Diffusion-Weighted Imaging in Meningioma: Prediction of Tumor Grade and Association with Histopathological Parameters

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 × 10^{-3} mm^2 s^{-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 × 10^{-3} mm^2 s^{-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 ADC_{min} 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 × 10^{-3} mm^2 s^{-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} ...
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 ADCmean values than grade I meningiomas. ADCmean correlated negatively with tumor proliferation index and ADCmin with tumor cell count. These associations were different in several meningiomas. ADCmean can be used for distinguishing between benign and atypical/malignant tumors.

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 $1.00 \times 10^{-3}$ mm$^2$s$^{-1}$ 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$^2$s$^{-1}$ with a median value of 0.59 ± 0.11 $10^{-3}$ mm$^2$s$^{-1}$ [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, Schnapfaufl 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 Ginzat 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 atypical/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 x 250 mm; slice thickness: 5 mm; acquisition matrix: 128 x 128), with 6 values of 0, 500, and 1000 s/mm$^2$. ADC maps were automatically generated by the implemented software according to the following equation: $ADC (mm^2s^{-1}) = \frac{ln(S^0/S^{1000})}{1000}$, 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].
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 mm² 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 mm² per field). All images were analyzed by using a research microscope, Jenalumar, with camera Diagnostic Instruments 4.2.
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 ADCmean values of meningiomas ranged from 0.71 to 1.78 × 10⁻³ mm²s⁻¹ with a median value of 0.9 × 10⁻³ mm²s⁻¹; the mean value was 0.94 ± 0.20 × 10⁻³ mm²s⁻¹ (Figures 1 and 2). The mean value of ADCmin was 0.68 ± 0.14 × 10⁻³ mm²s⁻¹, median value was 0.67 × 10⁻³ mm²s⁻¹, and range was 0.33 to 1.2 × 10⁻³ mm²s⁻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 ADCmean value was higher in grade I meningiomas in comparison to grade II/III tumors (0.96 vs 0.80 × 10⁻³ mm²s⁻¹, P = .006) (Figure 3a). Grade II/III meningiomas showed lower NADC values in comparison to grade I tumors (1.05 vs 1.26, P = .015) (Figure 3b). There was no significant difference in ADCmin values between grade I and II/III tumors (0.69 vs 0.63 × 10⁻³ mm²s⁻¹, P = .539) (Figure 3c).

In addition, no significant differences in ADCmean (0.90 vs 0.96 × 10⁻³ mm²s⁻¹, P = .074) and ADCmin (0.65 vs 0.73 × 10⁻³ mm²s⁻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

| Table 1. Investigated Parameter in Meningioma |
|-----------------------------------------------|
| Parameter         | M ± SD      | Median | Range      |
|-------------------|-------------|--------|------------|
| ADCmin × 10⁻³ mm²s⁻¹ | 0.68 ± 0.14 | 0.67   | 0.33-1.2   |
| ADCmean × 10⁻³ mm²s⁻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       |

Figure 3. Comparison of ADC/NADC values between meningiomas. (a) ADCmean values in grade I and II/III meningiomas. Grade I tumors showed higher mean ADCmean value in comparison to grade II/III tumors (0.96 vs 0.80 × 10⁻³ mm²s⁻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 (1.05 vs 1.26, P = .015). (c) ADCmin values in grade I and II/III meningiomas. There was no significant difference in ADCmin values between grade I and II/III tumors (0.69 vs 0.63 × 10⁻³ mm²s⁻¹, P = .539).
The significant correlations are given in boldface.

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

| Parameter | Cell Count | Ki-67, % |
|-----------|------------|----------|
| $\text{ADC}_{\text{mean}} \times 10^{-3} \text{ mm}^2\text{s}^{-1}$ | $r = -0.44$ | $r = -0.20$ |
| | $P = .002$ | $P = .129$ |
| $\text{ADC}_{\text{mean}} \times 10^{-3} \text{ mm}^2\text{s}^{-1}$ | $r = -0.22$ | $r = -0.50$ |
| | $P = .164$ | $P = .001$ |
| NADC | $r = -0.25$ | $r = -0.60$ |
| | $P = .079$ | $P = .001$ |

The significant correlations are given in boldface.

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

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

The significant correlations are given in boldface.

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

| Parameter | Cell Count | Ki-67, % |
|-----------|------------|----------|
| $\text{ADC}_{\text{mean}} \times 10^{-3} \text{ mm}^2\text{s}^{-1}$ | $r = -0.786$ | $r = -0.505$ |
| | $P = .036$ | $P = .247$ |
| $\text{ADC}_{\text{mean}} \times 10^{-3} \text{ mm}^2\text{s}^{-1}$ | $r = -0.143$ | $r = 0.748$ |
| | $P = .760$ | $P = .053$ |
| NADC | $r = -0.252$ | $r = -0.189$ |
| | $P = .385$ | $P = .685$ |

The significant correlations are given in boldface.

**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, Hakymez 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 ± 0.21 × 10^{-3} mm^2 s^{-1} and 0.75 ± 0.21 × 10^{-3} mm^2 s^{-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 ($r = -0.53$, $P = .02$)}
In our study, different associations between DWI findings and histopathological parameters were identified. Firstly, Ki-67 was negatively associated with ADCmean and NADC values. Secondly, NADC and ADCmean correlated well with tumor grade but not with cell count. Thirdly, ADCmin 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 ADCmin 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 ADCmean is more related to tumor cellularity than ADCmean [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 ADCmean value of less than $0.85 \times 10^{-3}$ mm$^2$s$^{-1}$ can differentiate grade I from grade II/III meningiomas. Furthermore, the identified threshold ADCmean 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 $0.70 \times 10^{-3}$ mm$^2$s$^{-1}$ to differentiate aggressive meningiomas from low-grade tumors. In addition, they postulated an ADC cutoff of greater than $0.85 \times 10^{-3}$ mm$^2$s$^{-1}$ 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 ADCmean values than grade I meningiomas. ADCmean values correlated negatively with tumor proliferation index and ADCmean with tumor cell count. Furthermore, these associations were different in several meningioma grades. ADCmean can be used for distinguishing between benign and atypical/malignant meningiomas.

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