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Araştırma Makalesi / Research Article

The Value of Diffusion Weighted Magnetic Resonance Imaging in Differentiation of Benign and Malignant Adrenal Lesions

Difüzyon Ağırlıklı Manyetik Rezonans Görüntülemenin Benign ve Malign Adrenal Lezyonları Ayırt Etmedeki Değeri

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ABSTRACT

Purpose: Diffusion weighted imaging (DWI) is a functional magnetic resonance imaging (MRI) technique that explores the random motion of water molecules in the body. Although DWI has been widely applied in the evaluation of intracranial disorders, there is growing interest for its use in detection and characterization of abdominal masses. In this study, the efficiency of DWI in distinguishing benign adrenal focal lesions from malignant ones is investigated.

Material and Methods: Sixty six adrenal focal lesions in 56 patients were included in the study. The lesions were characterized with dynamic adrenal computed tomography and/or adrenal MRI if there was not a histopathological result or radiological follow up. DWI was performed for these lesions and apparent diffusion coefficient (ADC) values were measured by using three different b values (b=500 sec/mm^2, b=750 sec/mm^2, b=1000 sec/mm^2).

Results: The mean ADC values of 39 benign lesions were 1.54 x 10^{-3} mm^2/sec for b=500 sec/mm^2, 1.01x 10^{-3} mm^2/sec for b=750 sec/mm^2 and 0.77 x 10^{-3} mm^2/sec for b=1000 sec/mm^2. The mean ADC values of 27 malignant lesions were found to be 1.69x 10^{-3} mm^2/sec, 1.14 x 10^{-3} mm^2/sec and 0.86 x 10^{-3} mm^2/sec for b=500 sec/mm^2, b=750 sec/mm^2, b=1000 sec/mm^2, respectively. There was not any statistically significant difference between ADC values of benign and malignant lesions for all three b values ($p<0.05$).

Conclusion: According to this study, DWI did not seem to be an effective radiological method for differentiating benign and malignant adrenal lesions; but for a more accurate decision, studies with improved and high resolution images, standard technical parameters and larger number of lesions may be needed.

Key Words: Adrenal tumor, malign, benign, magnetic resonance imaging, diffusion weighted imaging

ÖZET

Amaç: Difüzyon ağırlıklı görüntüleme (DAG) vücuttaki su moleküllerinin rastgele hareketlerini inceleyen bir fonksiyonel manyetik rezonans görüntüleme (MRG) tekniğidir. DAG intrakranial bozuklukların değerlendirilmesinde yaygın bir şekilde kullanılmasına rağmen, abdominal kitlelerin tespiti ve karakterizasyonunda kullanılmasına artan bir ilgi vardır. Bu çalışmada DAG'nin benign adrenal lezyonları malign olanlardan ayrımındaki yeterliliği araştırılmıştır.

Materyal ve Metod: Elli altı hastadaki 66 fokal adrenal lezyon çalışmaya dahil edildi. Histopatolojik sonucu veya radyolojik takibi olmayan lezyonlar dinamik adrenal bilgisayarlı tomografi ve/veya adrenal MRG ile karakterize edildi. Bu lezyonlar için DAG yapıldı ve üç farklı b değeri kullanılarak (b=500 s/mm^2, b=750 s/mm^2, b=1000 s/mm^2) apparent diffusion coefficient (ADC) değerleri ölçüldü.

Sonuçlar: Otuz dokuz benign lezyonun ortalama ADC değerleri b=500 s/mm^2 için 1.54 x 10^{-3} mm^2/s , b=750 s/mm^2 için 1.01x 10^{-3} mm^2/s ve b=1000 s/mm^2 için 0.77 x 10^{-3} mm^2/s ölçüldü. Yirmi yedi malign lezyonun ortalama ADC değerleri b=500 s/mm^2, b=750 s/mm^2 ve b=1000 s/mm^2 için sırasıyla 1.69x 10^{-3} mm^2/s, 1.14 x 10^{-3} mm^2/s ve 0.86 x 10^{-3} mm^2/s olarak tespit edildi. Her üç b değeri için benign ve malign lezyonların ADC değerleri arasında istatistiksel olarak anlamlı fark yoktu ($p<0.05$).

Tartışma: Bu çalışmaya göre DAG benign ve malign adrenal lezyonların ayrımı için etkili bir yöntem olarak bulunmamıştır fakat daha doğru bir karar için gelişmiş ve yüksek çözünürlüklü görüntüler, standart teknik parametreler ve daha fazla sayıda lezyona ihtiyaç duyulabilir.

Anahtar kelimeler: Adrenal tumor, malign, benign, manyetik rezonans görüntüleme, difüzyon ağırlıklı görüntüleme

INTRODUCTION

The prevalence of incidentally detected adrenal masses was reported to be 2.3% in autopsy series and 0.5-2% on abdominal computed tomography (CT) examinations performed for any reason[1].The most common pathology is a non-secretory cortical adenoma, whereas other pathologies like secretory adrenal adenoma (Conn syndrome and Cushing disease), pheochromocytoma, adrenal cancer and metastatic tumors can also be encountered[2]. Since the secretory adrenal mass is symptomatic in majority of cases, it is relatively easy to diagnose. However, non-secretory cortical adenoma may not present with specific symptoms, so detection and characterization can be more difficult. Moreover, the characterization of an adrenal mass in patients with a known primary cancer is crucial in order to decide for an optimal management which will be either curative or palliative. In these cases, adrenal CT, chemical shift magnetic resonance imaging (MRI) and radiological follow up can be used to avoid unnecessary interventions.

On unenhanced CT, an adrenal mass with an attenuation value of 10 Hounsfield Unit (HU) or less, is more likely to be an adenoma[3-5]. But, lipid-poor adenomas cannot be differentiated from metastatic masses by this method. Dynamic adrenal CT is useful to overcome this problem; however iodinated contrast material is administrated and the patient is exposed to additional radiation. Chemical shift MRI is also a useful technique to differentiate adenoma from metastasis, because most adenomas are rich from intracytoplasmic lipid. However, some lipid-poor adenomas are difficult to differentiate from metastatic tumors by this technique. Radiological follow up can be helpful but it needs a substantial amount of time (at least 12 months) to be sure[6].

Diffusion weighted imaging (DWI) is a promising functional MRI method in abdominal imaging, especially to detect and characterize focal/diffuse lesions. However, to our knowledge, there are only few studies about the role of DWI in characterization of adrenal masses[7-9]. The aim of this study is to investigate the efficacy of DWI, a non-invasive radiological technique, in distinguishing benign adrenal focal lesions from malignant ones.

MATERIALS AND METHODS

Local ethic committee approval was obtained for this prospective study which was carried out between May 2009 and January 2010. Informed concent was taken from all the participants. Fifty six patients (34 women and 22 men; mean age, 58.6 years; age range, 28-76 years) with a total of 66 adrenal masses, detected by other radiological modalities, constituted the study group. The dimensions of the lesions were 1 – 11 cm in range (mean 3.06 cm); the dimensions of 13 lesions were 1 cm, the dimensions of 53 lesions were larger than 1 cm. The lesions were characterized with dynamic adrenal CT and/or adrenal MRI and the results of these examinations were accepted as the final diagnosis for statistical analysis, unless there was a histopathological result or radiological follow up at least 6 months. Adrenal MRI was used for whole group of 56 patients while 8 of them had additional evaluated by dynamic adrenal CT.

Dynamic adrenal CT examinations were performed on 64 detector row Toshiba Aquilion (Toshiba Medical Systems, Tokyo, Japan) CT system. After the standardization of examination protocol (120 kv, 60 mAs, 5mm slice thickness), unenhanced and contrast enhanced axial images, obtained 70 seconds and 15 minutes after intravenous contrast administration, were acquired. The attenuation values were measured in each phase of the exam and always obtained at the same level of the lesions using region of interest (ROI). The ROI was kept as large as possible to cover the entire lesion while excluding calcifications and cystic/necrotic areas. Wash-out percentage of contrast enhancement was calculated. The lesions with a wash-out percentage of <60% were accepted as non-adenomas, while the lesions with a wash-out percentage of >60% were accepted as adenomas[10].

Adrenal MRI examinations were performed on 1.5T General Electric Excite II system (Milwaukee, Wisconsin,USA) using 4-channel Torso PA coils. Images were obtained with the following parameters: axial T1-weighted [repetition time (TR):160 msec, time to echo (TE): 4.2 msec, field of view (FOV): 34x27.2 cm, matrix: 288x160, section thickness: 5mm, number of excitations (NEX): 1), axial T2-weighted (TR: 1144 msec, TE: 83.4 msec, FOV: 34x34 cm, matrix: 320x256, section thickness: 5 mm , NEX: 0.56), dual echo (TR: 280 msec, TE: 4.5 msec, FOV: 34x30.6 cm, matrix: 320x160, section thickness: 5 mm , NEX: 1), coronal T2-weighted (TR: 1159 msec, TE: 88 msec, FOV: 42x42 cm, matrix: 320x256, section thickness: 4 mm, NEX: 0,56). On in phase and out of phase images, the signal intensities of both the adrenal lesions and spleen were measured on the same images. The same rules of measurement, as they were used in CT, were applied in measuring the signal intensities. Adrenal-to-spleen ratio was calculated for each lesion; the lesions with a ratio of <-28 were accepted as adenomas and the lesions with a ratio of >-28, as non-adenomas[11].

DWI was performed following dynamic adrenal CT and/or adrenal MRI examinations. Free-breathing technique was used with 3 different b values (b=500 sec/mm2, b=750 sec/mm2, b=1000 sec/mm2). Axial images were obtained using following parameters: TR: 2500msec, TE: 69.6msec, FOV: 36x36cm, matrix: 128x128, slice thickness: 4mm, NEX: 16. ADC maps were formed automatically and mean ADC values of all lesions were calculated using ROI. ROI was put in T2 echo planar imaging (EPI) DW image and was then copied to ADC map. The circle ROI was kept as large as possible to cover the entire lesion for the 13 lesions which diameters were 1 cm. For the 53 lesions, larger than 1 cm in diameter; the circle ROI with 1 cm diameter put on three different place of the lesions on the same images and the measurements were repeated for the consecutive images while excluding calcifications and cystic/necrotic areas. ADC values of the lesions were determined based on the average value obtained from these measurements.

The final diagnosis was made according to radiological results, clinical and laboratory findings and histopathological results.

Statistical analysis

The results were presented as rate for categorical values and as mean and median for continuous variables. Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) were used for estimation. The data were analyzed using SPSS version 11.5. (SPSS Inc., Chicago, IL) and a p value of <0.05 was considered statistically significant.

RESULTS

Of 66 adrenal lesions, 39 were accepted as benign and 27 were accepted as malignant. There were 9 functional adenomas (5 pheochromocytoma, 4 Cushing syndrome) (Fig 1) and 30 non-secretory adenomas (Fig 2) in the benign group. Histopathological diagnosis was obtained in 11 of these 39 lesions. Nineteen radiologically benign lesion did not change in size during radiological follow-up of 6 months; so they were presumed to be benign. Other 9 lesions were accepted as benign based on the radiological findings on dynamic adrenal CT and chemical shift MRI. All the patients with malignant adrenal lesions (n=27) had a prior histopathological diagnosis of lung cancer (Fig 3). Diagnosis of metastasis was made solely depending on the results of adrenal MRI (Table 1 and 2). In conclusion, the final diagnosis of 11 (malignant) lesions were made by histopathologically, 29 lesions (19 benign,10 malignant) were diagnosed by adrenal CT and/or MRI and at least 6 month radiologic follow up and 26 lesions (20 benign, 6 malignant) were diagnosed by adrenal CT and/or MRI with clinical and laboratory findings.

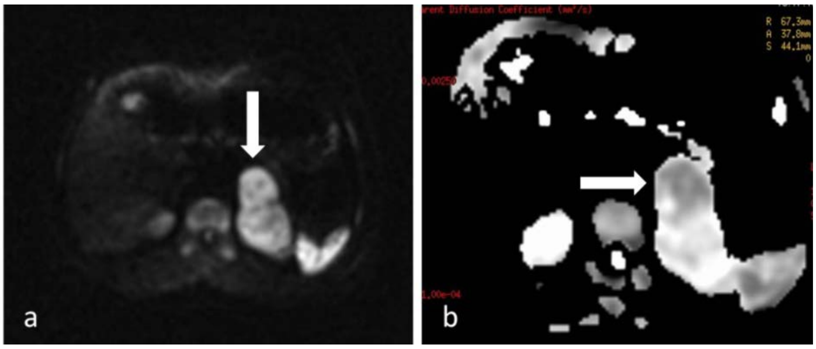

Figure 1. 54-year-old woman with pheochromocytoma.

a, Transverse spin-echo echo-planar diffusion-weighted image (b value, 500) shows heterogen hyperintense adrenal mass (arrow).

b, Apparent diffusion coefficient map shows the heterogen-hyperintense lesion (arrow), apparent diffusion coefficient value is 1.90 x 10^{-3} mm^2/sec.

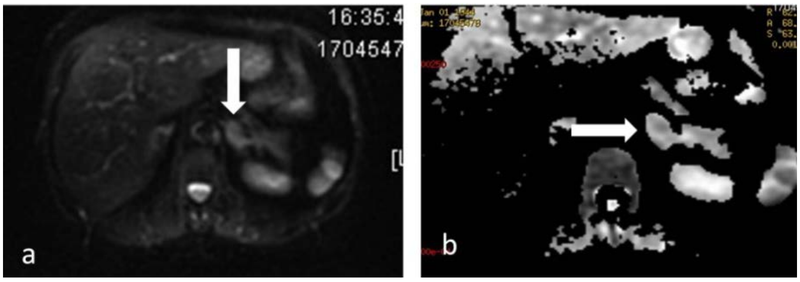

Figure 2. 64-year-old woman with non-secretory adrenal adenoma

a, Diffusion-weighted image (b value, 500) shows hyperintense lesion on left adrenal gland (arrow)

b, Apparent diffusion coefficient map shows the hyperintense lesion (arrow), apparent diffusion coefficient value is 1.43 x 10^{-3} mm^2/sec.

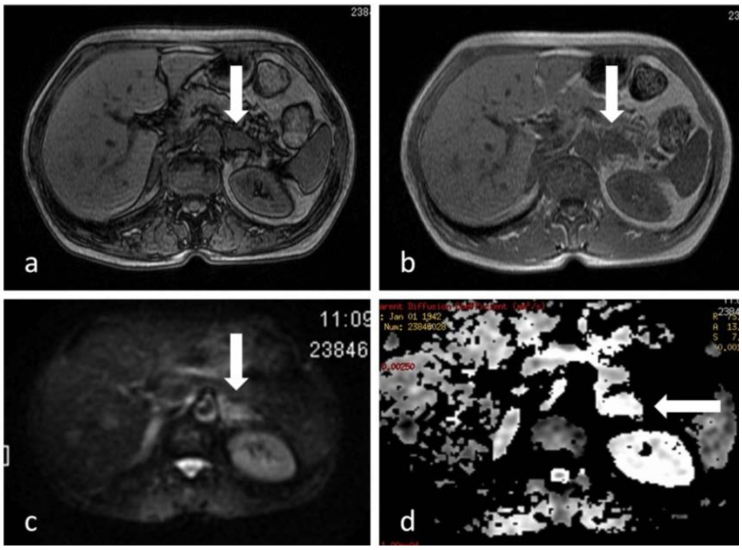

Figure 3. 68-year-old woman with adrenal metastasis from lung cancer.
a and b, Out-of-phase (a) and in-phase (b) transverse chemical shift images show that this adrenal gland mass (arrow) doesn't contain lipid.
c and d, Diffusion-weighted image (c) (b value, 500) shows hyperintense lesion on left adrenal gland (arrow) and apparent diffusion coefficient map (d) shows the hyperintense lesion (arrow), apparent diffusion coefficient value is 2.48 x 10^{-3} mm^2/sec.

Table 1. The diagnoses and numbers of the lesions

Lesions			Number
Benign	Secretory adenoma	Cushing syndrome	4
		Pheochromocytoma	5
	Non-secretory adenoma		30
Malignant	Lung cancer metastasis		27

Table 2. Methods for the final diagnosis of the lesions

	Benign	Malignant
Histopathological examination	11	-
Radiological findings and follow-up	19	-
Radiological findings	9	27
Total	39	27

The ADC values of 39 benign lesions for b=500 sec/mm^2 were between 0.97- 2.22 x 10^{-3} mm^2/sec for b=750 sec/mm^2 were between 0.30 – 1.48 x 10^{-3} mm^2/sec, for b=1000 sec/mm^2 were between 0.45 – 1.11 x 10^{-3} mm^2/sec and mean ADC values were calculated to be 1.54 x 10^{-3} mm^2/sec, 1.01x 10^{-3} mm^2/sec and 0.77 x 10^{-3} mm^2/sec, respectively.

The ADC values of 27 malignant lesions were between 0.85 – 2.61 x 10^{-3} mm^2/sec for b=500 sec/mm^2, between 0.56 – 1.76 x 10^{-3} mm^2/sec for b=750 sec/mm^2 and between 0.42 – 1.32 x 10^{-3} mm^2/sec for b=1000 sec/mm^2. The mean ADC values were found to be 1.69x 10^{-3} mm^2/sec, 1.14 x 10^{-3} mm^2/sec and 0.86 x 10^{-3} mm^2/sec, respectively.

ADC values of benign and malignant lesions for 3 different b values were shown in table 3 and figures 4-6.

In the statistical analysis using Independent Samples T test, a statistically significant difference was not detected between the ADC values of malignant and benign lesions ($p>0.05$).

Table 3: ADC values of benign and malignant lesions for different b values

	ADC value (mm^2/sec)					
	b = 500 sec/mm²		b = 750 sec/mm²		b = 1000 sec/mm²	
	Range	mean	range	mean	Range	mean
Benign	0.97- 2.22	1.54	0.30 – 1.48	1.01	0.45 – 1.11	0.77
Malignant	0.85 – 2.61	1.69	0.56 – 1.76	1.14	0.42 – 1.32	0.86

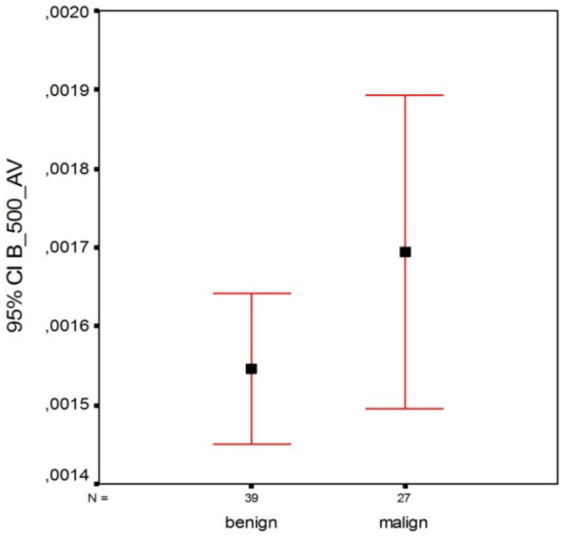

Figure 4: Mean ADC values of benign and malignant lesions for b=500 sec/mm^2

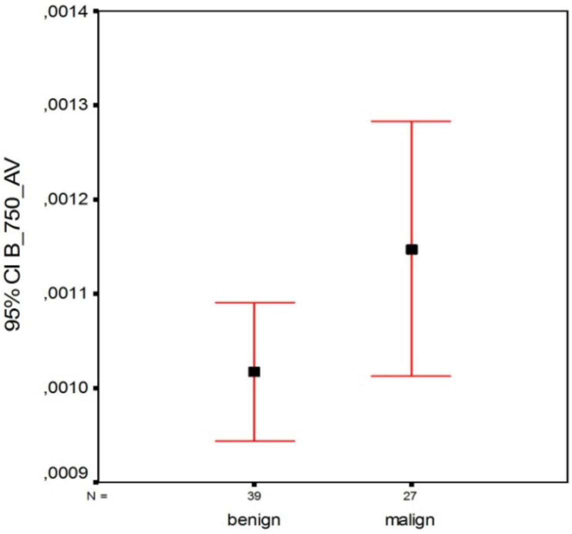

Figure 5: Mean ADC values of benign and malignant lesions for b=750 sec/mm^2

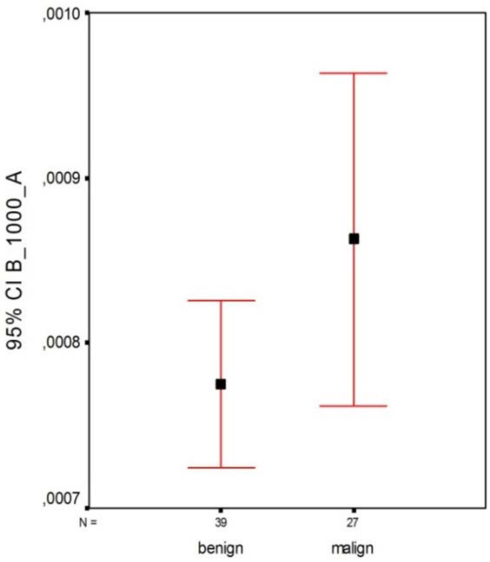

Figure 6: Mean ADC values of benign and malignant lesions for b=1000 sec/mm^2

DISCUSSION

Diffusion weighted imaging, which is a functional MRI technique, has first been performed in the diagnosis of acute ischemia in neuroradiology and following the improvements in MRI technology, it has also been used in abdominal and pelvic regions[12]. Diffusion is a physical process that results from the random motion of water molecules[13]. In tissues, apparent diffusion is observed since the movement of water molecules is modified by interactions with cell membranes and macromolecules. DWI derives its image contrast on the basis of differences in the mobility of protons between tissues. In tissues that are highly cellular, the tortuosity of the extracellular space and the higher density of hydrophobic cellular membranes restrict the apparent diffusion of water protons[14,15]. However, in cystic or necrotic tissues, the movement of water protons are relatively free. In DWI, b value or b factor was used to maintain the diffusion weight of the examination. By changing the b value, the sensitivity of the imaging sequence to water diffusion can also be altered. Performing DWI measurements by using two or more b values not only makes the characterization of a focal lesion possible, depending on the differences in water diffusivity, but also allows quantification of the apparent diffusion coefficient (ADC) of tissues or lesions. In abdominal region, low b values (< 100 sec/mm^2) are useful in lesion detection and high b values (> 500 sec/mm^2) provide lesion characterization. As a rule, both benign and malignant solid lesions may demonstrate residual high signal intensity on higher b values; however, automatically calculated ADC maps can help in differentiation of benign and malignant lesions, especially in liver. In general malignant lesions are shown to have lower ADC values when compared with the benign ones[16].

In the literature, there was relatively enough experience about DWI of various solid organs, such as liver, kidney, pancreas, and their different pathologies. However, differentiation of adrenal adenomas/benign solid lesions from metastasis/malignant lesions, which sometimes becomes a very challenging clinical problem, has not been investigated thoroughly. In our study, it was aimed to examine the utility of DWI in differentiation of benign and malignant adrenal lesions. However, statistical analysis did not show a significant difference between benign and malignant lesions in terms of ADC values.

The amount of intracytoplasmic lipid can vary significantly in focal lesions and this can result in broad variability of diffusion restriction. Extracellular space distance, cellular membrane structure and cell array in the tumor tissue can also affect diffusion characteristics[8,17].

B value is the most important factor altering the ADC value. Le Bihan et al and Ichiwaka et al showed that if b value was selected low, ADC value would be high[18,19]. They suggested that factors like perfusion and T2 time would significantly affect ADC value in abdominal diffusion studies if the b values were lower. According to this study, b values should be higher than 400 sec/mm^2 so it might reflect the ADC values and diffusion characteristics more accurately. In our study, b value was selected >400 sec/mm^2 and ADC measurements were performed for three different b values: 500 sec/mm^2, 750 sec/mm^2, 1000 sec/mm^2. We showed negative correlation between b and ADC values. These results were concordant with the previous reports in the literature: when b value increased, ADC values got lower. But, there was no statistical difference in ADC values for different b values between malignant and benign lesions.

To the best of our knowledge, there are two studies in literature about utility of DWI in adrenal masses. In the study of Tsushima et al, DWI was performed in 43 adrenal masses (11 secretory cortical adenomas, 20 non-secretory cortical adenomas, 7 metastatic tumors and 5 pheochromocytomas)[7]. B value was selected as 1000 sec/mm^2 and a significant difference between ADC values of adenomas and metastatic lesions was not detected. However, in this study the number of adrenal malignancies was relatively small with the large number of benign lesions and this limitation may lead to a potential statistical bias. On the other hand, Miller et al used DWI in 160 adrenal lesions (118 adenomas, 9 myelolipomas, 9 cysts, 4 adrenal hemorrhagic lesions, 1 angiomyolipoma, 4 adrenal cortical carcinomas, 3 pheochromocytomas, 1 neuroblastoma and 11 metastatic lesions)[8]. In their study, three different b values (b=50 sec/mm^2, b=500 sec/mm^2, b=1000 sec/mm^2) were used; yet there was not any significant difference between benign and malignant lesions, also they reported that ADC values of adenomas tended to be lower than those of malignant lesions and also concluded that there was no significant difference between the ADC values of lipid-rich and lipid-poor adenomas. However, in this study the number of malignant group was smaller than benign group and they accepted adrenal cysts and adrenal hemorrhages in the benign group, but we excluded cystic lesions and areas in our study. Concordant with the results of these two studies, we did not find any statistically significant difference between the ADC values of adenomas and non-adenomas/metastasis. This result is surprising, because in the literature ADC values of malignant focal lesions, especially those of liver, were reported to be lower than ADC values of the benign ones. It may be assumed that the parameters which affect tissue diffusion, such as cell array, cell membrane structure, width and tortuosity of extracellular space, are not clearly different in adrenal adenomas and non-adenomas/metastasis. Another conflict is also present in dynamic adrenal CT of adrenal lesions. In general, malignant lesions are expected to enhance and wash out relatively faster than benign ones because of neovascularity and arteriovenous shunts. However, adrenal adenomas/benign lesions show this rapid enhancement-wash out pattern, while metastasis/non-adenomas tend to enhance and wash out slower. This finding has not been elucidated properly, but some authorities have speculated that nonadenomas have a disturbed capillary permeability, with prolonged retention of contrast material in the effective extracellular space[20]. Though it is difficult to prove, the mechanism which reverses the established enhancement-wash out pattern in case of adrenal adenomas and metastasis can be presumed to be the responsible mechanism which makes the ADC values of adenomas and metastasis statistically insignificant.

Our study had some limitations. We could not reach a histopathological diagnosis for all lesions and radiological follow up was limited to 6 months. The dimensions of the lesions were variable; for small lesions, lesion delineation and for some of the large lesions, tumor heterogeneity created problems that ADC measurements could be performed suboptimally. Although DWI is a novel technique for abdominal region, standardization of image parameters and measurement techniques is lacking.

In conclusion, our study showed that DWI may not be a suitable radiological tool for discrimination of benign and malignant adrenal lesions. These results supported those of the previous two studies. For a more accurate decision, studies with improved and high resolution images, standard technical parameters and larger number of lesions may be needed.

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