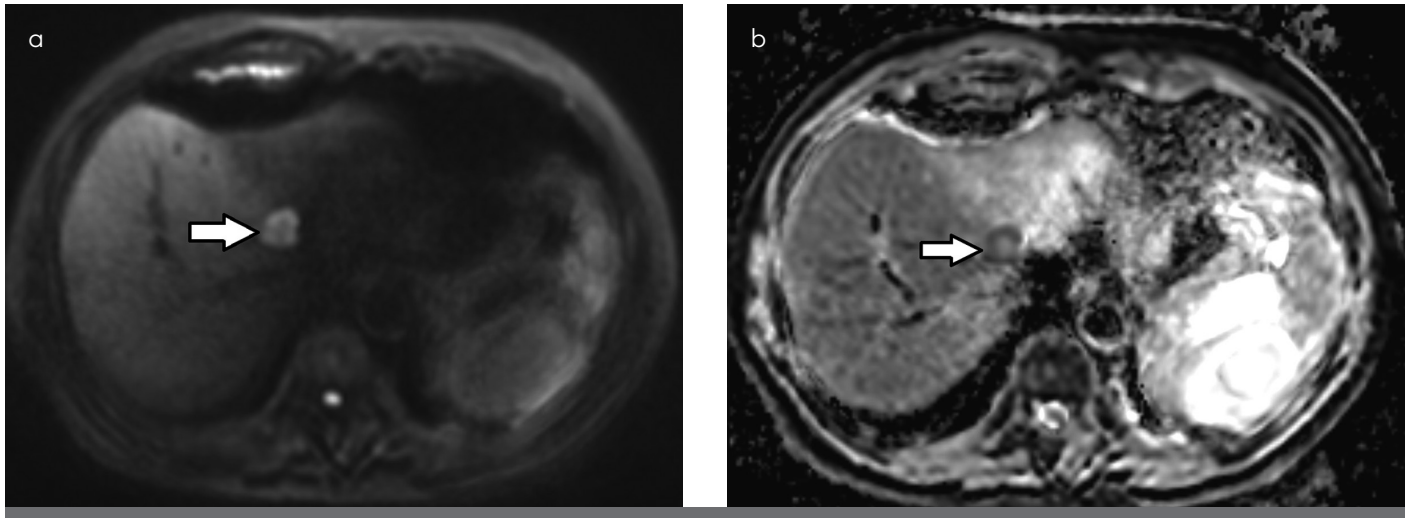

FIGURE 2. a, b. The periphery of a metastasis is seen hyperintense on b800 (a) and hypointense on ADC map (b)

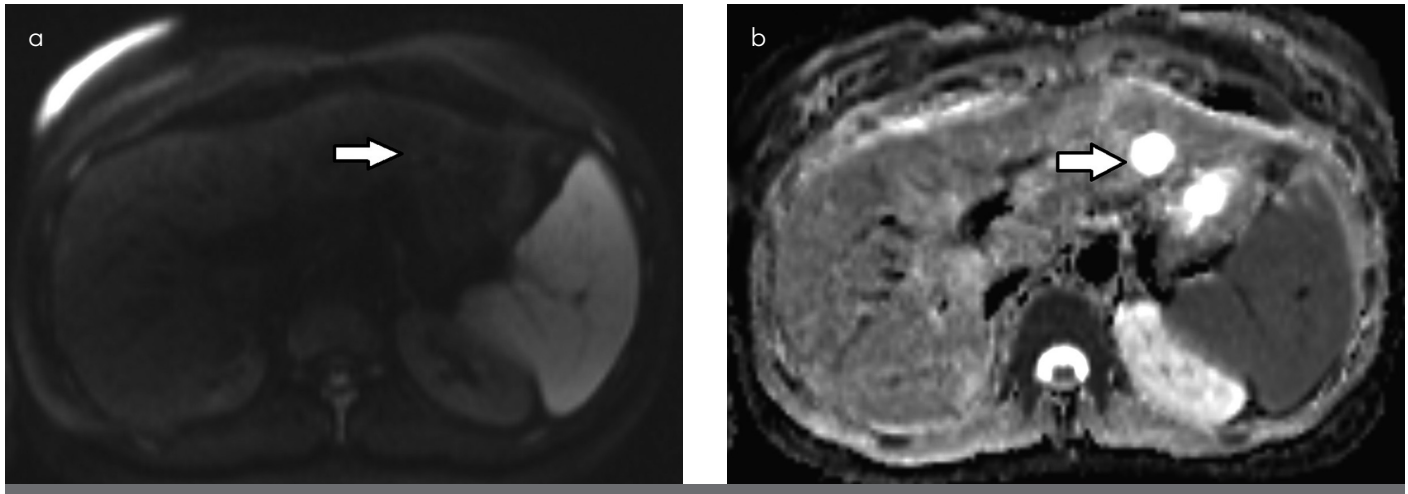

FIGURE 3. a, b. A cyst is totally suppressed on b800 image (a). Hyperintensity of the lesion is seen on ADC map (b)

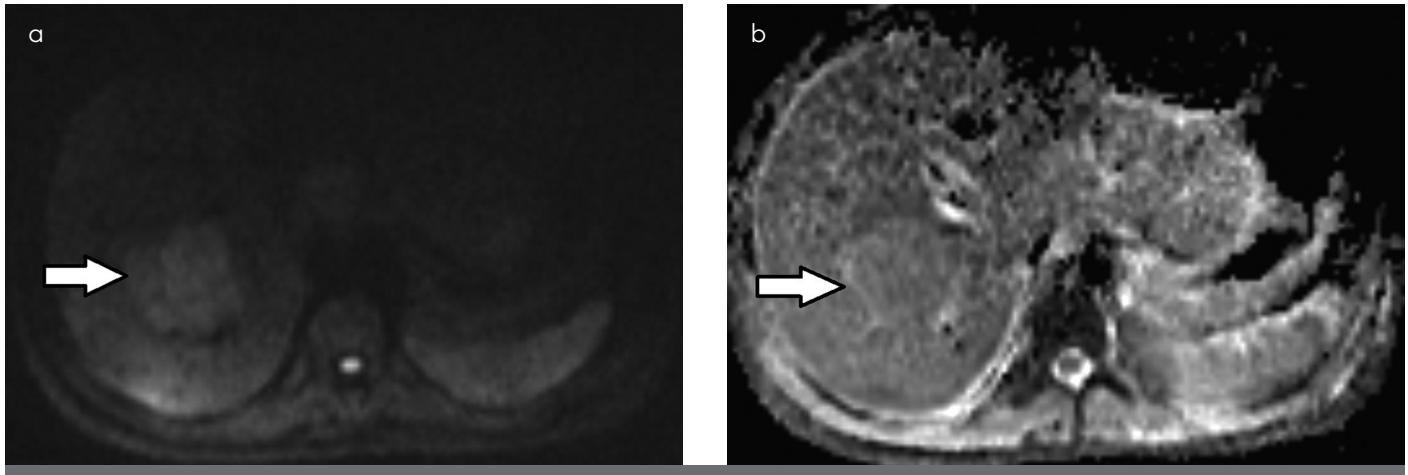

FIGURE 4. a, b. An adenoma is slightly hyperintense on b800 image (a) and slightly hyperintense on ADC map (b)

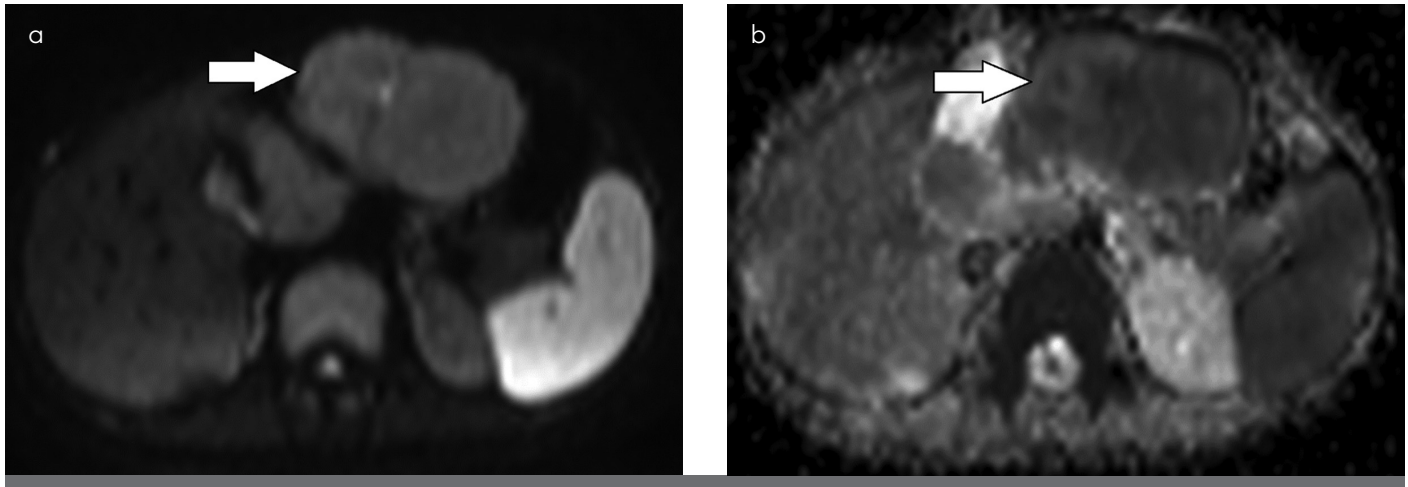

FIGURE 5. a, b. A fibrolamellar HCC located in the left liver lobe shows restriction of diffusion on b800 image (a). The lesion is hypointense on ADC map (b) compared to normal liver parenchyma

37 had benign lesions in MRI scans. The average age of patients with and without known primary malignancy was 58.3 (range 30–81) years and 49.4 (range 16–86) years, respectively. There were 32 female and 18 male patients. Eleven female patients had known malignancy, and seven had malignant liver lesions. Seven male patients had known malignancy, and six had malignant liver lesions. Number of lesions included in statistical analysis was 105. None of the patients had both malignant and benign FLLs. The average number of benign and malignant lesions in a liver was 1.89 (range 1–6) and 2.69 (range 1–6), respectively. Most common lesions were hemangiomas and metastases (Table 1). The DWI and ADC features

TABLE 2. Signal characteristics of the lesions in the DWI-800 and ADC maps. (↑↑: hyperintense, ↑: mildly hyperintense, —: isointense, ↓: hypointense). Numbers in the boxes are the count of lesions

Type of lesion	DWI-800 ↑↑	DWI-800 ↑	DWI —	ADC ↑↑	ADC ↑	ADC ↓	ADC —
Hemangioma	46	1	0	47	0	0	0
Metastasis	25	4	3	4	4	23	1
Cyst	0	0	10	10	0	0	0
Adenoma	1	2	4	0	2	1	4
HCC	3	0	0	0	0	3	0
Abscess	3	0	0	0	0	3	0
THAD	0	0	2	0	0	0	2
Focal fatty infiltration	0	0	1	0	0	0	1

DWI: diffusion-weighted imaging; ADC: apparent diffusion coefficient; HCC: hepatocellular carcinoma; THAD: Transient hepatic attenuation differences

TABLE 3. Distribution of all lesions according to the reference standard and DWI evaluation

		Reference standard		
		Benign	Malignant	Total
DWI evaluation	Benign	66	9	75
	Malignant	4	26	30
	Total	70	35	105

DWI: diffusion-weighted imaging

TABLE 4. Distribution of the lesions found in the patients without known malignancy according to the reference standard and DWI evaluation

		Reference standard		
		Benign	Malignant	Total
DWI evaluation	Benign	52	0	52
	Malignant	4	1	5
	Total	56	1	57

DWI: diffusion-weighted imaging

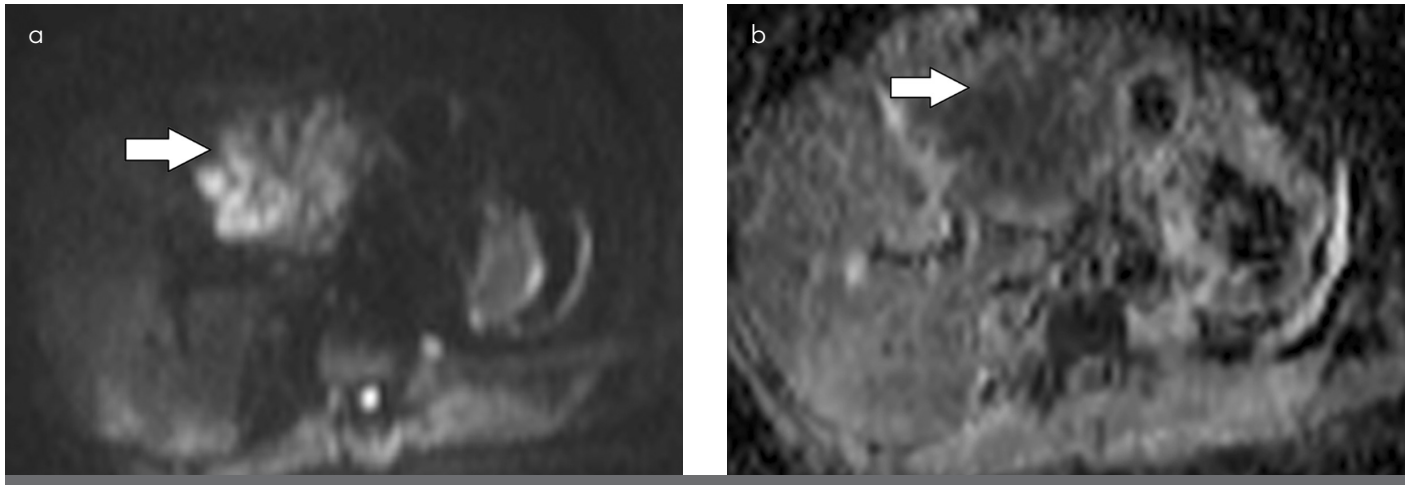

FIGURE 6. a, b. An abscesses in the left liver lobe of a patient shows restriction of diffusion on b800 image (a). The lesion is hypointense on ADC map (b) compared to normal liver parenchyma

of common lesions are demonstrated in Figure 1-5. All the hemangiomas and cysts were hyperintense in the ADC maps. The cysts were isointense, and the hemangiomas were either hyperintense or mildly hyperintense in the diffusion-weighted images with b value of 800 s/mm² (DWI-800). Except one, lesions evaluated as adenomas were seen as isointense or mildly hyperintense in the ADC maps and in the DWI-800. All of the HCCs showed hypointensity in the ADC maps and hyperintensity in the DWI-800. Twenty-three of the metastases showed peripheral hypointensity in the ADC maps and hyperintensity in the DWI-800. Nine of the metastases did not show hypointensity in ADC maps, and they were almost entirely necrotic. The abscesses were hypointense in the ADC maps and hyperintense in the DWI-800. The THADs and the focal fatty infiltration were isointense in the ADC maps and in the DWI-800. Features of all lesions in DWI evaluation are presented in Table 2.

According to the reference standard, 35 (33.33%) of all lesions were malignant, and 70 (66.66%) were benign. According to the DWI evaluation, 30 (28.5%) of all lesions were malignant, and 75 (71.4%) of them were benign (Table 3). The results derived from this table were as follows (the values in brackets are 95% confidence interval): sensitivity: 74.29% (56.75%–87.51%), specificity: 94.29% (86.01%–98.42%), positive predictive value: 86.67% (71.10%–94.50%), negative predictive value: 88.00% (80.63%–92.81%), and accuracy: 87.62% (79.76%–93.24%).

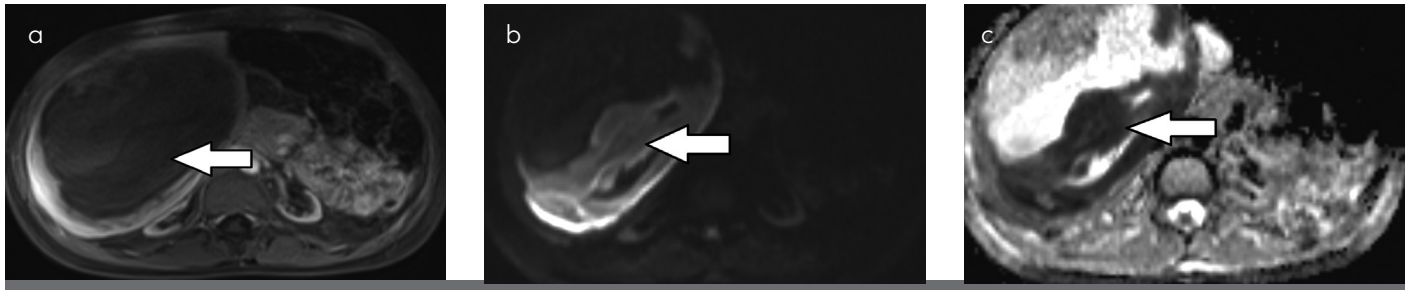

FIGURE 7. a-c. A very large lesion measuring 14 cm in the right liver lobe of a patient does not show contrast enhancement in the portal venous phase (a) where there is hyperintensity on b800 image (b) and hypointensity on ADC map (c), because of the effects of blood products

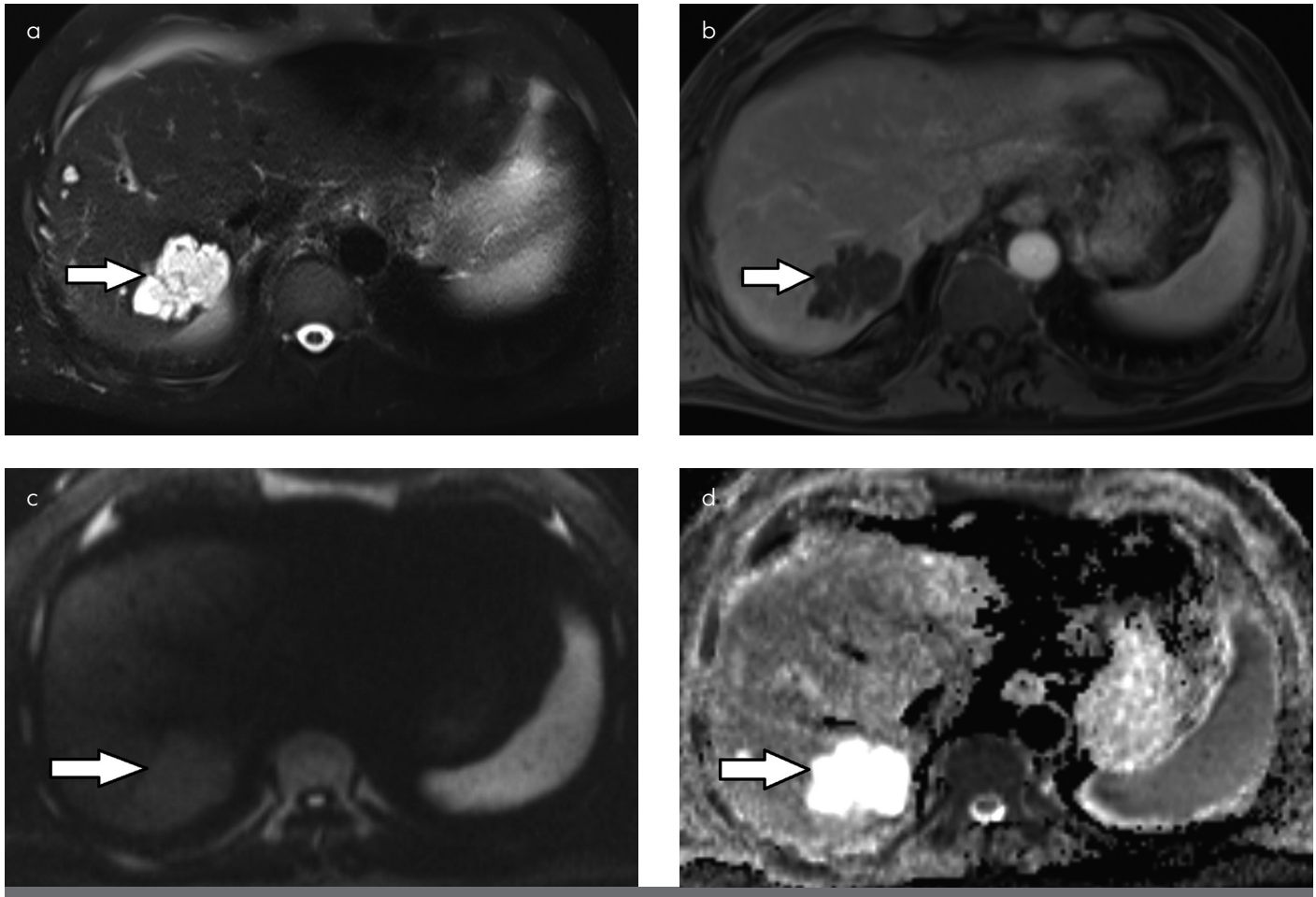

FIGURE 8. a-d. A necrotic metastasis. The lesion has septa on the T2-weighted image (a) and slight contrast enhancement on these septas on venous phase (b). It is slightly hyperintense on b800 (c) and obviously hyperintense on ADC map (d)

No malignant FLL was found in six patients with primary malignancy. Four of them had hemangiomas, one had a simple cyst, and one had an adenoma. In this respect, the DWI-alone interpretation was adequate to classify benign FLLs in patients with malignancy. In 28 patients without known malignancy, all FLLs were accurately interpreted as benign in the DWI-alone interpretation. The DWI-alone interpretation was accurate about 52 lesions in this group (Table 4). Only four lesions were misinterpreted as malignant in the DWI-alone interpretation. Three of these lesions were abscesses, and one of them was a hemorrhagic adenoma (Figure 6, 7). Only one patient without known malignancy had a malignant lesion, and it was an HCC. The DWI-alone interpretation was able to detect this HCC and classified as a malignant lesion. In the DWI-alone interpretation, nine lesions were misinterpreted as benign although they were malignant. All of these lesions were found in the livers of previously known malignancy patients, and they were diagnosed as necrotic metastases (Figure 8).

DISCUSSION

According to our results, upper abdominal MRI studies of 28 of 32 patients (87.5%) without known primary malignancy could be classified as benign or malignant with only signal characteristics on DWI sequences. All benign lesions in these patients were accurately classified by the DWI, which means that these MRI studies could have been completed without additional sequences and iv contrast media. These lesions were either

hyperintense or isointense in the ADC maps because of the absence of diffusion restriction and were classified as benign by visual assessment. In the formation of the DWI, density of atoms and T1 and T2 time differences of a tissue are influential (19, 24). In diffusion-weighted images with low b-values, the cystic or liquid components of tissues may have a high T2 effect (T2 shine-through effect). But in images with high b-values, this effect diminishes and the signal intensity highly depends on cellularity (25). Factors causing restriction of diffusion have been implicated to differences in cellularity, necrosis, nucleus/cytoplasm ratios, viscosity, and perfusion status (26-30). Tightly and randomly arrayed cells hinder the movement of extracellular water molecules. The increased cellularity of a tissue and the integrity of cell membranes are inversely proportional to the free diffusion of water molecules (26, 27). In addition, the movement of intracellular water molecules is restricted in tumors with high nucleus/cytoplasm ratio (26, 31). In the remaining four patients without known malignancy, the lesions were a hemorrhagic adenoma, three abscesses, and one HCC. These lesions were hypointense in the ADC maps suggesting restricted diffusion. Diffusion restriction of malignant tumors is the result of their high cellularity and smaller cell size as in the HCCs (32). Despite being benign, diffusion restriction in abscesses is associated with high viscous fluid containing large proteins, bacteria, and inflammatory cells that resist movement of molecules (30). Partial hypointensity of the hemorrhagic adenoma in the ADC map may be attributed to magnetic susceptibility effects of hemoglobin products (33). In our study, detection of malignant lesions by DWI evaluation was performed with 74.29% sensitivity and 88% negative predictive values. These values are relatively low for a screening test for patients with cancer. When we examined the cause of this, we found that false negative lesions according to the DWI-alone interpretation were the necrotic metastases under chemotherapy. These lesions were hyperintense or isointense in the ADC maps. Solid areas of these lesions that could restrict diffusion were almost vanished (34). They had only thin enhancing walls or septa. For this reason, we think that DWI imaging alone is not adequate especially in patients with known malignancy under treatment.

There are articles suggesting to use liver DWI for the detection of lesions and then subsequent characterization of lesions with iv contrast-enhanced T1-weighted sequences rather than using DWI alone (35). In this study, we did not intended to characterize the FLLs but classifying them as benign or malignant to eliminate iv contrast use and additional sequences.

The main difficulty in classifying FLLs with DWI is the differentiation of solid benign lesions (especially FNHs and adenomas) from malignant lesions (8, 36). FNHs and adenomas of liver are relatively rare according to the simple hepatic cysts and hemangiomas (37, 38). According to the data obtained from our study, the diagnosis of liver cysts and hemangiomas can mostly be made with DWI. In a study conducted by Girometti et al. (23) comparing visual assessment of ADC maps and quantification of ADC value to differentiate benign and solid lesions, accuracy of both methods was limited. We consider that the reason for this result is excluding hemangiomas and cysts from the study and analyzing only solid lesions. We included hemangiomas and cysts in our study since these lesions are common and may not be able to precisely diagnosed by US in patients with fatty liver or in conditions such as obesity and meteorism (39). Kenis et al. (40) found that visual assessment of DWI alone had the same performance as contrast-enhanced MRI in their study investigating the diagnosis of liver metastases in 68 patients. We think that visual assessment of DWI alone is sufficient for demonstrating benign features of common incidental FLLs in majority of cases. To do this, a radiologist must initially interpret the DWI images, and a decision must be made whether the examination should continue.

The limitations of our study are relatively low benign solid lesion diversity and lack of pathology reports in all solid lesions. Except one, biopsy was not required in patients without known malignancy because MRI findings and follow-up examinations were enough to show that the lesions were benign. In a patient with cirrhosis, the diagnosis of an HCC was straightforward depending on the detection of wash-out in contrast-enhanced sequences. In patients with previously known malignancy, the metastatic lesions were diagnosed by detecting peripheral halo type enhancement, contrast loss in late phases compared to normal liver parenchyma, nuclear medicine imaging results, and size changes because of treatment status. The diagnosis of benign lesions in these patients was made as in the patients without known malignancy, and no biopsy was required.

In summary, benign features of an FLL detected in a patient without known malignancy in modalities other than MRI can be shown using DWI alone. DWI is also capable of detecting malignant lesions in patients with or without known malignancy. However, it is not a suitable method for screening necrotic metastases under treatment. In appropriately selected patients, a liver MR examination can be completed with only DWI. This will contribute to reducing workload, allocating more time to the requiring patients, and reducing contrast agent usage and costs. A disadvantage of this practice is the need for a radiologist's interpretation for the decision whether to continue scan.

In conclusion, starting the upper abdominal MRI studies with DWI seems to be a practical approach to the management. We believe that researches from this perspective having more patients and more diverse lesions will make this opinion more acceptable.

Ethics Committee Approval: Ethics committee approval was received for this study from Near East University Ethics Committee for Scientific Researches.

Informed Consent: Informed consent was not taken due to retrospective design of the study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - S.G.; Design - S.G.; Supervision - M.K.; Resource - M.K., S.G.; Materials - S.G., M.K.; Data Collection and/or Processing - S.G.; Analysis and/or Interpretation - M.K.; Literature Search - S.G.; Writing - S.G.; Critical Reviews - M.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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