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Diffusion-Weighted Imaging in Meningioma: Prediction of Tumor Grade and Association with Histopathological Parameters[1,2]

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Abstract

OBJECTIVES: To analyze diffusion-weighted imaging (DWI) findings of meningiomas and to compare them with tumor grade, cell count, and proliferation index and to test a possibility of use of apparent diffusion coefficient (ADC) to differentiate benign from atypical/malignant tumors. *METHODS:* Forty-nine meningiomas were analyzed. DWI was done using a multislice single-shot echo-planar imaging sequence. A polygonal region of interest was drawn on ADC maps around the margin of the lesion. In all lesions, minimal ADC values (ADC_{min}) and mean ADC values (ADC_{mean}) were estimated. Normalized ADC (NADC) was calculated in every case as a ratio ADC_{mean} meningioma/ADC_{mean} white matter. All meningiomas were surgically resected and analyzed histopathologically. The tumor proliferation index was estimated on Ki-67 antigen–stained specimens. Cell density was calculated. Collected data were evaluated by means of descriptive statistics. Analyses of ADC/NADC values were performed by means of two-sided *t* tests. *RESULTS:* The mean ADC_{mean} value was higher in grade I meningiomas in comparison to grade II/III tumors (0.96 vs 0.80 $\times 10^{-3}$ mm^2s^{-1}, $P = .006$). Grade II/III meningiomas showed lower NADC values in comparison to grade I tumors (1.05 vs 1.26, $P = .015$). There was no significant difference in ADC_{min} values between grade I and II/III tumors (0.69 vs 0.63 $\times 10^{-3}$ mm^2s^{-1}, $P = .539$). The estimated cell count varied from 486 to 2091 (mean value, 1158.20 ± 333.74; median value, 1108). There were no significant differences in cell count between grade I and grade II/III tumors (1163.93 vs 1123.86 cells, $P = .77$). The mean level of the proliferation index was 4.78 ± 5.08%, the range was 1% to 18%, and the median value was 2%. The proliferation index was statistically significant higher in grade II/III meningiomas in comparison to grade I tumors (15.43% vs 3.00%, $P = .001$). Ki-67 was negatively associated with ADC_{mean} ($r = -0.61$, $P < .001$) and NADC ($r = -0.60$, $P < .001$). No significant correlations between cell count and ADC_{mean} ($r = -0.20$, $P = .164$) or NADC ($r = -0.25$, $P = .079$) were found.

ADC_{min} correlated statistically significant with cell count ($r = -0.44$, $P = .002$) but not with Ki-67 ($r = -0.22$, $P = .129$). Furthermore, the association between ADCmin and cell count was stronger in grade II/III tumors ($r = -0.79$, $P = .036$) versus grade I meningiomas ($r = -0.41$, $P = .008$). An ADC_{mean} value of less than 0.85 $\times 10^{-3}$ mm^2s^{-1} was determined as the threshold in differentiating between grade I and grade II/III meningiomas (sensitivity 72.9%, specificity 73.1%, accuracy 73.0%). The positive and negative predictive values were 33.3% and 96.8%, respectively. The same threshold ADC_{mean}

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value was used in differentiating between tumors with Ki-67 level ≥ 5% and meningiomas with low proliferation index (Ki-67 < 5%). This threshold yielded a sensitivity of 70.6%, a specificity of 81.2%, and an accuracy of 77.6%. The positive and negative predictive values were 66.6% and 83.9%, respectively. *CONCLUSIONS:* Grade II/III tumors had lower ADC_{mean} values than grade I meningiomas. ADC_{mean} correlated negatively with tumor proliferation index and ADC_{min} with tumor cell count. These associations were different in several meningiomas. ADC_{mean} can be used for distinguishing between benign and atypical/malignant tumors.

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Introduction

According to the literature, diffusion-weighted imaging (DWI) provides information regarding tissue microstructure [1–6]. Furthermore, it has been shown that DWI can be used to distinguish malignant from benign tumors [1,4,5]. As reported previously, malignant tumors showed lower apparent diffusion coefficient (ADC) values in comparison to benign lesions [1,3]. In addition, as suggested in previous reports, ADC values under 1.00×10^{-3} mm^2s^{-1} were suspicious for a malignancy [1].

However, according to the literature, some benign lesions had also very low ADC values and can mimic malignancies [7–9]. For example, ADC values of nasopharyngeal adenoid hypertrophy varied from 0.36 to 0.84×10^{-3} mm^2s^{-1} with a median value of $0.59 \pm 0.11 \times 10^{-3}$ mm^2s^{-1} [7]. In addition, in the study of Ikeda et al., the mean ADC of Warthin tumors was significantly lower than that of malignant parotid tumors [8]. Furthermore, it is well known that cholesteatomas also has low ADC values [9].

As reported previously, ADC values correlated well with cell count of the investigated lesions [2,6,9]. For instance, Driessen et al. reported that ADC was significantly and inversely correlated with cell density ($r = -0.57$, $P = .02$) in laryngeal and hypopharyngeal carcinomas [6]. In addition, Schnapauff et al. identified a linear relation between tumor cellularity and ADC in soft tissue sarcoma with a Pearson correlation coefficient of −0.88 [2]. Similar results were reported also for prostatic cancer and renal malignancies [10,11]. However, Wu et al. found no correlation between the ADC value and the tissue cellularity in patients with diffuse large B-cell lymphoma and follicular lymphoma [12]. Furthermore, according to another report, the ADC value for breast cancer did not significantly correlate with cancer cellularity but did correlate with histological types [13].

According to the literature, ADC can be used as a marker to predict response to therapy in different malignant diseases [14–16].

There were several reports describing features of meningiomas on DWI; however, the provided data were inconsistent [17–20]. Whereas some authors found an association between ADC and histological parameters of meningiomas [18,19,21], others did not [17,20]. In addition, in the analysis of Ginat et al., no association between ADC and Ki-67 level was found [22], whereas other authors reported a statistically significant correlation between these parameters [21].

Because of the fact that meningioma is the most frequent intracranial tumor and is often an incidental finding on magnetic resonance imaging (MRI), it is important to correctly estimate tumor grade and proliferation potential on imaging [21].

Therefore, the purpose of this study was to analyze DWI findings of meningiomas and to compare them with different histological parameters such as tumor grade and subtypes, cell count, and proliferation index and to test a possibility of ADC use to differentiate benign from matypical/malignant tumors.

Materials and Methods

This study was approved by the institutional review board (Martin Luther University medical ethic committee).

Patients and Imaging

Images of all meningiomas resected at our institution in the time period from 2006 to 2013 were analyzed retrospectively. Only tumors which were investigated by DWI with good quality of images were included into the study. Tumors below 10 mm in diameter, calcified meningiomas, and tumors with artifacts on DWI/ADC map were excluded from the study. After a thorough inspection of the images, 49 tumors were adopted for further analysis. These tumors were found in 38 women and 11 men with a mean age of 59.0 years (median age, 63 years; range, 20-82 years).

In all patients, MRI of the head was performed using a 1.5-T device (Magnetom Vision Sonata Upgrade, Siemens, Erlangen, Germany). The imaging protocol included axial T2-weighted fat-suppressed short-tau-inversion-recovery images and axial T1-weighted (T1w) spin echo images before and after intravenous application of contrast medium (gadopentate dimeglumine, Magnevist, Bayer Schering Pharma, Leverkusen, Germany). DWI was done using a multislice single-shot echo-planar imaging sequence (repetition time/echo time: 5900/96 milliseconds; field of view: 250 × 250 mm; slice thickness: 5 mm; acquisition matrix: 128 × 128), with b values of 0, 500, and 1000 s/mm^2. ADC maps were automatically generated by the implemented software according to the following equation: ADC (mm^2s^{-1}) = $[\ln(S^0/S^{1000})]$ / 1000, where S^0 and S^{1000} represent the signal intensities of the images. The slice with the largest diameter of meningioma was selected for ADC calculation. In this image. a polygonal region of interest (ROI) as large as possible was manually drawn on ADC maps around the margin of the lesion (whole lesion measurement) without risking partial volume effects. ROIs were placed to avoid cystic and necrotic areas as well as large vessels of the tumors. The position of every ROI was automatically placed also on all other images (T2 weighted, and pre- and postcontrast T1w). In all lesions, minimal ADC values (ADC_{min}) and mean ADC values (ADC_{mean}) were estimated. In addition, ROIs were drawn in the normal white matter of the contralateral hemisphere (ADC white matter). Normalized ADC (NADC) was calculated in every case as a ratio ADC_{mean} meningioma/ADC_{mean} white matter.

All images were analyzed retrospectively by one radiologist (A.S., 11 years of radiological experience).

Histopathological Analysis

All 49 meningiomas were surgically resected and analyzed histopathologically. Tumor grading was classified according to the World Health Organization [23].

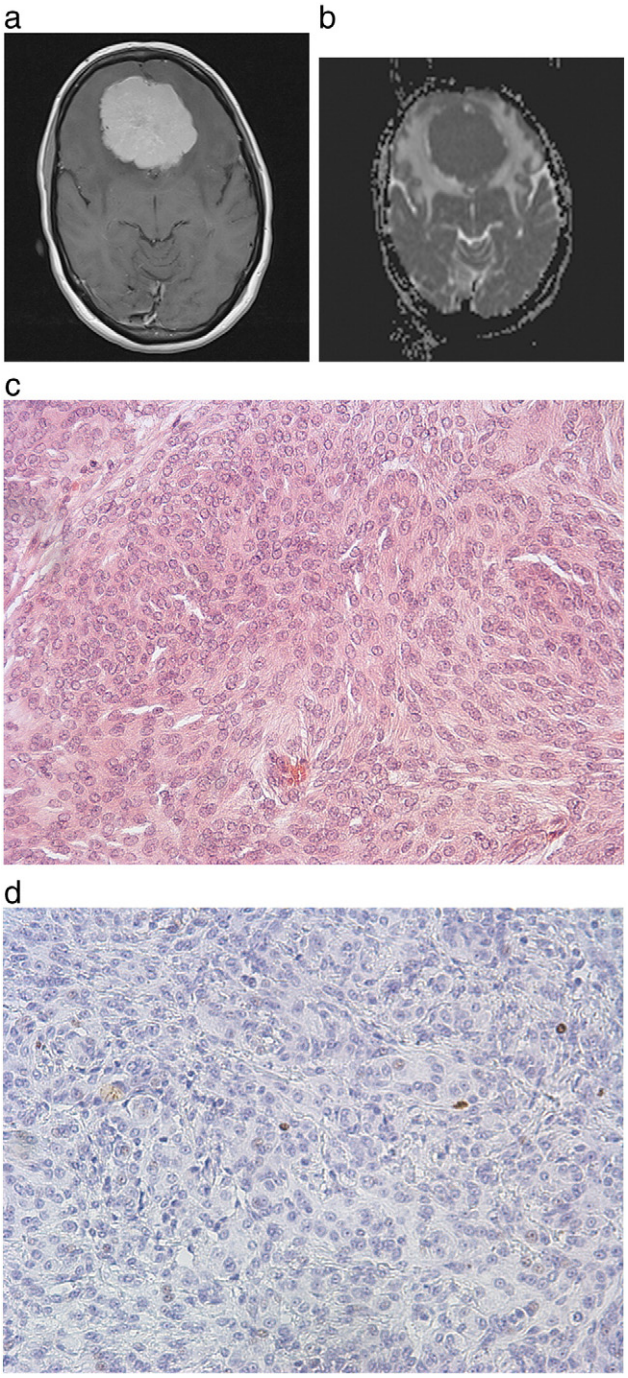

Figure 1. MRI and pathological findings in grade 1 meningioma. (a) Postcontrast T1w image showing a large tumor with marked enhancement. (b) ADC map of the tumor. ADC_{mean} value is 0.79×10^{-3} mm^2s^{-1}; ADC_{min} is 0.54×10^{-3} mm^2s^{-1}. ADC_{mean} value of the normal white matter of the contralateral hemisphere is 0.68×10^{-3} mm^2s^{-1}, yielding an NADC value of 1.16. (c) Histological investigation after surgical resection confirmed a meningothelial meningioma (hematoxilin and eosin stain). Cell count is 1090. Immunohistochemical stain (MIB-1 monoclonal antibody). Ki-67 index = 2%.

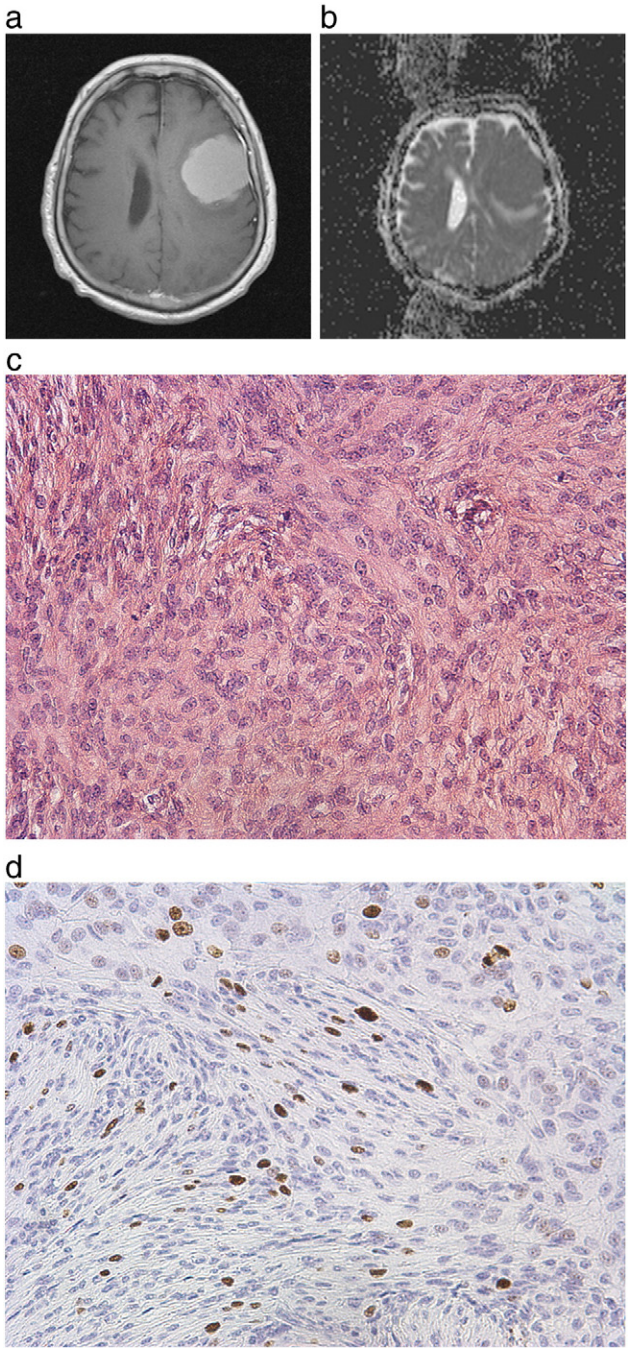

Figure 2. MRI and pathological findings in grade II meningioma. (a) Postcontrast T1w image showing a large tumor with markedly homogeneous enhancement. (b) ADC map of the tumor. ADC_{mean} value is 0.83×10^{-3} mm^2s^{-1}; ADC_{min} is 0.72×10^{-3} mm^2s^{-1}. ADC_{mean} value of the normal white matter of the contralateral hemisphere is 0.79×10^{-3} mm^2s^{-1}, yielding an NADC value of 1.05. (c) Histological findings after surgical resection (hematoxilin and eosin stain). Cell count is 1108. (d) Immunohistochemical stain (MIB-1 monoclonal antibody). Ki-67 index = 18%.

In every case, the tumor proliferation index was estimated on Ki-67 antigen–stained specimens by using MIB-1 monoclonal antibody (DakoCytomation, Denmark) as reported previously [24,25]. Overall, 5 high-power fields (0.16 mm^2 per field) with a magnification of ×400 were analyzed. The area with the highest number of positive tumor nuclei was selected.

Cell density was calculated in every case as an average cell count per 5 high-power fields (×400; 0.16 mm^2 per field). All images were analyzed by using a research microscope, Jenalumar, with camera Diagnostic Instruments 4.2.

Table 1. Investigated Parameter in Meningioma

Parameter	M ± SD	Median	Range
ADC_{min}, $\times 10^{-3}$ mm^2s^{-1}	0.68 ± 0.14	0.67	0.33-1.2
ADC_{mean}, $\times 10^{-3}$ mm^2s^{-1}	0.94 ± 0.20	0.9	0.71-1.78
NADC	1.23 ± 0.26	1.16	0.9-2.17
Cell count	1158.20 ± 333.74	1108	486-2091
Ki-67, %	4.78 ± 5.08	2	1-18

Statistical Analysis

For statistical analysis, the SPSS statistical software package was used (SPSS 17.0, SPSS Inc., Chicago, IL). All measurements were non-normally distributed according to Kolmogorov-Smirnov test. Collected data were evaluated by means of descriptive statistics (absolute and relative frequencies). Categorical variables were expressed as percentages. Analyses of ADC and NADC values were performed by means of two sided Mann-Whitney *U* tests. *P* values < .05 were taken to indicate statistical significance in all instances [26]. Spearman's correlation coefficient was used to analyze the association between ADC/NADC values and histological parameters.

Furthermore, the receiver operating characteristic (ROC) curve was used to evaluate the diagnostic ability of the ADC value to differentiate between benign and grad II/III meningiomas. The optimal cutoff value was determined according to the Youden index. In addition, sensitivity, specificity, negative and positive predictive values, accuracy, and area under the curve value were calculated for the diagnostic procedures.

Results

In most cases (n = 42, 86%), benign tumors (i.e., World Health Organization grade I) were diagnosed. Most frequently (n = 25, 51%), meningothelial meningiomas followed by transitional meningiomas (n = 11, 22%) were identified (Figure 1). Grade II tumors were found in six patients (12%) and grade III in one case (2%) (Figure 2).

The estimated ADC_{mean} values of meningiomas ranged from 0.71 to 1.78 × 10^{-3} mm^2s^{-1} with a median value of 0.9 × 10^{-3} mm^2s^{-1}; the mean value was 0.94 ± 0.20 × 10^{-3} mm^2s^{-1} (Figures 1 and 2). The mean value of ADC_{min} was 0.68 ± 0.14 × 10^{-3} mm^2s^{-1}, median value was 0.67 × 10^{-3} mm^2s^{-1}, and range was 0.33 to 1.2 × 10^{-3} mm^2s^{-1} (Table 1). The mean NADC value was 1.23 ± 0.26, and the median value was 1.16, ranging from 0.9 to 2.17.

The mean ADC_{mean} value was higher in grade I meningiomas in comparison to grade II/III tumors (0.96 vs 0.80 × 10^{-3} mm^2s^{-1}, *P* = .006) (Figure 3*a*). Grade II/III meningiomas showed lower NADC values in comparison to grade I tumors (1.05 vs 1.26, *P* = .015) (Figure 3*b*). There was no significant difference in ADC_{min} values between grade I and II/III tumors (0.69 vs 0.63 × 10^{-3} mm^2s^{-1}, *P* = .539) (Figure 3*c*).

In addition, no significant differences in ADC_{mean} (0.90 vs 0.96 × 10^{-3} mm^2s^{-1}, *P* = .074) and ADC_{min} (0.65 vs 0.73 × 10^{-3} mm^2s^{-1}, *P* = .054) values were identified between meningothelial and transitional meningiomas.

The estimated cell count varied from 486 to 2091 (mean value, 1158.20 ± 333.74; median value, 1108) (Table 1). There were no significant differences in cell count between grade I and grade II/III tumors (1163.93 vs 1123.86 cells, *P* = .77).

The mean level of the proliferation index was 4.78 ± 5.08%, the range was 1% to 18%, and the median value was 2%. The proliferation index was statistically significant higher in grade II/III

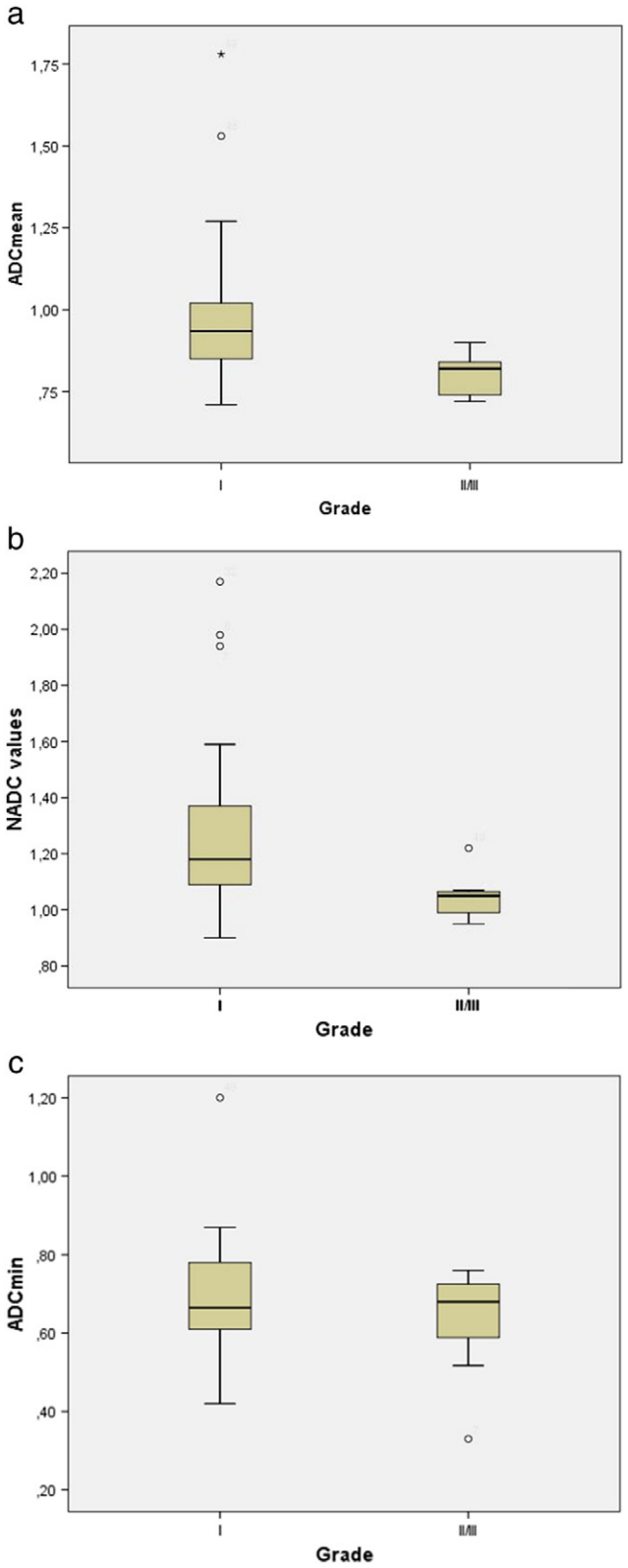

Figure 3. Comparison of ADC/NADC values between meningiomas. (a) ADC_{mean} values in grade I and II/III meningiomas. Grade I tumors showed higher mean ADC_{mean} value in comparison to grade II/III tumors (0.96 vs 0.80 × 10^{-3} mm^2s^{-1}, *P* = .006). (b) NADC values in grade I and II/III meningiomas. Grade I tumors showed higher NADC values in comparison to grade II/III tumors (1.26 vs 1.05, *P* = .015). (c) ADC_{min} values in grade I and II/III meningiomas. There was no significant difference in ADC_{min} values between grade I and II/III tumors (0.69 vs 0.63 × 10^{-3} mm^2s^{-1}, *P* = .539).

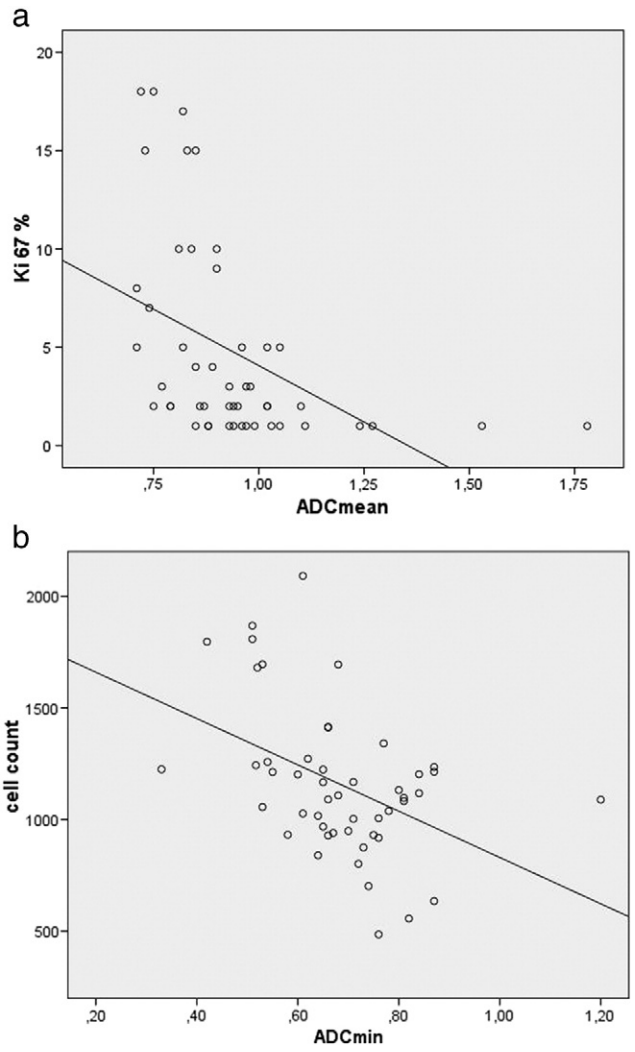

Figure 4. Statistically significant associations between ADC values, Ki-67 levels, and cell density. (a) Scatterplot for ADC_{mean} and Ki-67 values. Ki-67 was negatively associated with ADC_{mean} ($r = -0.61$, $P < .001$). (b) Scatterplot for ADC_{min} and cell count values. ADC_{min} correlated statistically significant with cell count ($r = -0.44$, $P = .002$).

meningiomas in comparison to grade I tumors (15.43% vs 3.00%, $P = .001$).

Ki-67 was negatively associated with ADC_{mean} ($r = -0.61$, $P = .001$) (Figure 4*a*) and NADC ($r = -0.60$, $P = .001$) (Table 2). No significant correlations between cell count and ADC_{mean} ($r = -0.20$, $P = .164$) or NADC ($r = -0.25$, $P = .079$) were found in the total collective of meningeomas (Table 2). The identified correlations were different in grade I and grade II/III tumors (Tables 3 and 4).

Table 2. Correlations between DWI and Histopathological Findings in the Total Collective of Meningiomas

Parameter	Cell Count	Ki-67, %
ADC_{min}, $\times 10^{-3}$ mm^2s^{-1}	**$r = -0.44$**	$r = -0.22$
	$P = .002$	$P = .129$
ADC_{mean}, $\times 10^{-3}$ mm^2s^{-1}	$r = -0.20$	**$r = -0.61$**
	$P = .164$	**$P = .001$**
NADC	$r = -0.25$ $P = .079$	**$r = -0.60$**
		$P = .001$

The significant correlations are given in boldface.

Table 3. Correlations between DWI and Histopathological Findings in Grade I Meningioma

Parameter	Cell Count	Ki-67, %
ADC_{min}, $\times 10^{-3}$ mm^2s^{-1}	**$r = -0.41$**	$r = -0.20$
	$P = .008$	$P = .195$
ADC_{mean}, $\times 10^{-3}$ mm^2s^{-1}	$r = -0.22$	**$r = -0.50$**
	$P = .158$	**$P = .001$**
NADC	$r = -0.23$	**$r = -0.55$**
	$P = .138$	**$P = .001$**

The significant correlations are given in boldface.

ADC_{min} correlated statistically significantly with cell count ($r = -0.44$, $P = .002$) (Figure 4*b*) but not with Ki-67 ($r = -0.22$, $P = .129$) (Table 2). Furthermore, the association between ADCmin and cell count was stronger in grade II/III tumors ($r = -0.79$, $P = .036$) versus grade I meningiomas ($r = -0.41$, $P = .008$) (Table 4).

An ADC_{mean} value of less than 0.85×10^{-3} mm^2s^{-1} was determined as the threshold in differentiating between grade I and grade II/III meningiomas (sensitivity, 72.9%; specificity, 73.1%; accuracy, 73.0%; Youden index, 0.571). ROC analysis showed that the area under the curve was 0.809 (Figure 5*a*). The positive and negative predictive values were 33.3% and 96.8%, respectively.

The same ADC_{mean} value ($\leq 0.85 \times 10^{-3}$ mm^2s^{-1}) was estimated as the threshold in differentiating between tumors with Ki-67 level ≥5% and meningiomas with low proliferation index (Ki-67 <5%). This threshold yielded a sensitivity of 70.6%, a specificity of 81.2%, an accuracy of 77.6%, and a Youden index of 0.518 (Figure 5*b*). The area under the curve was 0.791. The positive and negative predictive values were 66.6% and 83.9%, respectively.

Discussion

Previously, there were several reports to characterize meningiomas by DWI [17–22]. For example, Sanverdi et al. analyzed 177 different meningiomas and identified no significant difference between the mean ADC ratios of benign, atypical, and malignant tumors [17]. Similar results were reported also in the study of Pavlisa et al. investigating 26 patients [20]. However, Hakyemez et al. found in their analysis of 39 patients with meningioma that the mean ADC value of benign tumors was significant higher than the ADC value of atypical/malignant meningiomas, namely, $1.17 \pm 0.21 \times 10^{-3}$ mm^2s^{-1} and $0.75 \pm 0.21 \times 10^{-3}$ mm^2s^{-1}, respectively ($P < .001$) [18]. In addition, other authors also showed that atypical and malignant meningiomas had lower ADC values compared with benign lesions [19,21].

There were only three reports in which DWI was correlated with histopathological findings, such as cell count and proliferation index in meningiomas [21,22,27]. Tang et al. identified a statistically significant correlation ($r = -0.33$, $P = .0039$) between ADC and Ki-67 in low-grade and high-grade meningiomas [21]. Ginat et al., however, analyzed high-grade meningiomas and found no correlation between ADC and Ki-67 [22]. Also, Fatima et al. could not identify any association between ADC and Ki-67 level [27]. However, Fatima et al. found that ADC was negatively associated ($r = -0.53$, $P = .02$)

Table 4. Correlations between DWI and Histopathological Findings in Grade II/III Meningioma

Parameter	Cell Count	Ki-67, %
ADC_{min}, $\times 10^{-3}$ mm^2s^{-1}	**$r = -0.786$**	$r = -0.505$
	$P = .036$	$P = .247$
ADC_{mean}, $\times 10^{-3}$ mm^2s^{-1}	$r = 0.143$	$r = -0.748$
	$P = .760$	$P = .053$
NADC	$r = -0.252$	$r = -0.189$
	$P = .585$	$P = .685$

The significant correlations are given in boldface.

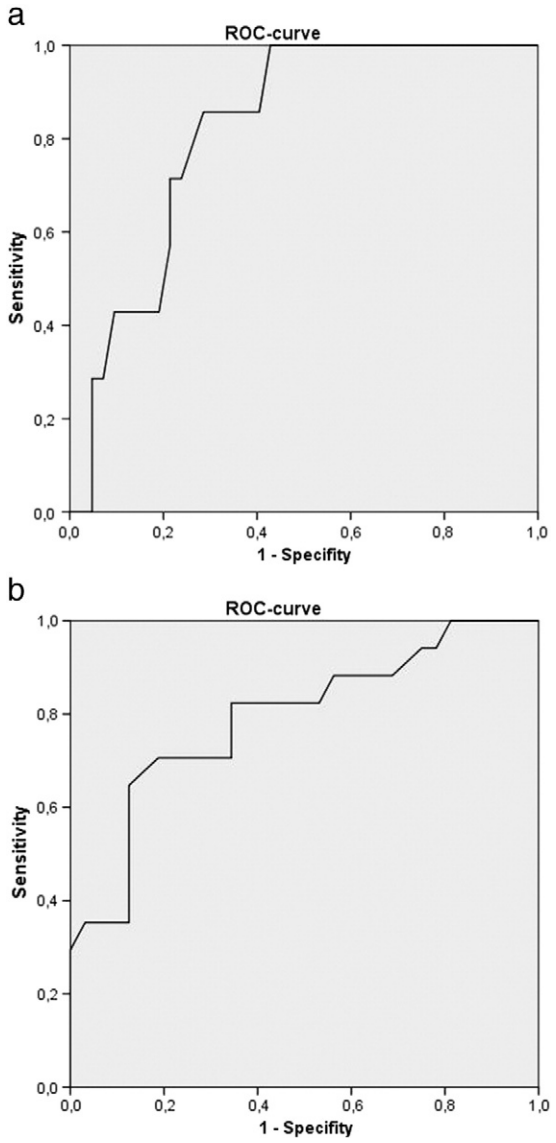

Figure 5. Use of ADC_{mean} values in distinguishing between benign and atypical/malignant meningiomas. (a) ROC curve for use of ADC_{mean} values in distinguishing high-grade meningiomas from benign tumors. The threshold ADC value is less than 0.85×10^{-3} mm^2s^{-1}. Sensitivity = 72.9%, specificity = 73.1%, accuracy = 73.0%. The area under the curve is 0.809. The positive and negative predictive values are 33.3% and 96.8%, respectively. (b) ROC curve for use of ADC_{mean} values in distinguishing meningiomas with high Ki-67 (≥5%) from meningiomas with low proliferation potential (Ki-67 <5%). The threshold ADC value is less than 0.85×10^{-3} mm^2s^{-1}. Sensitivity = 70.6%, specificity = 81.2%, accuracy = 77.6%. The area under the curve is 0.791. The positive and negative predictive values were 66.6% and 83.9%, respectively.

with tumor cell count [27]. Previously, the authors used different ADC values (min or mean, but not both values) in characterization of meningiomas. In addition, different methods of ADC estimation were performed. It may also explain controversial results of previous reports. In addition, Ginat et al. analyzed high-grade tumors [22], whereas in the analysis of Tang et al., most tumors were low-grade meningiomas [21]. Fatima et al. provided no data regarding tumor grading in their investigation [27].

In our study, different associations between DWI findings and histopathological parameters were identified. Firstly, Ki-67 was negatively associated with ADC_{mean} and NADC values. Secondly, NADC and ADC_{mean} correlated well with tumor grade but not with cell count. Thirdly, ADC_{min} was negatively associated with cell count of the investigated tumors but not with tumor grade. In accordance with these findings, we found no differences in cell count between benign and atypical/malignant tumors.

Our results also showed that the meningioma subgroups differed in their relationships between several ADC and histopathological parameters. For example, the identified significant correlation between ADC_{min} and cell count was stronger in high-grade meningiomas than in benign tumors. Furthermore, our study suggested that different ADC parameters reflected different histopathological findings in meningiomas. Our analysis confirms the hypothesis of Chen et al., who found in their meta-analysis that ADC_{min} is more related to tumor cellularity that ADC_{mean} [28].

A key question is how the identified findings can be helpful to distinguish benign meningiomas from grade II/III tumors. As seen, the use of an ADC_{mean} value of less than 0.85×10^{-3} mm^2s^{-1} can differentiate grade I from grade II/III meningiomas. Furthermore, the identified threshold ADC_{mean} value is also helpful to diagnose tumors with high proliferation potential.

Previously, Tang et al. performed a similar analysis [21]. The author suggested an ADC cutoff of less than 0.70×10^{-3} mm^2s^{-1} to differentiate aggressive meningiomas from low-grade tumors. In addition, they postulated an ADC cutoff of greater than 0.85×10^{-3} mm^2s^{-1} to identify low-grade meningiomas. However, both threshold values had a very low sensitivity (29%) [21].

Our study has several limitations. Firstly, it is retrospective. Secondly, it includes 49 tumors, and only 7 of these tumors had a grade higher than grade I. Greater numbers of high-grade tumors are needed to study the associations between DWI features and histological factors in different meningioma subgroups.

In conclusion, our analysis showed several associations between different DWI findings and histopathological parameters. Grade II/III tumors had statistically significant lower ADC_{mean} values than grade I meningiomas. ADC_{mean} values correlated negatively with tumor proliferation index and ADC_{min} with tumor cell count. Furthermore, these associations were different in several meningioma grades. ADC_{mean} can be used for distinguishing between benign and atypical/malignant meningiomas.

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