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Diagnostic Value of Target Sign and Apparent Diffusion Coefficient Measurements in the Differentiation between Hepatocelular Carcinoma and Liver Metastasis on Diffusion Weighted Magnetic Resonance Imaging

Difüzyon Ağırlıklı Manyetik Rezonans Görüntülemede Hepatoselüler Karsinom ve Karaciğer Metastazı Ayırımında Hedef İşaretinin ve Görünür Difüzyon Katsayısı Ölçümlerinin Tanısal Değeri

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Abstract

Aim: The aim of our study is to investigate probable differences between the incidence of target sign detected by diffusion-weighted magnetic resonance imaging (DWI) and apparent diffusion coefficient (ADC) values between liver metastases and hepatocellular carcinomas (HCC).

Material and Method: A total of 155 lesions obtained from 57 (female/male: 18/39) patients were included in the study. Dimensions of lesions, the appearance of lesions detected by DWI, minimum ADC (ADCmin) values, and average ADC (ADCav) values were evaluated with 1.5 Tesla MRI using b= 0 and b=1000 s/mm² values. Differences between metastases and HCC were investigated in terms of defined parameters. Also, ROC (receiver operating curve) analysis was used to evaluate the performance of ADCmin and ADCav parameters in distinguishing metastases from HCC.

Results: Of the lesions, 131 were metastases, while 24 were HCC. The image showing centrally hypointense, periphery hyperintense signal in DWI defined as target sign. Target sign detected in 72 metastatic lesions (55%) and 6 HCC lesions (25%) with DWI, and the rate of target sign detection was higher in the metastatic group compared with HCC ($p<0.007$). Also, ADCmin and ADCav values were found to be higher in the HCC group compared with the metastatic group ($p<0.001$). Based on ROC analysis optimal ADCmin and ADCav values were $<758\times10^{-6}$ and $<817\times10^{-6}$ mm²/s, respectively, in distinguishing metastasis from HCC (Sensitivity: 0.412, 0.412; Specificity: 0.875, 0.917 respectively).

Conclusion: Target sign detected by DWI and ADC values can be used as MRI markers that enhance diagnostic accuracy in distinguishing between liver metastases and HCC.

Keywords: Target sign, diffusion-weighted magnetic resonance imaging, metastasis, hepatocellular carcinoma

Öz

Amaç: Çalışmamızın amacı, karaciğer metastazları ve hepatoselüler karsinom (HCC)'da difüzyon ağırlıklı manyetik rezonans görüntüleme (DWI) ile tespit edilen hedef işaret insidansı ve görünür difüzyon katsayısı (ADC) değerleri arasındaki olası farklılıkları araştırmaktır.

Gereç ve Yöntem: 57 (kadın/erkek: 18/39) hastadan elde edilen toplam 155 lezyon çalışmaya dahil edildi. Lezyonların boyutları, DWI ile tespit edilen lezyonların görünümü, minimum ADC (ADCmin) değerleri ve ortalama ADC (ADCav) değerleri, b= 0 ve b=1000 s/mm² değerleri kullanılarak 1,5 Tesla MRG ile değerlendirildi. Tanımlanan parametreler açısından metastazlar ve HCC arasındaki farklar araştırıldı. Ayrıca metastazları HCC'den ayırmada ADCmin ve ADCav parametrelerinin performansını değerlendirmek için ROC analizi kullanıldı.

Bulgular: Lezyonların 131'i metastaz, 24'ü HCC idi. Hedef işareti olarak tanımlanan, DWI'da merkezi hipointens, periferik hiperintens izlenen imaj DWI ile 72 metastatik lezyonda (%55) ve 6 HCC lezyonunda (%25) saptandı ve metastatik grupta hedef işareti saptanma oranı HCC'ye göre daha yüksekti ($p<0,007$). Ayrıca HCC grubunda, ADCmin ve ADCav değerleri metastatik gruba göre daha yüksek bulundu ($p<0.001$). ROC analizine dayalı olarak, metastazı HCC'den ayırmada optimal ADCmin ve ADCav değerleri sırasıyla $<758\times10^{-6}$ ve $<817\times10^{-6}$ mm²/s idi (Duyarlılık: 0.412, 0.412; Özgüllük: sırasıyla 0.875, 0.917).

Sonuç: DWI ile saptanan hedef işareti ve ADC değerleri, karaciğer metastazı ve HCC ayrımında tanısal doğruluğu artıran MRI belirteçleri olarak kullanılabilir.

Anahtar Kelimeler: Hedef İşareti, difüzyon ağırlıklı manyetik rezonans görüntüleme, metastaz, hepatosellüler karsinom

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INTRODUCTION

Metastases are the most frequent liver masses, and dynamic contrast-enhanced magnetic resonance imaging (MRI) has an important role in the diagnosis of liver metastases.[1] However, conditions in which contrast agents are contraindicated and probable side effects caused by contrast agents limit the use of contrast-enhanced imaging methods.[2-5] In studies in recent years, it has been stated that addition of diffusion-weighted MRI (DWI) to the MRI protocol enhances the rate of diagnostic accuracy, and DWI can be used as an assisting imaging method.[5,6]

DWI is an effective and practical MRI technique that is based on the free motion of water molecules. It does not require contrast agent use, and it is quickly completed. As is well known, metastatic masses exhibit diffusion limitations in DWI because of their high cellular content. The degree of diffusion restriction can be quantitatively expressed using apparent diffusion coefficient (ADC) measurements.[5-8] General condition failures and contraindications of contrast agent use are more frequently observed in metastatic patients. Thus, the use of DWI, which does not require a contrast agent, becomes crucial in this patient group.[4] In the literature, there are various studies on the evaluation of metastases using DWI. However, in most of these studies, metastases were evaluated together with other lesions under the title of focal liver masses, and ADC measurements were taken into account in the evaluations.[9-19] In recent years, target sign appearance, which is formed based on signal properties of liver masses in DWI sequences, was defined in several studies.[20-22] In these studies, it was stated that target sign on DWI was observed more frequently in intrahepatic cholangiocellular carcinoma (ICC) compared with hepatocellular carcinoma (HCC) and hypovascular solitary metastases. In our opinion, there is not a study in the literature that investigates differences in the incidence of target sign detected by DWI between metastatic liver lesions and hepatocellular carcinoma (HCC), which is the most frequent primary liver mass.[23] Therefore, our aim is to investigate probable differences in target sign on DWI and ADC values between metastases and HCC.

MATERIAL AND METHOD

Study Population

The study started after obtaining ethics committee approval from Clinical Investigations Ethics Committee of Tokat Gaziosmanpaşa University Medical Faculty (21.12.2020 /16-KAEK-057). The study was financially supported by the Scientific Research Projects Unit of Tokat Gaziosmanpaşa University Medical Faculty. Patients with a liver mass and with a diagnosis of metastasis or HCC were included in the study, and these patients were imaged using upper abdominal diffusion MRI. The diagnoses was determined using histopathological sections obtained from liver lesions. All patients gave informed written consent. Age and gender data and histopathological evaluation reports of patients were collected from the hospital database.

MRI Technique

Patients were imaged with a 1.5 Tesla (T) MRI instrument (Signa Explorer 25.0, General Electric Medical System Waukesha, WI) using 16 channels phased-array body coil. DWI sections were obtained by echo planar diffusion weighted sequences in the axial plan using b= 0 and b=1000 s/mm². DWI parameters were as follows: TR:~ 9000 ms; TE: 91.1 ms; field-of-view (FOV): 410×410 mm; matrix size: 80×128; slice thickness: 7 mm; inter-slice gap: 1.5 mm.

Image Analysis

Analysis of the images was carried out using a workstation (Advantage Workstation Volume Share.7, General Electric Medical Systems, Milwaukee, WI, USA), by two radiologists independent of each other with eight to nine years' experience. Radiologists were blinded to diagnosis of patients and to each other's measurements.

Lesion dimensions were obtained by measuring the largest diameter in the DWI sections. Some lesions were visualized as having a hypointense center and a circular hyperintense periphery in DWI sections and were visualized as having a hyperintense center and a circular hypointense periphery in ADC maps. This sign was defined as target sign both in DWI sections and in ADC map (**Figure 1**). Lesions other than target sign were visualized as diffuse hyperintense in DWI and diffuse hypointense in ADC maps (**Figure 2**) or were visualized with a heterogeneic signal intensity containing hypo- and hyperintense areas (**Figure 3**). Lesions were divided into two groups, those with target sign and others based on DWI signal intensity. Then, ADC measurements were performed by placing a circular region of interest (ROI) in lesions. Measurements were performed in the peripheral hypointense part of the lesion in patients with the target sign, in the hypointense part of the lesion in lesions with heterogeneic signal intensity, and around the periphery of the lesion in completely hypointense lesions. The instrument automatically calculated average (ADCav) and minimum (ADCmin) values as mm²/s after ROIs were placed. Totally 3 measurements were performed on each lesion. The average of these 3 values was accepted as the mean ADCav and ADCmin value. ROI dimensions and obtained ADC values were recorded.

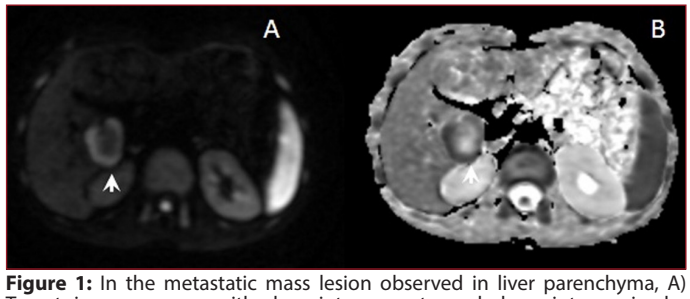

Figure 1: In the metastatic mass lesion observed in liver parenchyma, A) Target sign appearance with a hypointense center and a hyperintense circular periphery in DWI; B) In contrast to DWI, target sign appearance with a circular hypointense periphery and a hyperintense center in an ADC map passing through the same section

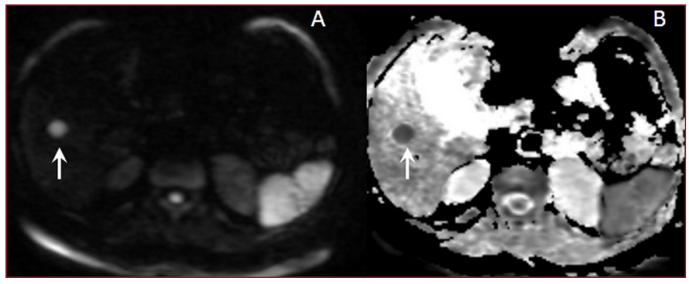

Figure 2: The metastatic mass lesion observed in liver parenchyma A) Diffuse hyperintense appearance in DWI; B) Diffuse hypointense appearance in ADC map passing through the same section

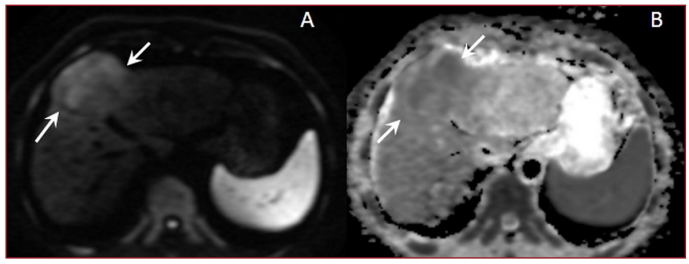

Figure 3: HCC case observed to have hypo-, hyper-, and isointense areas with heterogeneous intensity in both A) DWI; B) ADC map

Statistical Analysis

Complementary analyses were performed in order to give information about general properties of the variables. Continuous variables are given as average±standard deviation; data for categorical variables are given as n (%). Independent sample t test was used to compare the continuous normal data between groups. Cross tabs and chi-square tests were used to compare the categorical data among groups. Receiver operating curve (ROC) analysis was used to evaluate performances of ADCmin and ADCav variables in distinguishing metastases from HCC. Cohen's kappa coefficient was used for interobserver agreement. P-values calculated to be smaller than 0.05 were considered statistically significant. Statistics software was used in calculations (IBM SPSS Statistics 19, SPSS Inc., an IBM Co., Somers, NY).

RESULTS

Fifty-seven patients (female/male: 18/39) were included in the study. The average age was 63.93±10.85 years. Of the 57 patients, 39 had metastatic liver masses, while 18 had HCC. There was not a statistically significant difference in terms of age or gender between the groups (p>0.05). The primary cancers of metastatic patients were as follows in order of frequency: 11 colon (28.2%), 8 lung (20.5%), 6 rectal (15.3%), 6 stomach (15.3%), 3 breast (7.7%), 2 prostate (5.1%), 1 pancreas (2.6%), 1 ovarian (2.6%), and 1 esophagus (2.6%). A total of 155 lesions obtained from 57 patients were evaluated. Of these lesions, 131 were metastases and 24 were HCC. Distribution of quantitative variables based on lesions by groups is given in **Table 1**.

Table 1. Distribution of quantitative variables by group

Variables	Group		p
	Metastasis (n=131)	HCC (n=24)	
Lesion size	29.37±18.59	35.79±25.44	0.248
ROI size (mm)	8.30±1.16	8.28±0.36	0.940
ADCmin ($\times10^{-6}$ mm² /s)	807.83±255.6	1020.42±318.12	<0.001
ADCav ($\times10^{-6}$ mm² /s)	909.03±243.63	1109.98±304.81	<0.001

ROI: region of interest, ADC: apparent diffusion coefficient, Data are given as average±SD, HCC: Hepatocelular carcinoma

With respect to this, ADCmin and ADCav values were significantly lower in the metastasis group compared with the HCC group.

When 155 lesions were evaluated for target sign, target sign was found in 55% of metastases, while this rate was 25% in the HCC group. The difference of the incidence of target sign detection between the two groups was statistically significant (p=0.007) and this ratio was higher in metastases. The distribution of target sign in groups is given in **Table 2**.

Table 2. The distribution of target signs in groups

		Total	Nature of lesion		p
			Target Sign	Others	
	Metastasis	131(84.5)	72(55.0)	59(45.0)	0.007
	HCC	24(15.5)	6(25.0)	18(75.0)	
Primary lesion	Lung	18(11.6)	3(16.7)	15(83.3)	-
	Colon	40(25.8)	20(50)	20(50)	
	Breast	12(7.7)	3(25)	9(75)	
	Stomach	30(19.4)	20(66.7)	10(33.3)	
	Over	2(1.3)	0(0)	2(100)	
	Esophagus	3(1.9)	3(100)	0(0)	
	Pancreas	1(0.6)	0(0)	1(100)	
	Prostate	5(3.2)	5(100)	0(0)	
	Rectal	20(12.9)	18(90)	2(10)	
	HCC	24(15.5)	6(25.0)	18(75.0)	

Data are expressed as frequency or percentage. HCC: Hepatocellular carcinoma

When an evaluation was performed based on the number of patients, the presence of target sign was again significantly higher in the metastasis group (p=0.039) (**Table 3**).

Table 3. The evaluation of the presence of target sign based on the number of patients

		Total	Nature of lesion		p
			Target Sign	Others	
	Metastasis	39(68.4)	20(51.3)	19(48.7)	0.039
	HCC	18(31.6)	4(22.2)	14(77.8)	
Primary lesion	Lung	8(14)	3(37.5)	5(62.5)	-
	Colon	11(19.3)	5(45.5)	6(54.5)	
	Breast	3(5.2)	1(33.3)	2(66.7)	
	Stomach	6(10.5)	4(66.7)	2(33.3)	
	Over	1(1.8)	0(0)	1(100)	
	Esophagus	1(1.8)	1(100)	0(0)	
	Pancreas	1(1.8)	0(0)	1(100)	
	Prostate	2(3.5)	2(100)	0(0)	
	Rectal	6(10.5)	4(66.7)	2(33.3)	
	HCC	18(31.6)	4(22.2)	14(77.8)	

Data are expressed as frequency or percentage. HCC: Hepatocellular carcinoma

ADCmin and ADCav values for distinguishing metastasis from HCC were <758 ×10^{-6} and <817×10^{-6} mm²/s, respectively, with respect to ROC analysis (**Table 4**). Cohen's kappa coefficient (***κ***) is 0.893 (p<0.001) for which measures inter-rater agreement for target sign detection. Correlation coefficients (r) are 0.969 (p<0.001) and 0.934 (p<0.001) for ADCmin and ADCav respectively.

Table 4. ROC analysis results in regard to distinguishing metastasis from HCC

	Cutoff	AUC	Se	Sp	PPV	NPV	p
ADCmin (×10^{-6} mm² /s)	<758	0.680	0.412	0.875	0.947	0.214	0.005
ADCav (×10^{-6} mm² /s)	<817	0.682	0.412	0.917	0.964	0.222	0.005

AUC, area under curve; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value, HCC: Hepatocelular carcinoma

DISCUSSION

This study demonstrates that target sign is observed more frequently in metastasis compared with HCC. Also, ADC values were found to be lower in the metastasis group compared with HCC. These results indicate that target sign detected by DWI and ADC values can be used as MRI markers contributing to differential diagnosis in distinguishing metastasis and HCC.

Target sign detected by DWI was investigated in the evaluation of liver masses in a few studies.[20-22,24] Min et al. found the detection rate of target sign to be higher in ICCcompared with HCC both in hepatobiliary phase-contrast sequences obtained using the liver-specific contrast agent gadoxetic acid and in DWI in their studies.[21] In target sign detected by DWI, the central part was observed to be hypointense and the peripheral part to be hyperintense, as in our study. They stated that central hypointensity detected in DWI might be related to dense collagen, loose fibrotic tissue, or necrosis.[21] Kovač et al. compared hypovascular metastases and ICC in terms of target sign detected in DWI and found that detection rates of target sign were higher in ICC compared with hypovascular metastases. Target sign was also found in a similar appearance, and it was suggested that central hypointensity was the result of fibrous tissue.[20] For the first time in the literature, our study compares metastases and HCC in terms of DWI target sign, and target sign was detected at higher rates in metastases. In our study, metastases were not grouped based on vascularization properties; they were studied as a single group, in contrast to the study by Kovač et al.

Gourtsoyianni et al. noticed a ring-like pattern with a hyperintense central part and a hypointense periphery in ADC maps in colorectal, breast, and lung metastases in their study, in which they compared DWI images and ADC values of benign and malignant focal liver lesions. They indicated that they did not observe such a pattern in pancreatic and intestinal cancer metastases or metastases with an unknown primary tumor and other liver masses. They confirmed that central hyperintensity was related to necrosis using T2 weighted and contrasted T1 weighted sequences.[19] The ring-like appearance described in that study had similar properties with the target appearance. ADC measurements were also performed in the peripheral hypointense part, which was thought to have a cellular content, in lesions with the ring sign, as was done in our study.[19] Gourtsoyianni et al. detected a diffuse hypointense appearance as a second pattern apart from the ring-like pattern in ADC maps. In our study, we detected three different patterns, target sign, diffuse hypointensity, and heterogeneic appearance, in which hypo- and hyperintense regions were found together heterogeneously in ADC maps in metastases and HCC.

Granata et al. evaluated colorectal metastases using gadoxetic acid-MRI sections and detected a target appearance that had a lower degree of hypointensity in the center in 46.7% of lesions. They claimed that the different degree of gadoxetic acid uptake detected in the center of the lesion resulted from interstitial diffusion of the contrast agent in the central necrosis area. They suggested that a comparative evaluation with DWI should be performed to support this hypothesis.[25] Ha et al. detected a target appearance that had a higher hyperintensity in the center and a hypointense rim at the periphery, in hepatobiliary phase obtained by gadoxetic acid-MRI in breast cancer metastases and indicated that the relative contrast formed in the center resulted from desmoplastic reaction.[26] In our study, target sign could not be compared with histopathological sections since there were not histopathological sections obtained from metastases; however, in support of the hypotheses of Granata et al., Min et al., and Gourtsoyianni et al., we also think that hypointensity in the center detected in DWI is caused by a necrosis-related diffusion increase, and the hyperintense area at the periphery indicates a diffusion restriction caused by cellular intensity; central hyperintensity and peripheral hypointensity observed in all lesions with a target sign in ADC support this hypothesis.[19,21,25,27]

Another sign in our study is that metastases have lower ADC values compared with HCC. In the literature, there are several studies investigating ADC values of focal liver masses.[9-19] In these studies, ADC values in benign lesions were found to be higher than those of malignant lesions.[9-19] However, there are overlaps of ADC values in both benign and malignant lesions.[5,9,10,28] Therefore, the ADC value alone is not enough to characterize the lesion; morphological changes detected in DWI should also be taken into consideration. In the literature, ADC values of metastases range from 0.94 to 2.87.[29] The reason for this wide range may be the application of different DWI sequence parameters such as different b values and use or non-use of a parallel imaging technique.[15] In our study, we used a high b value, and as a result of this, we found an average ADC value for metastases close to the lower limit in the literature. In a large number of studies, ADC values of metastases were found to be lower than those of HCC,[9,10,13,14,18,19] while ADC values of metastases were found to be higher than those of HCC in several other studies.

[11,12,16,17] However, the difference between two groups was not statistically significant in these studies.[9,12,14,16,18] In our study, we found that ADC values in the metastasis group were lower than those of the HCC group; this difference was statistically significant.

In the literature, evaluation of focal liver masses with ROC curve is present in several studies; cut-off ADC values were used in distinguishing benign and malignant liver masses in several studies.[9,14-19] ADC values obtained by ROC analysis to distinguish metastatic liver lesions from HCC were determined in our study for the first time.

There are several limitations of our study. First, due to small number of patients, the statistical power the study has limited. Second, DWI-target sign was evaluated in metastases and HCC since these are the most frequent liver masses; other liver masses were not included in the study. In future studies, DWI-target sign in a larger series containing a higher number of liver masses should be performed. Moreover, DWI-target sign and contrast-enhanced MRI series should be compared to investigate whether there is an association between hypervascular or hypovascular liver lesions and target sign on DWI.

CONCLUSIONS

The target sign detected by DWI and ADC values can be used as MRI markers that enhance diagnostic accuracy in distinguishing the most frequent liver masses, metastatic liver lesions and HCC.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Clinical Investigations Ethics Committee of Tokat Gaziosmanpaşa University Medical Faculty (21.12.2020 /16-KAEK-057).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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