Akademik Gastroenteroloji Dergisi • *2023; 22(2): 90-97*

Manuscript Received: *05.07.2023* • ***Accepted:*** *29.07.2023*

ORIGINAL ARTICLE

The role of different apparent diffusion coefficient values in differentiating malignant from benign solid tumors of the pediatric abdomen and pelvis

Farklı görünür diffüzyon katsayısı değerlerinin pediatrik abdomen ve pelvisin solid malign ve benign tümörlerini ayırt etmedeki yeri

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Background and Aims: Diffusion-weighted magnetic resonance imaging is a non-invasive method that can be used in the characterization of tumors, by the quantification of highly cellular tumor components with the use of region of interest measurements on the generated apparent diffusion coefficient maps. The diffusion characteristics of the solid benign tumors of the abdomen and pelvis in children, and the role of apparent diffusion coefficient values in distinguishing solid malignant from solid benign tumors are not well defined. **Materials and Method:** This study retrospectively evaluated the role of different fractions of the measured and calculated apparent diffusion coefficient values in 49 children with a solid mass lesion of the abdomen or pelvis to determine whether those values allow for distinguishing malignant from benign solid lesions. A subgroup evaluation included the analysis of the apparent diffusion coefficient values in distinguishing Wilms tumor from neuroblastoma. **Results:** All fractions of apparent diffusion coefficient values were statistically significantly lower in the solid malignant tumors than in the solid benign tumors, with the mean normalized apparent diffusion coefficient values having higher sensitivity and specificity rates. The apparent diffusion coefficient values did not significantly differ between Wilms tumor and neuroblastoma. **Conclusions:** Apparent diffusion coefficient values can help differentiate malignant from benign solid tumors. Their role can be limited in differentiating Wilms tumor from neuroblastoma.

Key words: Abdominopelvic, apparent diffusion coefficient, diffusion-weighted imaging, pediatric malignancy, solid tumor

Giriş ve Amaç: Diffüzyon ağırlıklı manyetik rezonans görüntüleme, tümörlerin karakterize edilmesinde kullanılabilen invaziv olmayan bir görüntüleme yöntemidir. Diffüzyon görüntülerinden elde olunan görünür diffüzyon katsayısı haritaları üzerinde ilgili bölge ölçümleri ile yoğun hücresellik içeren tümör komponentlerinin niceliği saptanabilir. Çocukların abdominopelvik incelemelerinde solid benign tümörlerin diffüzyon özellikleri ile görünür diffüzyon katsayısı değerlerinin bu bölgenin solid benign ve solid malign tümörlerini birbirinden ayırt etmedeki rolü iyi tanımlanmamıştır. **Gereç ve Yöntem:** Bu çalışmada abdomen ya da pelviste solid kitlesi saptanan 49 çocuk hastada, farklı görünür diffüzyon katsayısı değeri ölçümlerinin solid malign kitleleri solid benign kitlelerden ayırt etmedeki yerinin araştırılması hedeflenmiştir. Altgrup analizi olarak, bu görünür diffüzyon katsayısı değerlerinin Wilms tümörü ve nöroblastomun birbirinden ayırt edilmesindeki yeri araştırılmıştır. **Bulgular:** Tüm görünür diffüzyon katsayısı değerlerinin solid malign abdominopelvik kitlelerde benign olanlara kıyasla istatistiksel olarak anlamlı düşük olduğu bulunmuştur. Wilms tümörü ve nöroblastom arasında ise ölçülen görünür diffüzyon katsayısı değerlerinde farklılık saptanmamıştır. **Sonuç:** Görünür diffüzyon katsayısı değerleri solid malign tümörleri benign tümörlerden ayırmada yardımcıdır. Wilms ve neruoblastom ayrımında yeri kısıtlı olabilir.

Anahtar kelimeler: Abdomen, diffüzyon ağırlıklı görüntüleme, görünür diffüzyon katsayısı, pediatrik malignite, pelvis, solid tümör

INTRODUCTION

In imaging evaluation of the abdominopelvic mass lesions in the pediatric population, magnetic resonance imaging (MRI) is currently the first choice of modality, largely due to its superior soft tissue contrast allowing lesion characterization and its lack of ionizing radiation (1). Since the management of these abdominopelvic mass lesions may differ widely, conventional MR images are helpful for a

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diagnosis by detecting the organ or tissue origin of the lesion, assessing the lesion extent, and predicting the lesion type. While some benign mass lesions can accurately be diagnosed from their typical conventional MRI features and be followed up or managed accordingly, an MRI diagnosis can be challenging or impossible in some mass lesions, particularly in large-sized solid heterogeneous mass lesions of adjacent organs or tissues (1-3).

DWI is a method that allows in vivo characterization of biological tissues. The method is based on the visualization of the random movement of water molecules at a microscopic level which can be quantified by the calculation of apparent diffusion coefficient (ADC) values (2,4,5). In MRI evaluation of tumors, DWI can be used for tumor detection and characterization, biopsy guiding, and treatment response monitoring (3,5-9).

In children, most malignant tumors are composed of tissues with high cellularity or a high nucleus-to-cytoplasm ratio. The high cellularity of those tumors results in a high number of cell membranes in the imaging area and causes restriction of water molecules and low ADC values. This DWI feature has been studied in differentiating malignant from benign tumors of various organs and tissues in children (6,10-13). Diffusion characteristics of abdominopelvic tumors in children have also been studied in predicting the type of large-sized solid malignant tumors, not only in tumors of the same organ or tissue but also in tumors originating from adjacent organs of the abdominopelvic area such as the retroperitoneum, adrenal glands, and kidneys (3,7,14,15).

By using ADC map quantification, several studies have assessed the role of DWI in differentiating benign from malignant mass lesions of the pediatric abdomen and pelvis (16-18). These studies have differed in their quantification methods, as well as in the types of lesions included in the analyses.

The present study mainly focused on the role of ADC values in DWI in distinguishing solid malignant from solid benign tumors of the abdominopelvic area in children. For this purpose, different fractions of the measured and calculated ADC values in children with a solid mass lesion of the abdomen or pelvis were analyzed to determine whether those values allow for distinguishing malignant from benign solid lesions. A secondary aim was to determine whether the same ADC fractions are useful in distinguishing the most common malignant tumors of the kidney and adrenal glands in children, namely the Wilms tumor and neuroblastoma.

MATERIALS and METHODS

Approval for this retrospective study was obtained from the institutional review board (Decision no: 19; Date: 04.10.2022).

Patient Selection

Between June 2015 and September 2020, the abdominopelvic MRIs of the patients in the pediatric age group obtained in the radiology department of a single tertiary hospital at a 3T MR scanner were retrospectively reviewed. The patients with a solid mass lesion of the abdomen or pelvis on MRI were included in the initial evaluation. Using the medical records of the patients, the patients who had not received any medical, surgical, or interventional treatments before MRI were chosen to include in the image quality analysis. Upon completion of the image quality analysis, the final study group included the MRIs of pediatric patients that had high-quality DWI and contrast-enhanced T1-weighted images as a part of their MR imaging protocol.

MRI Protocol

All abdominopelvic MRIs were obtained at a 3T MRI scanner (MR750W General Electric Health-

care, Milwaukee, WI), using a 48-channel body coil. The MRI protocol included coronal T2-weighted (FSE, TR 622.8 ms, TE 111.8 ms), axial T2-weighted (FSE, TR 604.8 ms, TE 112.8 ms, TE 112.8 ms), axial fat-saturated T2-weighted (PROPELLER, TR 8000 ms, TE 86.7 ms), axial fat-saturated pre- and post-contrast T1-weighted images (LAVA, TR 4.6 ms, TE 1.7 ms, slice thickness 3.8 mm, FOV 42 cm), as well as DW images and their ADC maps (EPI, TR 25000 ms, TE 64.1 ms, b:0, b:500 and b:1000 s/mm2). Post-contrast T1-weighted images were obtained in the portal venous phase, using intravenous (IV) injection of gadoterate meglumine (0.25 mmol/mL,10 mL), at an injection rate of 2mL/s. The slice thickness was 4 mm for T2-weighted and DW images, and the field of view (FOV) was between 38 cm to 42 cm.

Image Analysis

ADC measurements were performed on the ADC maps, using a region of interest (ROI). The region of measurement in a mass lesion was determined by two radiologists in consensus. Using T2-weighted and post-contrast T1-weighted images for correlation, the most intensely enhancing and non-hemorrhagic-non-cystic solid part of a lesion was chosen. The measurements were then performed in the predetermined regions by a single radiologist, without the knowledge of the final diagnosis. The ROI was kept between 0.8-1 cm2 (Figure 1). Three ROI measurements were performed on each lesion to obtain an average ADC value. The minimum, mean and maximum ADC values were recorded for each lesion. To eliminate confounding imaging and patient factors that can potentially affect the measured ADC values, the mean ADC measurements were normalized for each lesion, by placing a second ROI on the spleen of the patient and dividing the lesion's ADC value by the ADC value of the spleen.

Statistical Analysis

All statistical analyses were performed by using SSPS for Windows (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

The quantitative variables were expressed as means ± standard deviation (SD) and the qualitative variables as percentages (%). The normality of the variables was tested with the Shapiro-Wilk test. Parametric and nonparametric tests were used in comparison between the groups. The ADC values were compared with the Mann-Whitney U test or independent samples t-test. The chi-square test was used in analyses of the crosstabs. Receiver operating characteristics (ROC) curve analysis

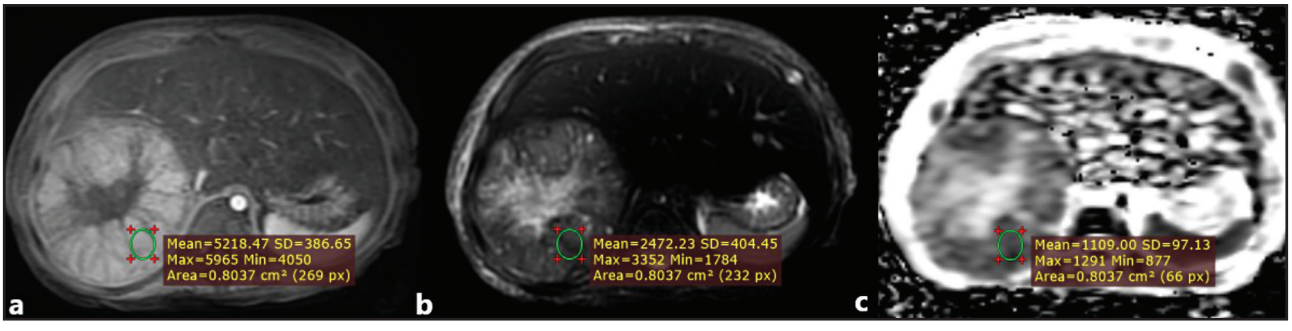

Figure 1 ADC measurements in a 9-month-year-old girl. In post-contrast T1-weighted **(a),** T2-weighted **(b),** and corresponding ADC map **(c)** images show a heterogeneous mass in the right lobe of the liver with central cystic hemorrhagic parts. The ADC measurements were obtained from the most enhancing non-hemorrhagic non-cystic part of the tumor, using ROIs. The mean ADC value for the selected ROI was 1,1109x10^{-3} mm^2/s. The tumor proved to be hepatoblastoma.

was used to obtain the optimal cutoff ADC values that discriminate malignant and benign mass lesions with maximum sensitivity and minimum false positive results. The area under the curve (UAC) was calculated for each parameter.

RESULTS

Demographics

A picture archiving and communication system (PACS) search of the pediatric abdominopelvic 3T MRIs at our institution revealed 60 pediatric patients who had a solid mass lesion of the abdomen or pelvis between June 2015 to September 2022. Of these, 5 patients did not have DW or contrast-enhanced images as a part of their MRI protocols, 3 patients received treatment before MRI and 3 patients had poor-quality images that were inadequate for image evaluation. Thus, abdominopelvic MRIs of a total of 49 pediatric patients were included in the study.

Of the patients in the study, 30 were male (61.2%) and 19 were female (38.8%). The mean age of the patients was 59.7 ± 54 months (1 - 198) (median, 41 months).

Of the 30 male patients, 19 had a malignant (63.3%) and 11 had a benign (36.7%) lesion. Of the female patients, 13 had a malignant (68.4%) and 6 had a benign (31.2%) lesion. The distribution of the malignant and benign lesions between males and females was not statistically significantly different ($p = 0.955$).

The mean age of the patients with a malignant lesion was 56 ± 51.9 months (1 - 198) (median 39.5 months), and the mean age of the patients with a benign lesion was 64 ± 58.3 months (1 - 186) (median 74 months). The statistical analysis did not find a significant difference between the mean age of the patients with malignant and benign mass lesions ($p = 0.298$).

Lesions

In all patients with a malignant lesion included in the study, the diagnosis was confirmed with histopathologic analysis. Of the 32 patients with a malignant lesion, 9 had Wilms tumor, 7 had neuroblastoma, 4 had rhabdomyosarcoma, 4 had hepatoblastoma, 3 had lymphoma, 2 had adrenocortical carcinoma, 1 had testicular teratoma, 1 had mixed germ cell tumor and 1 had clear cell sarcoma.

In 17 patients with a benign lesion in the study, 6 were diagnosed with the typical dynamic contrast-enhanced MR imaging findings (4 had focal nodular hyperplasia and 2 had hemangioendothelioma). In the remaining 11 patients, the diagnosis of a benign lesion was confirmed histopathologically: two patients had hemangioendothelioma, 4 patients had ganglioneuroma, 1 had mesoblastic nephroma, 1 had Castleman disease, 1 had lipoblastoma, 1 had a dysgerminoma and 1 patient had sclerosing angiomatoid nodular transformation (SANT).

Quantitative Evaluation of ADC Maps

The minimum, mean and maximum ADC values and the mean normalized ADC values of the benign and malignant solid lesions are presented in Table 1. The minimum, mean and maximum ADC values of the malignant solid lesions were all statistically significantly lower than that of the benign solid lesions ($p < 0.001$). The mean normalized ADC value of the malignant lesions was also significantly lower than that of the benign lesions ($p < 0.001$).

In the ROC analysis of the minimum ADC values (AUC = 0.848; 0.742 - 0.955), a cutoff value of ≤ 1.03×10^{-3} mm^2/s was found to differentiate the malignant from benign lesions with a sensitivity of 75% and a specificity of 82.4%. In the ROC analyses of the mean, maximum, and normalized ADC values, a cutoff value of ≤ 1.195 x 10-3 mm^2/s, ≤

1.436 x 10-3 mm²/s, and ≤ 1.398195 x 10-3 mm²/s was found to differentiate the malignant from benign lesions with sensitivity and specificity rates of 75% / 76.5%, 75% / 70.6%, and 84.4% / 94.1%, respectively (Figure 2).

Comparative Evaluation of Wilms Tumor and Neuroblastoma

The mean age at diagnosis did not significantly differ between the patients with Wilms tumor and neuroblastoma. The minimum, mean, maximum, and normalized ADC values also did not significantly differ between the patients with Wilms tumor and neuroblastoma. The results are presented in Table 2.

DISCUSSION

Obtaining ADC measurements from the solid-appearing part of a tumor has been shown to yield more accurate results in the DWI evaluation of the tumors, since both the cystic components of solid benign tumors and necrotic components of solid malignant tumors may demonstrate low ADC values (9). Also, in the measurement of mean ADC values, placing the ROI only in the solid-appearing

Table 1 The minimum, mean, and maximum ADC values and the mean normalized ADC values of the benign and malignant solid lesions

	Groups		p (*,**)
	Malignant	Benign	
Min. ADC[a]	0.8 ± 0.39	1.32 ± 0.37	p < 0.001*
Mean ADC[a]	0.94 ± 0.44	1.51 ± 0.43	p < 0.001**
Max. ADC[a]	1.12 ± 0.52	1.73 ± 0.5	p < 0.001*
Normalized ADC[a]	1.06 ± 0.51	1.78 ± 0.30	p < 0.001**

a: Mean ± SD x10 $^{-3}$ mm²/s. *Mann-Whitney U test. **Independent sample t test. Min: Minimum; Max: Maximum.

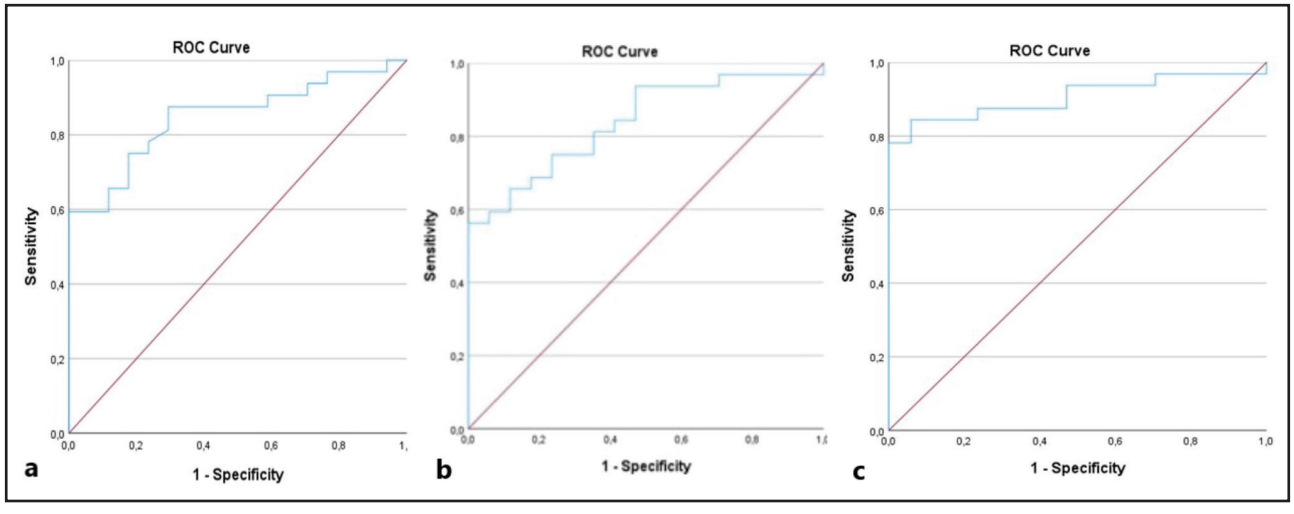

Figure 2 ROC curve analyses for the minimum (a) mean (b) and normalized (c) ADC values in differentiating malignant from benign lesions.

Table 2 The minimum, mean, and maximum ADC values and the mean normalized ADC values of the Wilms tumor and neuroblastoma

	Groups		p*
	Wilms Tumor	Neuroblastoma	
Age[a]	38.44 ± 25.74	37.43 ± 28.03	0.941
Min. ADC[λ]	0.62 ± 0.22	0.77 ± 0.34	0.299
Mean ADC[λ]	0.72 ± 0.2	0.90 ± 0.33	0.220
Max. ADC[λ]	0.86 ± 0.2	1.06 ± 0.36	0.202
Normalized ADC[λ]	0.85 ± 0.25	0.98 ± 0.34	0.289

a: Age at diagnosis, in months. λ: Mean±SD x10 $^{-3}$ mm^2/s. *Mann-Whitney U test. Min: Minimum; Max: Maximum.

part of a tumor is more effective in differentiating malignant and benign tumors than placing the ROI in the whole tumor area (18).

By obtaining ADC values only from the non-cystic non-hemorrhagic parts of the solid tumors with small ROIs, the present study found the mean ADC values of the solid malignant tumors of the abdomen and pelvis of children to be significantly lower than that of the solid benign tumors (0.94 ± 0.44 x 10^{-3} mm^2/s and 1.51 ± 0.43 x 10^{-3} mm^2/s, for malignant and benign tumors, respectively). This result was different from the work of Humphries et al., who, in the analysis of 19 pediatric patients, did not find a significant difference in the mean ADC values between the malignant and benign lesions of the abdomen and pelvis (16). The discordance between the results may be due to the use of large ROIs in the tumors of a small number of patients in Humphries et al.'s study. In accordance with the results of the present study, by using 10 mm^2 ROIs, Kocaoğlu et al. found the mean ADC values of the abdominopelvic tumors in the pediatric age group to be significantly lower than that of the benign tumors (17). The mean ADC value of the benign tumors in their study, however, was higher than in ours and was found to be 2.28 x 10^{-3} mm^2/s, which could have resulted from the inclusion of cystic benign lesions in the study. Using 30 - 60 mm2 ROIs in a total of 64 children, Gawande et al. also found the mean ADC values of the solid malignant and solid benign tumors of the abdomen and pelvis to be 1.07 ± 0.34 x 10^{-3} mm^2/s and 1.68 ± 0.54 x 10^{-3} mm^2/s, respectively (18), which was in accordance with the results of the present study.

In the ROC analysis of the mean ADC values, we found a cutoff mean ADC value of ≤ 1.195 x 10^{-3} mm^2/s, to differentiate the solid malignant from the solid benign tumors of the abdomen and pelvis in children with specificity and sensitivity rates of 75% and 76.5%, respectively. This was in accordance with the previous studies, which found the mean ADC cutoff values between 1.11 x 10^{-3} mm^2/s to 1.29 x 10^{-3} mm^2/s (16-18).

In the ROI analysis of ADC values of the tumors, the minimum ADC value is less likely to be affected by the presence of low-cellularity or cystic-necrotic components in a tumor. Compared to the mean ADC value, a minimum ADC value is found to detect high cellularity and differentiate malignant from benign tumors more accurately (19,20). In the ROC analysis of the minimum ADC values (AUC = 0.848; 0.742 - 0.955), we found a cutoff value of ≤ 1.03x10^{-3} mm^2/s to differentiate the malignant from benign lesions with a sensitivity of 75% and a specificity of 82.4%. With a cutoff value of ≤ 1.195 x 10^{-3} mm^2/s, the sensitivity rate of the mean ADC measurements was similar to that of the minimum

ADC measurements (75%), however, the specificity rate was lower (76.5%). The maximum ADC values of the solid malignant tumors in the present study were also significantly lower than that of the solid benign tumors. Because the maximum ADC value of a tumor is more prone to be affected by the presence of cystic-necrotic components and low tissue cellularity, use of it is avoided if the high tumor cellularity is to be detected (19,20). The significant difference between the maximum ADC values of the malignant and benign tumors in our study is most probably due to the inclusion of only small solid tumor parts in the ROI analyses.

The normalized ADC values were calculated in this study to eliminate the effects of the imaging- and patient-specific variables on the results (21). This was achieved by dividing the measured mean ADC value of the sampled tumor by the mean ADC value of the spleen, for each patient. In the ROC analysis of the normalized ADC values, we found a cutoff value of ≤ 1.398 to differentiate the malignant from the benign solid tumors with sensitivity and specificity rates of 84.4% and 94.1%, respectively. Those rates were higher than the sensitivity and specificity rates obtained with the use of minimum and mean ADC values in our study. Reports on the use of normalized ADC values in the differentiation of malignant from benign abdominopelvic tumors of children are scarce: In 2017, Caro-Dominguez et al. used the normalized ADC values in hepatic lesions of children and found the mean normalized ADC values of the malignant and benign liver lesions to be 1.23 ± 0.28 and 1.62 ± 0.67, respectively. With a cutoff ADC value of ≤ 1.20 x 10^{-3} mm^2/s, the sensitivity rate in their study was 78%, however, the specificity rate was 54% (10).

The ADC values of the two most common pediatric malignant abdominal tumors of the kidneys and adrenal glands, the Wilms tumor, and the neuroblastoma, were comparatively analyzed in the present study. That subgroup analysis was done because although the management and treatment of these two tumors are different, both tumors are usually large-sized at the time of the imaging diagnosis and their differentiation from one another can occasionally be problematic on conventional MR images (3). In the analysis of the minimum, mean, maximum, or normalized ADC values, we did not find a significant difference between the two tumor types. Using mean ADC values in the small-sized ROI analysis of 17 pediatric patients, Aslan et al. found that the neuroblastomas had significantly lower ADC values than the Wilms tumors (3). The contradiction between the results of the two studies could be due to the small number of patients in both studies or due to the inclusion of different numbers of differentiated, poorly differentiated, or undifferentiated tumors in each study.

The retrospective design and the small number of certain lesions could be the limitations of this study. Although, for each tumor in the study, the regions for ADC measurements were determined by two radiologists in consensus, the performance of the ROI measurements by a single observer and the lack of an interobserver reliability assessment could also be a limitation.

In conclusion, quantitative analysis of ADC maps helps differentiate solid malignant from solid benign tumors of the abdomen and pelvis in children. The use of small-sized ROIs and performing the ROI measurements on the non-cystic non-hemorrhagic contrast-enhancing tumor parts can increase the sensitivity and specificity rates. Although the present study found higher sensitivity and specificity rates in the use of the mean normalized ADC value for discrimination, further studies on the use of normalized ADC value in differentiating malignant from benign tumors of childhood are needed, as the use of it has also been shown to yield low specificity rate in discriminating malignant from benign pediatric liver lesions in one study (10).

Ethics: *The study protocol was approved by Osmangazi University Ethics Committee (Decision no: 19; Date: 04.10.2022).*

Conflict of Interest: *None*

Financial Disclosures: *None*

Author Contributions: *All 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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