Received:
18 January 2018

Revised:
23 April 2018

Accepted:
12 May 2018

<https://doi.org/10.1259/bjr.20180088>

Cite this article as:

Aslan K, Gunbey HP, Tomak L, Incesu L. The diagnostic value of using combined MR diffusion tensor imaging parameters to differentiate between low- and high-grade meningioma. *Br J Radiol* 2018; **91**: 20180088.

FULL PAPER

The diagnostic value of using combined MR diffusion tensor imaging parameters to differentiate between low- and high-grade meningioma

¹KERIM ASLAN, MD, ¹HEDIYE PINAR GUNBEY, MD, ²LEMAN TOMAK, MD and ¹LUTFI INCESU, MD

¹Department of Radiology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey

²Department of Biostatistics, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey

Address correspondence to: Kerim Aslan

E-mail: mdkerim@hotmail.com

Objective: The purpose of this study was to examine whether the combined use of MR diffusion tensor imaging (DTI) parameters [DTI-apparent diffusion coefficient (ADC), fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD)] could provide a more accurate diagnosis in differentiating between low-grade and atypical/anaplastic (high-grade) meningioma.

Methods: Pathologically proven 45 meningioma patients [32 low-grade, 13 high-grade (11 atypical and 2 anaplastic)] who had received DTI before surgery were assessed retrospectively by 2 independent observers. For each lesion, MR DTI parameters (ADCmin, ADCmax, ADCmean, FA, AD, and RD) and ratios (rADCmin, rADCmax, rADCmean, rFA, rAD, and rRD) were calculated. When differentiating between low- and high-grade meningioma, the optimum cutoff values of all MR DTI parameters were determined by using receiver operating characteristic (ROC) analysis. Area under the curve (AUC) was measured with combined ROC analysis for different combinations of MR DTI parameters in order to identify the model combination with the best diagnostic accuracy in differentiation between low and high-grade meningioma.

Results: Although the ADCmin, ADCmax, ADCmean, AD, RD, rADCmin, rADCmax, rADCmean, rAD, and rRD values of high-grade meningioma were significantly low ($p = 0.007$, $p = 0.045$, $p = 0.035$, $p = 0.045$, $p =$

0.003 , $p = 0.02$, $p = 0.03$, $p = 0.03$, $p = 0.045$, and $p = 0.01$, respectively), when compared with low-grade meningioma, their FA and rFA values were significantly high ($p = 0.007$ and $p = 0.01$, respectively). For all MR DTI parameters, the highest individual distinctive power was RD with AUC of 0.778. The best diagnostic accuracy in differentiating between low- and high-grade meningioma was obtained by combining the ADCmin, RD, and FA parameters with 0.962 AUC.

Conclusion: This study shows that combined MR DTI parameters consisting of ADCmin, RD, and FA can differentiate high-grade from low-grade meningioma with a diagnostic accuracy of 96.2%.

Advances in knowledge: To the best of our knowledge, this is the first study reporting that a combined use of all MR DTI parameters provides higher diagnostic accuracy for the differentiation of low- from high-grade meningioma. Our study shows that any of the model combinations was superior to use of any individual MR DTI parameters for differentiation between low and high-grade meningioma. A combination of ADCmin, RD, and FA was found to be the best model for differentiating low-grade from high-grade meningioma and sensitivity, specificity, and AUC values were found to be 92.3%, 100%, and 0.96, respectively. Thus, a combination of MR DTI parameters can provide more accurate diagnostic information when differentiation between low and high-grade meningioma.

INTRODUCTION

Meningioma are the most frequent intracranial, extraaxial tumors and their frequency among all primary intracranial tumors is between 13 and 26%.¹ According to the World Health Organization (WHO), although a great majority of meningioma are Grade I (low-grade), up to 20% are Grade II or III (high-grade).²

The histopathological grade of meningioma is the most important factor in determining the clinical outcome.³ Due to their more aggressive biological characteristics, high-grade meningioma have high recurrence, morbidity, and mortality rates. Although surgery is a therapy option in all meningioma cases, radiation therapy is another useful option for treating high-grade meningioma.^{4,5} As

a result, the ability to make preoperative predictions of high-grade meningioma is important because it aids in surgical and treatment planning.

It is easy to diagnose meningioma with characteristic imaging findings in conventional MRI. However, the ability of conventional MRI to differentiate low-grade from high-grade meningioma remains uncertain. Some studies have reported that conventional MRI findings are not specific and reliable in identifying meningioma grade.^{6–8} However, Kawahara et al⁹ and Lin et al¹⁰ have suggested that the presence of heterogeneous enhancement, an unclear tumor-brain interface, and capsular enhancement can be useful in predicting high-grade meningioma. Thus, a non-invasive diagnostic method that can differentiate between low- and high-grade meningioma is required.

Diffusion-weighted MRI (DWI), which measures the average magnitude of water motion in the apparent diffusion coefficient (ADC) provides microscopic information about tissue properties. Some studies have reported that ADC values are useful when determining high-grade meningioma and have shown that high-grade meningioma have lower ADC values associated with high cellularity when compared with low-grade meningioma.^{11–18} However, a limited number of studies have reported that ADC values are not reliable when differentiating between low- and high-grade meningioma.^{19,20}

Diffusion tensor imaging (DTI) shows the magnitude and directionality of water molecule diffusion and thus gives information about the microstructural integrity of the tissue. DTI parameters consist of mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD). FA measures anisotropic water diffusion in the tissue and reflects the directionality; MD measures total magnitude of water diffusion in the tissue independent from direction; RD reflects the magnitude of diffusivity perpendicular to the maximum diffusion direction; AD measures the magnitude of diffusivity along the maximum diffusion direction.²¹ The results of studies conducted to identify meningioma grade using DTI and the most frequent FA parameter are controversial.^{22–24} Jolapara et al²² and Toh et al²³ reported that high-grade meningioma had significantly higher FA values when compared with low-grade meningioma, whereas Zikou et al²⁴ reported that they had lower FA values. However, none of these studies researched the difference between low- and high-grade meningioma by using a combination of DTI parameters. Nor did they report the diagnostic accuracy of RD and AD parameters in differentiation between low and high-grade meningioma in terms of sensitivity and specificity. Wang et al²⁵ showed that a histogram analysis of DTI parameters that included FA, MD, the linear anisotropy coefficient, the planar anisotropy coefficient, the spherical anisotropy coefficient, and eigenvalue skewness could help determine the meningioma grade. To the best of our knowledge, we have not come across any study in the literature that reports the combined use of MR DTI parameters including minimum (ADCmin), mean (ADCmean), and maximum (ADCmax) ADC, and FA, AD, and RD parameters to differentiate between low- and high-grade meningioma.

The purpose of this study was to research whether the combined use of MR DTI parameters (DTI–ADCmin, ADCmax, ADCmean, FA, AD, and RD) could give a more accurate diagnosis of low- and high-grade meningioma. Another purpose was to find out the diagnostic accuracy of each individual MR DTI parameter when differentiation between low and high-grade meningioma in terms of sensitivity, specificity, and area under the curve (AUC).

METHODS AND MATERIALS

Patients

This study was approved by the local ethics committee of our institution. This study retrospectively analyzed the MRI records of 56 adult patients (>18 years old) who had been diagnosed histopathologically with meningioma between February 2012 and June 2016 and who had undergone MR including preoperative DTI. The following patients were excluded from the study: 3 with giant cell calcification, 1 with tumor hemorrhage, 2 patients with small size (<10 mm), and 5 patients for whom reliable measurements of DTI parameters could not be taken due to the artefact in DTI. Finally, 45 patients were included in the study. The pathological diagnosis included 32 low-grade meningioma cases (WHO grade I; 11 males, 21 females; mean age ($\pm$ SD), 51.1 $\pm$ 16.9 years; age range, 19–74 years) and 13 high-grade meningioma cases (WHO Grade II/III; 4 males, 9 females; mean age ($\pm$ SD), 55.0 $\pm$ 13.2 years; age range, 24–70 years). Low-grade meningioma cases comprised 18 meningothelial, 10 transitional, 2 fibroblastic and 2 angiomatous subtypes.

Imaging techniques

MRI examinations were performed using a 1.5 T scanner (Gyrosan Intera; Philips Healthcare, Best, The Netherlands) with an 8-channel head coil. Routine MRI protocols included axial T_1 weighted (W) conventional spin-echo sequence with and without gadolinium [repetition time (TR)/echo time (TE): 450/15 ms, slice thickness: 5 mm, field of view (FOV): 230, matrix: 256 $\times$ 163; number of excitations (NEX): 2, intersection gap: 1 mm, scanning time: 2 min 30 s], axial T2W turbo spin-echo sequence (TR/TE: 4443/100 ms, section thickness: 5 mm, FOV: 230, matrix: 384 $\times$ 240, NEX: 3, intersection gap: 1 mm, scanning time: 3 min 37 s), coronal fluid attenuation inversion recovery (TR/TE/TI: 8000/140/2800 ms, section thickness: 5 mm, FOV: 230, matrix: 224 $\times$ 148, NEX: 2, intersection gap: 0.4 mm, scanning time: 2 min 40 s), sagittal T2W turbo spin-echo sequence (TR/TE: 4027/100 ms, section thickness: 5 mm, FOV: 230, matrix: 236 $\times$ 205, NEX: 2, intersection gap: 1 mm, scanning time: 1 min 05 s), and contrast-enhanced coronal T1W conventional spin-echo sequence (TR/TE: 461/10 ms; section thickness: 5 mm, FOV: 230, matrix: 240 $\times$ 166, NEX: 2, intersection gap: 0.89 mm, scanning time: 1 min 43 s).

DTI was acquired using a single-shot spin-echo EPI with parallel imaging by using GRAPPA and an acceleration factor of 2 (TR/TE: 7721/96 ms, section thickness: 2 mm, FOV: 230, matrix: 128 $\times$ 128, NEX: 2, intersection gap: 0 mm, number of gradient directions: 16, b values: 0 and 1000 s mm⁻², scanning time: 8 min 37 s).

Figure 1. A 51-year-old female patient whose low-grade meningioma (meningothelial subtype) was pathologically confirmed. T_2 weighted (A) and contrast-enhanced T_1 weighted (B) MR images show the lesion at a left frontal extraaxial distance. (A, B) In T_2 weighted and contrast-enhanced T_1 weighted images, the lesion was observed not clear tumor-brain interface and it was found to have shifted to the right due to the surrounding edema. Conventional MRI findings of the lesion would suggest high-grade meningioma. However, in ADC (C), AD (D), RD (E) and FA (F) maps, the DTI parameters of the lesion had high ADCmin ($0.84 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$), ADCmax ($1.10 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$), ADCmean ($0.94 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$), AD ($1.31 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$), RD ($0.93 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$), rADCmin (1.29), rADCmax (1.32), rADCmean (1.30), rAD (1.07), and rRD (1.41) values, and low FA (0.23) and rFA (0.5) values, as is compatible with its pathological grade.

Image analysis

Conventional MRI and DTI datasets were transferred to an independent workstation (IntelliSpace, software v. v6.0.4.03700, Philips Healthcare, Best, The Netherlands). At the workstation, ADC, FA, AD, and RD maps were formed automatically from DTI. Two neuroradiologists (KA and HPG, both with 6 years of experience) were blinded to the histopathological findings, of the patients' other clinical information. They performed the measurements and calculations independently. Regions of interest (ROIs) were drawn manually in circular shapes in solid portions by avoiding the cystic, necrotic and calcified areas of lesions from ADC maps. These areas were identified in T_2 W and contrast-enhanced T_1 W images. Circular ROIs which were drawn at workstation manually to lesions from ADC maps were placed automatically to lesions on FA, AD, and RD maps with the same localization and size. Based on the morphology and sizes of the lesions, two ROIs were placed on each slice per four, three and two consecutive axial slices and the averages of eight, six and four ROIs were taken, respectively in total. ROI area was between 34 and 111 mm^2 (mean $76 \pm 6 \text{ mm}^2$). With a similar method, a total of four same size ROIs (123 mm^2)—two on each slice per two consecutive slices were drawn on normal-appearing white matter (NAWM) at contralateral centrum semiovale of each lesion and average ADCmin-nawm, ADCmax-nawm, ADCmean-nawm, FAnawm, ADnawm, and RDnawm values were measured. ADCmin, ADCmax,

ADCmean, FA, AD, and RD ratios of the lesions (rADCmin, rADCmax, rADCmean, rFA, rAD, and rRD) were calculated by dividing average ADCmin, ADCmax, ADCmean, FA, AD, and RD values by average ADCmin-nawm, ADCmax-nawm, ADCmean-nawm, FAnawm, ADnawm, and RDnawm values.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics v. 21, IBM, Armonk, NY). Data are presented as the mean (SD), as median (min-max), or as frequency (%). The Shapiro-Wilk test was used to analyze the normal distribution assumption of the quantitative outcomes. To identify the differences between low- and high-grade meningioma, we used the Student's *t*-test for normally distributed data (age, ADCmin, ADCmean, ADCmax, FA, AD, RD, rADCmin, rADCmax, rADCmean, rFA, rAD, and rRD values). The frequencies were compared using the continuity correction χ^2 . AUC was evaluated as the measure of a diagnostic test's discriminatory power. For the differentiation of low- and high-grade meningioma, optimum cutoff values of all MR DTI parameters (ADCmin, ADCmean, ADCmax, FA, AD, RD, rADCmin, rADCmax, rADCmean, rFA, rAD, and rRD) were found using ROC analysis. The combined ROC curve was performed for combinations of the all MR DTI parameters in differentiation between low and high grade meningioma and sensitivity and specificity values were found. AUC was

Figure 2. A 47-year-old female patient whose high-grade meningioma was pathologically confirmed. T_2 weighted (A) and contrast-enhanced T_1 weighted (B) MR images show the lesion at the right cerebellar hemisphere extraaxial distance. A, B. In T_2 weighted and contrast-enhanced T_1 weighted images, the lesion observed had a clear tumor-brain interface and was found to have surrounding mild edema. Conventional MRI findings of the lesion suggest low-grade meningioma. However, in ADC (C), AD (D), RD (E) and FA (F) maps, the DTI parameters of the lesion had low ADCmin ($0.71 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$), ADCmax ($0.91 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$), ADCmean ($0.78 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$), AD ($1.12 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) RD ($0.72 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$), rADCmin (1.09), rADCmax (1.10), rADCmean (1.08), rAD (0.91), and rRD (1.09) values, and high FA (0.34) and rFA (0.74) values, as is compatible with its pathological grade. AD, axial diffusivity; ADC, apparent diffusion coefficient; FA, fractional anisotropy; RD, radial diffusivity.

calculated for each individual classifier's ROC curve as well as for the combined ROC curves, and the best model combination was formed. Interobserver agreement between the 2 readers was assessed using weighted Cohen kappa (κ) statistics. A κ value of 0.4 or lower indicated poor agreement, 0.41–0.60 indicated moderate agreement, 0.61–0.80 indicated good agreement, and 0.81–1.0 indicated excellent agreement. A p value < 0.05 was considered significant.

RESULTS

Examples of low- and high-grade meningioma are shown in Figures 1 and 2, respectively.

Table 1 summarizes the quantitative values including mean $\pm$ SD and median (min-max) and the corresponding statistical analysis of ADCmin, ADCmax, ADCmean, AD, RD, and FA, rADCmin, rADCmax, rADCmean, rAD, rRD, and rFA in the solid portion of the tumor for both low- and high-grade meningioma. Although the ADCmin, ADCmax, ADCmean, AD, RD, rADCmin, rADCmax, rADCmean, rAD, and rRD values of high-grade meningioma ($p = 0.007$, $p = 0.045$, $p = 0.035$, $p = 0.045$, $p = 0.003$, $p = 0.02$, $p = 0.03$, $p = 0.03$, $p = 0.045$, and $p = 0.01$, respectively) were significantly lower when compared

with low-grade meningioma, FA and rFA values were significantly higher ($p = 0.007$ and $p = 0.01$, respectively) (Table 1). The agreement between the 2 readers was excellent for ADCmin, ADCmax, ADCmean, AD, RD, and FA values (κ coefficient = 0.823, 0.856, 0.891, 0.816, 0.904, and 0.933, respectively). The agreement between the 2 readers was good for rADCmin, rADCmax, rADCmean, rAD, rRD, and rFA values (κ coefficient = 0.726, 0.771, 0.754, 0.691, 0.785, and 0.802, respectively) (Table 2).

In differentiating high-grade meningioma from low-grade meningioma based on ROC curve analysis, cutoff, sensitivity, specificity, and AUC values for ADCmin, ADCmax, ADCmean, AD, RD, FA, rADCmin, rADCmax, rADCmean, rAD, rRD, and rFA are shown in Table 2. ROC curve analysis results for all MR DTI parameters are exhibited in Figure 3a,b. For all MR DTI parameters, the highest individual distinctive power was RD, with an AUC of 0.778.

The sensitivity, specificity, and AUC values of the different combinations of MR DTI parameters used in differentiating high-grade from low-grade meningioma are listed in Table 3. For combinations of MR DTI parameters, ROC curve analysis

Table 1. Results of quantitative MR DTIn^a parameter values in low- and high-grade meningioma^a

Parameter	Low-grade meningioma		High-grade meningioma		<i>p</i> ^b value
	Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	
ADCmin	0.82 ± 0.12	0.82 (0.48–1.09)	0.69 ± 0.14	0.69 (0.41–0.97)	0.007
ADCmax	0.98 ± 0.14	0.97 (0.69–1.36)	0.87 ± 0.15	0.84 (0.63–1.28)	0.045
ADCmean	0.90 ± 0.15	0.87 (0.56–1.28)	0.79 ± 0.17	0.78 (0.50–1.17)	0.035
AD	1.25 ± 0.18	1.23 (0.97–1.63)	1.14 ± 0.14	1.12 (0.90–1.41)	0.045
RD	0.93 ± 0.21	0.92 (0.58–1.25)	0.72 ± 0.13	0.71 (0.47–1.02)	0.003
FA	0.21 ± 0.08	0.21 (0.10–0.39)	0.31 ± 0.13	0.30 (0.15–0.43)	0.007
rADCmin	1.26 ± 0.21	1.23 (0.74–1.67)	1.06 ± 0.16	1.03 (0.63–1.49)	0.02
rADCmax	1.18 ± 0.16	1.15 (0.83–1.63)	1.05 ± 0.16	1.02 (0.76–1.54)	0.03
rADCmean	1.25 ± 0.19	1.22 (0.78–1.78)	1.09 ± 0.18	1.09 (0.71–1.62)	0.03
rAD	1.02 ± 0.12	1.02 (0.79–1.34)	0.92 ± 0.11	0.91 (0.74–1.16)	0.045
rRD	1.41 ± 0.26	1.39 (0.89–1.92)	1.12 ± 0.20	1.10 (0.72–1.57)	0.01
rFA	0.45 ± 0.11	0.45 (0.23–0.83)	0.64 ± 0.14	0.63 (0.32–0.90)	0.01

^aExcept for the *p*-values.^bStudent's *t*-test, minimum, maximum, and mean apparent diffusion coefficient (ADCmin, ADCmax, and ADCmean), AD, RD, and FA; ratio of the ADCmin, ADCmax, ADCmean AD, RD, and FA values (rADCmin, rADCmax, rADCmean, rAD, rRD, and rFA).

results are exhibited in Figure 4. differentiation between low and high-grade meningioma any one of the model combinations (Figure 4) was superior to using any individual MR DTI parameter (Figure 3a,b). The best model in differentiating high-grade meningioma from low-grade meningioma was the combination of ADCmin, RD and FA parameters and sensitivity, specificity and AUC values were 92.3%, 100%, and 0.96, respectively.

DISCUSSION

Treatment strategies for low- and high-grade meningioma can differ.²⁶ Thus, a non-invasive diagnostic method is important

when differentiation between low and high-grade meningioma. However, conventional MRI has shown to be of limited use in differentiating between low- and high-grade meningioma.^{6–8}

The most commonly used MR diffusion parameter when differentiating low-grade from high-grade meningioma is ADC. ADC measures the total magnitude of water diffusion in tissue, independent of direction, while giving information about the cellularity of the tissue and the nucleus-to-cytoplasm ratio. Some studies have shown that ADC values are useful in identifying high-grade meningioma and have lower ADC values.^{11–18} In a

Table 2. Cutoff, sensitivity, specificity, and AUC values of MR DTI parameters to differentiate low-grade from high-grade meningioma using ROC curve analysis^a

Parameter	Cutoff	Sensitivity	Specificity	AUC	κ values
ADCmin	0.76	69.2%	71.9%	0.732	0.823
ADCmax	0.91	69.2%	62.5%	0.696	0.856
ADCmean	0.82	69.2%	65.6%	0.702	0.891
AD	1.16	61.5%	68.7%	0.683	0.816
RD	0.74	69.2%	78.1%	0.778	0.904
FA	0.26	69.2%	68.7%	0.770	0.933
rADCmin	1.17	69.2%	68.7%	0.716	0.726
rADCmax	1.10	69.2%	62.5%	0.696	0.771
rADCmean	1.15	69.2%	62.5%	0.696	0.754
rAD	0.95	61.5%	68.7%	0.683	0.705
rRD	1.23	69.2%	65.6%	0.702	0.785
rFA	0.53	69.2%	65.6%	0.702	0.804

AUC, minimum, maximum, and mean apparent diffusion coefficient (ADCmin, ADCmax, and ADCmean), AD, RD, and FA; ratio of the ADCmin, ADCmax, ADCmean AD, RD, and FA values (rADCmin, rADCmax, rADCmean, rAD, rRD, and rFA).

^aExcept for the κ values.

Figure 3. ROC analysis with AUC for each MR DTI parameter when differentiating between low- and high-grade meningioma [AUC for ADCmin, ADCmax, ADCmean, AD and RD (A) and FA (B)].

recent study, it was found that when the cutoff ADC value was set as $0.85 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, sensitivity was 72.9%, specificity was 73.1%, and accuracy was 73.0% in low- and high-grade meningioma differentiation.¹⁷ Similarly, in our study, the ADCmin, ADCmax, ADCmean, rADCmin, rADCmax, and rADCmean values of high-grade meningioma were significantly lower when compared with low-grade meningioma ($p = 0.007$, $p = 0.045$, $p = 0.035$, $p = 0.02$, $p = 0.03$, and $p = 0.03$, respectively). When differentiating low-grade from high-grade meningioma, cutoff, sensitivity, specificity, and AUC values for ADCmin, ADCmax, ADCmean, rADCmin, rADCmax, and rADCmean, according to ROC curve analysis, were 0.76, 69%, 72% and 0.732; 0.91, 69%, 62% and 0.696; 0.82, 69%, 66%, and 0.702; 1.17, 69%, 69% and 0.716; 1.10, 69%, 63%; and 0.696; and 1.15, 69%, 63%, and 0.696, respectively. However, Santelli et al¹⁹ and Sanverdi et al²⁰ reported that ADC values were not reliable in the differentiation of low- and high-grade meningioma. Watanabe et al²⁷ compared ADCmin, ADCmean, and ADCmax values when detecting meningioma grade and showed that ADCmin values were correlated with the histological grade of meningioma in high b values ($b = 4000$). In our study, the ADCmin value (AUC: 0.732) was superior to ADCmean (AUC: 0.702), ADCmax (AUC: 0.696), rADCmin (AUC: 0.716), rADCmax (AUC: 0.696), and rADCmean (AUC: 0.696) values when differentiating between

low- and high-grade meningioma. In the current study, decreased ADC values in high-grade meningioma can show increased cellularity and high nucleus-to-cytoplasm ratio.

FA measures anisotropic water diffusion, gives information about the directionality of water diffusion and shows tissue integrity.¹³ In high-grade meningioma, tumor cells do not form typical fascicles, whorls, or nodes, as in low-grade meningioma, and they have more directionality. In addition, high-grade meningioma are characterized by uninterrupted, patternless, or sheetlike growth, histologically,² which reflects the higher microstructural organization of the tumor. In our study, we showed that FA was higher in high-grade meningioma (FA, and rFA were 0.21, and 0.45 and 0.31, and 0.64, respectively, for low- and high-grade meningioma, $p = 0.007$ and $p = 0.01$, respectively), which was similar to the results of previous studies.^{22,23} In addition, when differentiating low-grade from high-grade meningioma, cutoff, sensitivity, specificity, and AUC values for FA, and rFA, according to ROC curve analysis, were 0.26, 69%, 69% and 0.770; and 0.53, 69%, 66% and 0.702, respectively. In the current study, increased FA values in high-grade meningioma suggest higher anisotropic diffusion and microstructural integrity when compared with low-grade meningioma. However, Zikou et al²⁴ and Wang et al²⁵ reported low FA values in atypical meningioma. This finding was

Table 3. AUC, sensitivity, specificity, PPV, and NPV values of different combinations of MR DTI parameters to differentiate low-grade from high-grade meningioma using ROC curve analysis

Models	AUC	Sensitivity	Specificity	PPV	NPV
ADCmin + RD	0.845	84.6%	84.4%	68.8%	93.1%
ADCmin + FA	0.845	84.6%	84.4%	68.8%	93.1%
RD + FA	0.899	92.3%	87.5%	75.0%	96.6%
ADCmin + RD + FA	0.962	92.3%	100%	100%	97.0%

AUC, Area under the curve; ADCmin, minimum apparent diffusion coefficient; AD, axial diffusivity; RD, radial diffusivity; FA, fractional anisotropy; NPV, negative predictive value; PPV, positive predictive value.

Figure 4. ROC analysis with AUC for combinations of MR DTI parameters in differentiating between low- and high-grade meningioma. AUC, area under the curve; ROC, receiver operating characteristic.

not in parallel with our study or and with other studies.^{22,23} This difference may have resulted from the fact that their studies had more fibroblastic meningioma cases, a subtype of typical meningioma, when compared with previous studies^{22,23} and our study (which includes only 2 cases of fibroblastic meningioma).

Although FA and ADC have high sensitivity with regards to microstructural tissue changes, they are not very specific. Recently, the directional diffusivity metrics, RD and AD, have been used to improve the characterization of tissue microstructure where diffusion-tensor eigenvalues (λ_1 , λ_2 , λ_3) represent the diffusion magnitude. $AD = \lambda_1$ is defined as the magnitude of diffusivity parallel to the maximum diffusion direction, whereas $RD = \lambda_2 + \lambda_3/2$ is defined as the magnitude of diffusivity perpendicular to the maximum diffusion direction.^{28,29} Toh et al²³ have shown that in low-grade meningioma, high λ_2 and λ_3 indicate that microscopic water movement is more disorganized than in high-grade meningioma. In our study, we showed higher AD, RD, rAD, and rRD values in low-grade meningioma when compared with high-grade meningioma ($p = 0.045$, $p = 0.003$, $p = 0.045$, and $p = 0.01$, respectively), which was similar to the results of Xing et al study.³⁰ In our study, the cutoff values used for AD, RD, rAD, and rRD in differentiation between low and high-grade meningioma were 1.16, 0.74, 0.95, and $1.23 \times 10^{-3} \text{ s mm}^{-2}$, respectively. Sensitivity, specificity and AUC values were 62%, 69%, 0.683; 69%, 78%, and 0.778; 62%, 69%, 0.683; 69%, 66%, 0.702, respectively. In addition, the highest individual power among all MR DTI parameters in differentiation between low and high-grade meningioma belonged to RD, with 0.78 AUC. Thus, our results suggest that high-grade meningioma are characterized by stronger microstructural organization when compared with low-grade meningioma.

MR DTI parameters (ADC, FA, AD, and RD) measure diffusion size and directionality to differentiate between different tumor types and to give information about cellularity and the

microstructural organization of tumors. In addition, using these parameters alone has a limited role in characterizing tumors. In our study, although using RD on its own offers the best MR DTI parameter in terms of differentiating low-grade from high-grade meningioma, its specificity was low (78%). A combination of two or more imaging parameters is required for the accurate characterization of a complicated tissue such as a tumor. A combination of multiple parameters can improve diagnostic accuracy. Svalos et al³¹ combined diffusion (ADC and FA) and perfusion (relative cerebral blood volume) techniques with classification methods when differentiating glioblastomas and metastases from atypical meningiomas. They reported that it provided additional information for a definitive diagnosis. Piper et al³² reported that multimodel MRI parameters (AD, RD, FA, and quantitative longitudinal relaxation time and magnetization transfer ratio) could be useful in differentiating between low-grade glioma and meningioma. To the best of our knowledge, this is the first study reporting that a combined use of all MR DTI parameters (ADCmin, ADCmean, ADCmax, FA, AD, RD, rADCmin, rADCmax, rADCmean, rFA, rAD, and rRD) provides higher diagnostic accuracy for the differentiation of low- from high-grade meningioma. Our study shows that any model combination (Figure 4) has higher diagnostic accuracy than can be obtained using any of the MR DTI parameters on their own (Figure 3a,b). In our study, ROC curve analysis shows that ADCmin, FA and RD combination is the model that best differentiation between low and high-grade meningioma and sensitivity, specificity, and AUC values were found to be 92.3%, 100%, and 0.96, respectively. Results of our work confirmed the hypothesis that the additional diagnostic information provided by each parameter can be combined for yield improved diagnostic performance.

There are, however, some limitations to our study. First, since the study was designed retrospectively, it was not possible to match ROIs for the measurement of MR DTI parameters with the tissue places sampled for pathological analysis. A future study similar to the one conducted by Price et al³³ would be helpful for this issue. Secondly, MR DTI parameters can differ according to histological subtypes. Some studies have reported that fibroblastic meningioma have lower ADC and higher FA values when compared with other low-grade meningioma cases.^{22,25,33} In our study, fibroblastic meningioma cases were particularly limited, we lacked a number of low-grade meningioma subtypes (such as secretory and psammomatous), and the incidence of high-grade meningioma was relatively small. Thus, our study did not have an adequate patient population. Studies which include a larger patient group are needed to confirm the results of our study. Lastly, in this study, a monoexponential model was used. In future studies, a biexponential model should be used.

CONCLUSION

Our study showed that individual use of any of the MR DTI parameters was useful for low- and high-grade meningioma differentiation. Among the MR DTI parameters, RD had the highest accuracy in differentiation between low and high-grade meningioma, with a diagnostic accuracy of 77.8%. This study reported that any of the model combinations was superior to use

of any individual MR DTI parameters for differentiation between low and high-grade meningioma. A combination of ADCmin, RD, and FA was found to be the best model for differentiating low-grade from high-grade meningioma, with a diagnostic accuracy of 96.2%. Thus, a combination of MR DTI parameters can provide more accurate diagnostic information when differentiation between low and high-grade meningioma.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

REFERENCES

- Bondy M, Ligon BL. Epidemiology and etiology of intracranial meningiomas: a review. *J Neurooncol* 1996; **29**: 197–205. doi: <https://doi.org/10.1007/BF00165649>
- Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 2007; **114**: 97–109. doi: <https://doi.org/10.1007/s00401-007-0243-4>
- Commins DL, Atkinson RD, Burnett ME. Review of meningioma histopathology. *Neurosurg Focus* 2007; **23**: E3. doi: <https://doi.org/10.3171/FOC-07/10/E3>
- Dashti SR, Sauvageau E, Smith KA, Ashby LS. Nonsurgical treatment options in the management of intracranial meningiomas. *Front Biosci* 2009; **1**: 494–500. doi: <https://doi.org/10.2741/e45>
- Palma L, Celli P, Franco C, Cervoni L, Cantore G. Long-term prognosis for atypical and malignant meningiomas: a study of 71 surgical cases. *J Neurosurg* 1997; **86**: 793–800. doi: <https://doi.org/10.3171/jns.1997.86.5.0793>
- Verheggen R, Finkenstaedt M, Bockermann V, Markakis E. Atypical and malignant meningiomas: evaluation of different radiological criteria based on CT and MRI. *Acta Neurochir* 1996; **65**: 66–9.
- Zee CS, Chin T, Segall HD, Destian S, Ahmadi J. Magnetic resonance imaging of meningiomas. *Semin Ultrasound CT MR* 1992; **13**: 154–69.
- Maiuri F, Iaconetta G, de Divitiis O, Cirillo S, Di Salle F, De Caro ML. Intracranial meningiomas: correlations between MR imaging and histology. *Eur J Radiol* 1999; **31**: 69–75. doi: [https://doi.org/10.1016/S0720-048X\(98\)00083-7](https://doi.org/10.1016/S0720-048X(98)00083-7)
- Kawahara Y, Nakada M, Hayashi Y, Kai Y, Hayashi Y, Uchiyama N, et al. Prediction of high-grade meningioma by preoperative MRI assessment. *J Neurooncol* 2012; **108**: 147–52. doi: <https://doi.org/10.1007/s11060-012-0809-4>
- Lin BJ, Chou KN, Kao HW, Lin C, Tsai WC, Feng SW, et al. Correlation between magnetic resonance imaging grading and pathological grading in meningioma. *J Neurosurg* 2014; **121**: 1201–8. doi: <https://doi.org/10.3171/2014.7.JNS132359>
- Filippi CG, Edgar MA, Ulug AM, Prowda JC, Heier LA, Zimmerman RD. Appearance of meningiomas on diffusion-weighted images: correlating diffusion constants with histopathologic findings. *AJNR Am J Neuroradiol* 2001; **22**: 65–72.
- Hakyemez B, Yildirim N, Gokalp G, Erdogan C, Parlak M. The contribution of diffusion-weighted MR imaging to distinguishing typical from atypical meningiomas. *Neuroradiology* 2006; **48**: 513–20. doi: <https://doi.org/10.1007/s00234-006-0094-z>
- Nagar VA, Ye JR, Ng WH, Chan YH, Hui F, Lee CK, et al. Diffusion-weighted MR imaging: diagnosing atypical or malignant meningiomas and detecting tumor dedifferentiation. *AJNR Am J Neuroradiol* 2008; **29**: 1147–52. doi: <https://doi.org/10.3174/ajnr.A0996>
- Yin B, Liu L, Zhang BY, Li YX, Li Y, Geng DY. Correlating apparent diffusion coefficients with histopathologic findings on meningiomas. *Eur J Radiol* 2012; **81**: 4050–6. doi: <https://doi.org/10.1016/j.ejrad.2012.06.002>
- Tang Y, Dundamadappa SK, Thangasamy S, Flood T, Moser R, Smith T, et al. Correlation of apparent diffusion coefficient with Ki-67 proliferation index in grading meningioma. *AJR Am J Roentgenol* 2014; **202**: 1303–8. doi: <https://doi.org/10.2214/AJR.13.11637>
- Surov A, Gottschling S, Mawrin C, Prell J, Spielmann RP, Wienke A, et al. Diffusion-weighted imaging in meningioma: prediction of tumor grade and association with histopathological parameters. *Transl Oncol* 2015; **8**: 517–23. doi: <https://doi.org/10.1016/j.tranon.2015.11.012>
- Surov A, Ginat DT, Sanverdi E, Lim CC, Hakyemez B, Yogi A, et al. Use of diffusion weighted imaging in differentiating between malignant and benign meningiomas. A multicenter analysis. *World Neurosurg* 2016; **88**: 598–602. doi: <https://doi.org/10.1016/j.wneu.2015.10.049>
- Baskan O, Silav G, Bolukbasi FH, Canoz O, Geyik S, Elmaci I. Relation of apparent diffusion coefficient with Ki-67 proliferation index in meningiomas. *Br J Radiol* 2016; **89**: 20140842. doi: <https://doi.org/10.1259/bjr.20140842>
- Santelli L, Ramondo G, Della Puppa A, Ermani M, Scienza R, d'Avella D, et al. Diffusion-weighted imaging does not predict histological grading in meningiomas. *Acta Neurochir* 2010; **152**: 1315–9. doi: <https://doi.org/10.1007/s00701-010-0657-y>
- Sanverdi SE, Ozgen B, Oguz KK, Mut M, Dolgun A, Soylemezoglu F, et al. Is diffusion-weighted imaging useful in grading and differentiating histopathological subtypes of meningiomas? *Eur J Radiol* 2012; **81**: 2389–95. doi: <https://doi.org/10.1016/j.ejrad.2011.06.031>
- Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G. Diffusion tensor MR imaging of the human brain. *Radiology* 1996; **201**: 637–48. doi: <https://doi.org/10.1148/radiology.201.3.8939209>
- Jolapara M, Kesavadas C, Radhakrishnan VV, Thomas B, Gupta AK, Bodhey N, et al. Role of diffusion tensor imaging in differentiating subtypes of meningiomas. *J Neurosurg* 2010; **37**: 277–83. doi: <https://doi.org/10.1016/j.neurad.2010.03.001>
- Toh CH, Castillo M, Wong AM, Wei KC, Wong HF, Ng SH, et al. Differentiation between classic and atypical meningiomas with use of diffusion tensor imaging. *AJNR Am J Neuroradiol* 2008; **29**: 1630–5. doi: <https://doi.org/10.3174/ajnr.A1170>
- Zikou A, Alexiou GA, Goussia A, Kosta P, Xydis V, Voulgaris S, et al. The role of diffusion tensor imaging and dynamic susceptibility perfusion MRI in the evaluation of meningioma grade and subtype. *Clin Neurol Neurosurg* 2016; **146**: 109–15. doi: <https://doi.org/10.1016/j.clineuro.2016.05.005>
- Wang S, Kim S, Zhang Y, Wang L, Lee EB, Syre P, et al. Determination of grade and

- subtype of meningiomas by using histogram analysis of diffusion-tensor imaging metrics. *Radiology* 2012; **262**: 584–92. doi: <https://doi.org/10.1148/radiol.11110576>
26. Oya S, Kawai K, Nakatomi H, Saito N. Significance of Simpson grading system in modern meningioma surgery: integration of the grade with MIB-1 labeling index as a key to predict the recurrence of WHO Grade I meningiomas. *J Neurosurg* 2012; **117**: 121–8. doi: <https://doi.org/10.3171/2012.3.JNS111945>
 27. Watanabe Y, Yamasaki F, Kajiwara Y, Takayasu T, Nosaka R, Akiyama Y, et al. Preoperative histological grading of meningiomas using apparent diffusion coefficient at 3T MRI. *Eur J Radiol* 2013; **82**: 658–63. doi: <https://doi.org/10.1016/j.ejrad.2012.11.037>
 28. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. *Neurotherapeutics* 2007; **4**: 316–29. doi: <https://doi.org/10.1016/j.nurt.2007.05.011>
 29. Bassar PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. *Magn Reson Med* 2000; **44**: 625–32. doi: [https://doi.org/10.1002/1522-2594\(200010\)44:4<625::AID-MRM17>3.0.CO;2-O](https://doi.org/10.1002/1522-2594(200010)44:4<625::AID-MRM17>3.0.CO;2-O)
 30. Xing F, Tu N, Koh TS, Wu G. MR diffusion kurtosis imaging predicts malignant potential and the histological type of meningioma. *Eur J Radiol* 2017; **95**: 286–92. doi: <https://doi.org/10.1016/j.ejrad.2017.08.019>
 31. Svolos P, Tsolaki E, Theodorou K, Fountas K, Kapsalaki E, Fezoulidis I, et al. Classification methods for the differentiation of atypical meningiomas using diffusion and perfusion techniques at 3-T MRI. *Clin Imaging* 2013; **37**: 856–64. doi: <https://doi.org/10.1016/j.clinimag.2013.03.006>
 32. Piper RJ, Mikhael S, Wardlaw JM, Laidlaw DH, Whittle IR, Bastin ME. Imaging signatures of meningioma and low-grade glioma: a diffusion tensor, magnetization transfer and quantitative longitudinal relaxation time MRI study. *Magn Reson Imaging* 2016; **34**: 596–602. doi: <https://doi.org/10.1016/j.mri.2015.12.006>
 33. Tropine A, Dellani PD, Glaser M, Bohl J, Plöner T, Vucurevic G, et al. Differentiation of fibroblastic meningiomas from other benign subtypes using diffusion tensor imaging. *J Magn Reson Imaging* 2007; **25**: 703–8. doi: <https://doi.org/10.1002/jmri.20887>