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CLINICAL ARTICLE

# Diffusion-weighted imaging does not predict histological grading in meningiomas

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**Abstract**

*Purpose* This study aims to verify the reliability of diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) measurements to differentiate benign from atypical/malignant meningiomas and among different sub-types.

*Methods* Pre-operative DWI of 102 patients (74 females, mean age 58 years, age range 34–85 years) affected by a pathologically proven intracranial meningioma were retrospectively reviewed. DWI signal intensity of tumors was classified as hypo-, iso- or hyper-intense to grey matter. ADC values and normalised $ADC_{ratio}$ ($ADC_{meningioma}$/$ADC_{normal\ appearing\ white\ matter}$) of the neoplastic tissue (avoiding calcifications and cystic or necrotic areas) were measured by two neuroradiologists unaware of each others' reading. MRI and histological findings were compared.

*Results* Meningiomas were histologically graded as malignant (1%), atypical (21.5%) and benign (77.5%). Meningothelial, transitional and fibrous were the most frequent benign sub-types (44, 16 and 10 cases, respectively). There was no statistical difference between typical and atypical/malignant meningiomas when considering mean ADC values ($0.964 \pm 0.192 \times 10^{-3}$ vs $0.923 \pm 0.085 \times 10^{-3}\ cm^2/s$, $p=0.3$ *t*-Student) or $ADC_{ratio}$ ($1.266 \pm 0.290$ vs $1.185 \pm 0.115$, $p=0.2$ *t*-Student). ADC values or $ADC_{ratio}$ did not differ significantly among meningioma sub-types although a nearly significant difference was found between meningothelial and transitional (post hoc analysis $p=0.06$). Inter-observer agreement of ADC and $ADC_{ratio}$ measurements was high ($r=0.95$ and 0.92, respectively, Pearson's linear coefficient). DWI intensity did not reach a significant correlation with meningioma's grading ($p=0.08$).

*Conclusions* According to our study, DWI and ADC measurement do not seem reliable in grading meningiomas or identifying histological sub-types. Hence, these parameters should not be recommended for surgical or treatment planning.

**Keywords** Meningioma · DWI · ADC · Brain MRI · Grading

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## Introduction

Meningiomas are the most frequent extra-axial brain tumours accounting for about 24–30% of all primary intracranial tumours. According to the WHO, they are divided into benign (WHO type I, about 70–80% of all meningiomas), atypical (WHO type II, about 15–20%) and malignant (WHO type III, about 1–3%) [10, 11]. After surgery, recurrence of benign meningiomas is infrequent, while atypical and malignant meningiomas do recur within 5 years in about 40% and 50–80% of cases, respectively [11]. Therefore, a pre-operative reliable characterisation of meningiomas would be of paramount importance for a tailored surgical planning. On MR imaging, meningiomas present typically as well circumscribed mass, with strong enhancement after gadolinium administration, with a peri-tumoural rim and a dural tail [10]. Uncommon features such as intra-tumoural haemorrhage, intra- or extratumoural cystic or necrotic foci can be observed in about 15% of the patients [1]. Until now, it is not possible to distinguish between different histotypes on the basis of conventional MR imaging. Diffusion-weighted (w) imaging (DWI) and apparent diffusion coefficient (ADC) measurements have been used in brain tumour in order to characterise the cellularity and the response to therapy [13]. However, there are only few studies attempting to differentiate typical and atypical/malignant meningiomas or among histological subtypes by means of DWI [3, 5, 8]. These studies have been performed on relatively small series, and their results have shown significant discordances.

The purpose of this study was to examine DWI features and ADC values in meningiomas in a large population in order to define their relationship with histological grading and their reliability in the pre-operative evaluation (Fig. 1).

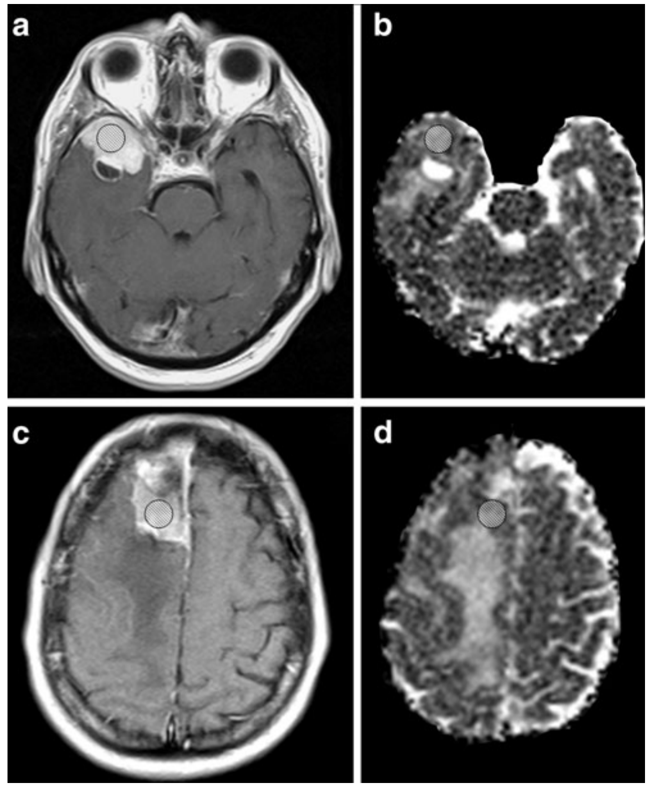


**Fig. 1** Brain MRI axial images (**a**, **c** contrast-enhanced T1-weighted images; **b**, **d** apparent diffusion coefficient maps): ROI inside meningiomas avoiding cystic (*superior row*) or necrotic areas (*inferior row*)

## Materials and methods

Among patients treated in our centre between 2003 and 2009, we consecutively enrolled all patients presenting a pathologically proved intracranial meningioma with a pre-operative DWI study. Previously treated meningiomas were excluded. One hundred two patients (74 females, mean age 58.1 years, age range 34–85 years) fulfilled the inclusion/exclusion criteria, and their MR examinations were retrospectively evaluated.

### Imaging techniques

Brain MRI examinations were performed before surgery (mean time gap of 19 days, median 7 days) with a 1.0-T scanner (Marconi Picker-Polaris) with a circularised coil. Pre- and post-contrast spin-echo T1-weighted, fast spin-echo (FSE) DP/T2, FSE fluid attenuated inversion recovery and diffusion-weighted images were obtained on axial planes, with the same position, thickness (5 mm), inter-slices gap (0.5 mm) and field of view (24 cm). DWI was performed with a single-shot spin-echo echo-planar imaging sequence (6,597:113.4:1 TR/TE/NEX) with *b* values of 0 and 800 s/mm$^2$ applied in three orthogonal directions. Trace ADC maps were automatically generated. Two neuroradiologists unaware of each others' reading calculated the mean ADC values by means of software (Medstation 4.6) available at our institution; region of interest (ROI) were manually drawn within the tumour. ROIs were traced avoiding cystic and necrotic areas, which were identified on T2-w and post-contrast T1-w images (Fig. 1). ROI area ranged between 0.5 and 3 cm$^2$ and differed according to the size and morphology of meningiomas. Neuroradiologists were blinded to histological findings. ADC values were, also, measured within normal appearing frontoparietal deep white matter, and an $ADC_{ratio}$ was obtained ($ADC_{meningioma}/ADC_{white\ matter}$). DWI signal intensity of meningiomas was evaluated and classified as hypo-intense, iso-intense or hyper-intense compared to grey matter.

### Histological studies

Histological samples were included in paraffin and stained with haematoxyline–eosine. Meningiomas were classified according to the WHO (2007) grading criteria [10] by pathologists with experience in brain tumours. Meningiomas are graded in three types: classical or benign (grade I), atypical (grade II) and malignant (grade III). Grades II and III meningiomas are more aggressive and have a higher recurrence rate. Atypical meningiomas have increased mitotic activity, which is defined as four or more mitoses per 10 high-power fields, brain invasion, or three or more of the following features: (1) increased cellularity, (2) small cells with a high nucleus-to-cytoplasm ratio, (3) prominent nucleoli, (4) uninterrupted patternless or sheetlike growth, and (5) foci of 'spontaneous' or 'geographic' necrosis. Malignant meningiomas are characterised by both of the following criteria: (1) 20 or more mitoses per 10 high-power fields and (2) presence of anaplasia. Tumours with large calcifications, haemorrhages or both were excluded. Benign meningiomas were 79 (77.45%) and atypical 22 (21.56%); only one patient harboured a malignant meningioma (0.98%). The most frequent benign histological sub-type was meningothelial with 44 patients (43.13%), followed by transitional and fibrous, 16 and 10 cases, respectively.

### Statistical analysis

Grades II and III meningiomas were grouped and compared to classical meningiomas. Normally distributed variables were analysed using the *T* test for independent group or the analysis of variance when the group were more than two. Although distribution of ADC was not statistically different from normality, a non-parametric analysis was also performed using the Mann–Whitney *U* test. Post hoc analysis was performed using the least significant difference method. For qualitative non-ordinal variables, the $\chi^2$ test was used. The correlation between DWI intensity and meningioma grading was studied using the Spearman's rho. Inter-observer agreement was evaluated by the Pearson's linear correlation analysis. A value of $p \leq 0.05$ was considered statistically significant.

## Results

Inter-observer agreement of ADC measurements was high ($r=0.95$ for ADC, $r=0.92$ for $ADC_{ratio}$). The mean ADC values were $0.964 \pm 0.192 \times 10^{-3}$ cm$^2$/s (range 0.631–1.872) in typical meningiomas and $0.923 \pm 0.085 \times 10^{-3}$ cm$^2$/s in atypical/malignant meningiomas. There was no statistical difference between the two groups when considering ADC values ($p=0.3$; *t*-Student) or $ADC_{ratio}$ ($p=0.2$; *t*-Student). The median ADC values and $ADC_{ratio}$ according to histological sub-types are reported in Table 1.

Considering the sub-groups of meningiomas with more than or equal to 10 cases (meningothelial, transitional, fibrous and atypical), ADC or $ADC_{ratio}$ values did not differ significantly (Fig. 2) although a significant difference was found between meningothelial and transitional (post hoc analysis $p=0.02$ only for ADC value). Among rare cases of classical meningiomas, the mixoid sub-type showed very high ADC values (Fig. 2). DWI signal intensity did not reach a significant correlation with meningioma grading ($p=0.08$).

## Discussion

### Relevant results of the present study

A diagnostic method able to differentiate between benign and atypical/malignant meningiomas has been widely searched for surgical planning. To sort out the reliability of DWI in grading meningiomas, we applied this technique on a large series of 102 meningiomas and compared DWI signal intensity, ADC values and $ADC_{ratio}$ to histological findings. None of these variables was able to reliably discriminate pre-operatively benign from atypical/malignant meningiomas, although we tried to avoid any confounding factor as major calcifications, haemorrhages or necrotic areas.

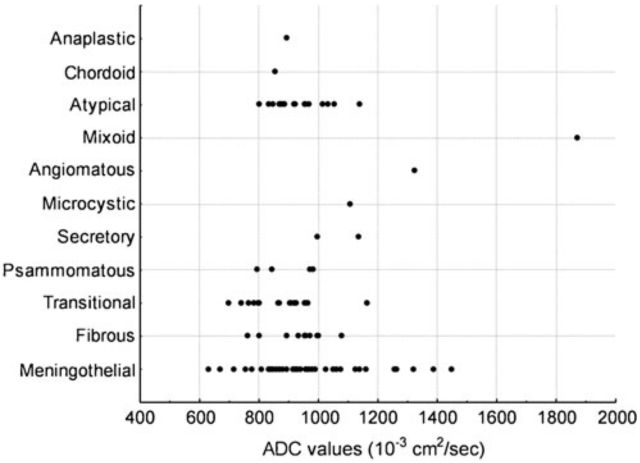


**Fig. 2** Histology and ADC values in meningiomas (*scatterplot*). The distribution of the mean ADC value is similar between typical and atypical/malignant; there is also a great variability among the benign histological sub-types

### Comparison with previous studies

Up to date, four studies have used mean diffusivity to grade meningiomas [3, 5, 8, 13], producing contradictory results. Although some authors have found that ADC values of atypical/malignant meningiomas were significantly lower than benign meningiomas [3, 5, 8], ADC accuracy and threshold to distinguish between benign and atypical/malignant meningiomas has not been established yet. It should be noted that these studies referred to small samples, included few cases of atypical meningiomas and had not been duplicated by other studies [13].

In some studies, DWI has been applied also in differentiating benign sub-types. Hakyemez et al. found lowest ADC values in meningothelial ($1.09 \pm 0.20 \times 10^{-3}$ cm$^2$/s) followed by transitional ($1.19 \pm 0.\ 07 \times 10^{-3}$ cm$^2$/s), fibrous ($1.29 \pm 0.28 \times 10^{-3}$ cm$^2$/s) and angiomatous ($1.48 \pm 0.10 \times 10^{-3}$ cm$^2$/s) and showed a significant difference between the angiomatous one sub-type and the meningothelial and transitional ones [5]. In our series, ADC values ranked in a different way (Table 1), thus showing no reliability of DWI in identifying meningioma sub-types. Furthermore, we did not find any significant difference across sub-types when considering those sub-groups with enough cases for a proper statistical analysis. On the other

**Table 1** Median ADC values, $ADC_{ratio}$ and DWI signal intensity according to histological sub-types and demographic characteristics of patients

| Grade | Sub-type | Number of patients | | | Age of patients | | ADC | | $ADC_{Ratio}$ | | DWI signal intensity | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Male | Female | Total | Median | Range | Median | Range | Median | Range | Hypo | Iso | Hyper |
| I | Meningothelial | 7 | 37 | 44 | 54 | 35–84 | 0.94 | 0.63–1.45 | 1.19 | 0.77–2.08 | 3 | 25 | 16 |
| | Fibrous | 2 | 8 | 10 | 69 | 49–79 | 0.95 | 0.76–1.08 | 1.18 | 0.91–1.48 | 2 | 4 | 4 |
| | Transitional | 5 | 11 | 16 | 64 | 42–71 | 0.88 | 0.69–1.16 | 1.20 | 0.89–1.46 | 3 | 5 | 8 |
| | Psammomatous | 0 | 4 | 4 | 60 | 53–70 | 0.90 | 0.79–0.98 | 1.14 | 0.93–1.28 | 1 | 0 | 3 |
| | Secretory | 0 | 2 | 2 | 55 | 34–76 | 1.06 | 0.99–1.13 | 1.43 | 1.30–1.56 | 1 | 1 | 0 |
| | Microcystic | 0 | 1 | 1 | 36 | – | 1.10 | – | 1.44 | – | 0 | 0 | 1 |
| | Angiomatous | 1 | 0 | 1 | 48 | – | 1.32 | – | 1.73 | – | 0 | 0 | 1 |
| | Mixomatous | 0 | 1 | 1 | 41 | – | 1.87 | – | 2.68 | – | 0 | 0 | 1 |
| II | Atypical | 12 | 9 | 21 | 62 | 35–77 | 0.88 | 0.80–1.14 | 1.20 | 1.00–1.41 | 1 | 6 | 14 |
| | Chordoid | 1 | 0 | 1 | 43 | – | 0.85 | – | 1.10 | – | 0 | 0 | 1 |
| III | Anaplastic | 0 | 1 | 1 | 85 | – | 0.89 | – | 1.07 | – | 0 | 0 | 1 |
| | Total | 28 | 74 | 102 | 59 | 34–85 | 0.92 | 0.63–1.87 | 1.20 | 0.77–2.68 | 11 | 41 | 50 |

hand, even among rare sub-types, ADC values range consistently: The secretory sub-type for example has been found to range from 1.07 in the study of Filippi et al. [3] to 1.32 in the paper of Yamasaki et al. [13].

### Strengths and limitations of the present study

Differences of ADC measurements between our and previous studies could be attributed to different scanner field strength, to different *b* values used in the studies or to different MR protocols which might have applied DWI sequences before or after contrast administration. Actually, none of these factors should heavily bias ADC values [4, 6, 9], especially when considering a normalised ADC ratio [8]. ROI's size might be a bias when comparing different studies: Hakyemez et al. used ROIs ranging from 0.1 to 0.5 $cm^2$, Nagar et al. used ROIs ranging from 0.3 to 1.3 $cm^2$ while Filippi et al. used standardised ROI of 0.25 $cm^2$ [3, 5, 8]. In our study, ROI size varied between 0.5 and 3 $cm^2$ according to the tumour size and the need to avoid regions non-suitable for measurement (necrosis, calcifications, cystic areas or haemorrhages) revealed by T2-w and contrast-enhanced T1-w images. Actually, there is no recommendation about the optimal ROIs size to be used. Large ROI have a high probability to include undetected microcystic or necrotic areas. On the other hand, ADC mean values of small ROIs might vary with small changes in ROI positioning even in normal white matter due to relatively high standard deviation of ADC values [2, 7]. Furthermore, small ROIs do not help to avoid undetected microcystic or necrotic areas, thus increasing the variability of ADC measurements within tumours. The good inter-observer agreement observed in this study seems to suggest that relatively large ROIs minimise the impact of differences of position and size of ROI thus supporting the reliability of our measurements. Finally, a single scanner and a standardised MR protocol were used throughout the whole study so that also technical factors should be considered negligible.

Recently, Toh et al. showed in a small cohort that intratumoural microscopic water motion is less organised in classic than in atypical meningiomas and that diffusion tensor imaging could differentiate the grading [12]. The reason for this phenomenon has not been unravelled yet, and it is still unclear why higher-grade tumours should present a much more organised microstructure. Further studies are needed to confirm these data before using them for surgical planning in the daily clinical practice.

## Conclusions

DWI and ADC measurements, even when performed under the best conditions, do not seem reliable in grading meningiomas or identifying histological sub-types. Therefore, according to our study, these parameters should not be suggested for surgical or treatment planning.

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## Comments

Rather infrequent atypical meningiomas (WHO grade II) recur more often and more rapidly after a seemingly complete microsurgical removal than the benign ones (I). Rare anaplastic meningiomas (III) are malignant soft tissue sarcomas that kill with rapid recurrences and metastases in a few years. In clinical routine, both seem to pop up as nasty histologic surprises without warning in routine pre-operative T1 and T2 images.

Consequently, the colleagues from Padova studied whether pre-operative DWI and ADC analysis of meningioma tissue (calcification, haemorrhages and necroses excluded) would differentiate 79 benign meningiomas from 22 atypical + one anaplastic ones. They did not—important clinical data though predictable in hindsight. Why would DWI and ADC be sensitive to tens of genomic and signalling pathway changes in grade II and III meningiomas?

Why to indentify at least the rare (1%) anaplastic meningiomas before first removal? Would the approach change the result? It would not because sarcoma resection with healthy margins cannot be performed. It remains to be seen, however, whether radio/chemotherapy given pre-operatively would prevent microscopic seeding although not effective against visible disease.

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The authors present a simple, well-crafted and well-written paper about the predictive value of DWI in the histological grading of intracranial meningiomas. Although the concept is not original, the conclusions of the paper help to clarify contradictory data issued from previously related papers. In fact, the study enrolled 102 patients, which is a significant number to avoid sampling errors, and solve the question, raised by this and similar studies. In this regard, Fig. 1 shows a particularly illustrative scatter plot. Most likely, a study on water movements inside the tumours is not the best way to predict the malignancy of a meningioma, starting by the high standard deviation of ADC values obtained from patients, as Table 1 nicely demonstrates.

Although I agree with the concept of extracting an ADC tumour/white matter ratio to overcome institutional differences in the acquisition protocol of the MRI scans, I would criticise in the "Materials and methods" section the concept of variable size ROI. Unfortunately, this introduced another variable to the study besides the main variable in analysis—the meningioma grading—that hinders the scientific rigor.

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