

# Multiparametrical diffusion tensor imaging for the detection of anaplastic transformation of low-grade gliomas

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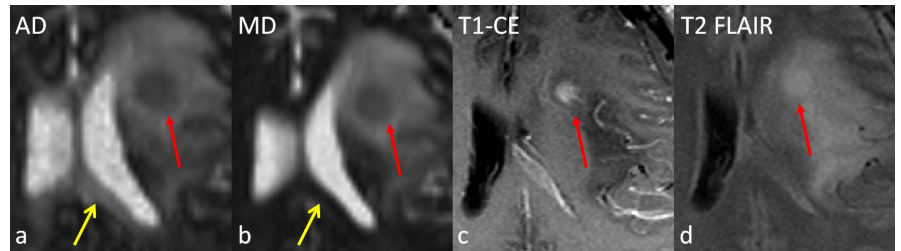
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## Introduction

The precise detection of anaplastic transformation in low-grade gliomas using magnetic resonance imaging (MRI) is impeded by postoperative changes in brain tissue adjacent to the resection cavity. From the current point of view, either contrast enhancement in T1 and/or rapidly increasing T2 FLAIR hyperintensity may indicate a progress of the disease but both signs may also result from post-therapeutic changes [1]. In many cases, only follow-up examinations can ultimately clarify the course of the disease. Based on previous studies in glioblastomas [2], we hypothesized, that anaplastic transformations should result in increase of tumor cellularity earlier or parallel to the time point of contrast enhancement and should thus be detectable using diffusion tensor imaging (DTI). In this context we tested the diagnostic value of diffusion tensor-derived axial diffusivity (AD), mean diffusivity (MD) (= apparent diffusion coefficient or ADC), radial diffusivity (RD) and fractional anisotropy (FA) maps in comparison to T1w and T2w sequences.

## Materials and Methods

The study was conducted in accordance to the declaration of Helsinki with institutional approval by the local ethics committee. 48 patients with histopathologically proven low-grade glioma WHO grade II were included (astrocytoma = 32, oligoastrocytoma = 12, oligodendroglioma = 4). 20 patients had an anaplastic transformation after operation (astrocytoma = 14, oligoastrocytoma = 4, oligodendroglioma = 2). The anaplastic transformation was confirmed histologically in 40% and radiologically in 60% (as novel and rapidly increasing contrast enhancement in follow-ups). 28 patients were stable controls to the date of study evaluation (astrocytoma = 18, oligoastrocytoma = 8, oligodendroglioma = 2). All patients underwent pre-operative MRI, received surgery and subsequent post-operative long-term MRI follow-ups on a 1.5T scanner (Siemens Avanto) including T1w, T2w imaging and a 2D echoplanar diffusion sequence, with the following parameters: TR/TE 3600/96 ms, matrix 128 × 128, FOV 256 × 256, resolution 2 × 2 × 4 mm<sup>3</sup>, 2 b-values (0,1000 s/mm<sup>2</sup>) and 6-12 independent diffusion weighting directions. The scalar indices AD, MD, RD and FA were calculated voxel-by-voxel for all patients from the tensor eigenvalues using MITK Diffusion [3] following:



**Figure 1:** Anaplastic transformation (red arrows) of primary gemistocytic astrocytoma WHO II 2 months after surgical resection in a 43 year-old female. AD map (a), MD map (b), contrast-enhanced T1 (c) and T2 Flair (d) are shown. AD and MD maps show a ball-shaped hypodensity (red arrows) corresponding to circular contrast uptake in c forming within the T2 hyperintensity as seen in d. Note the subtle differences between AD and MD map: white matter is depicted hyperintense in the AD and hypointense in the MD map (yellow arrows) using identical level/window values.

$$AD = \lambda_1; RD = \frac{(\lambda_2 + \lambda_3)}{2}; MD = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{3}; FA = \frac{\sqrt{3} \sqrt{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}; \text{ where } \lambda_1 > \lambda_2 > \lambda_3.$$

To determine the contrast-to-noise ratio (CNR), between the anaplastic tumor region and the surrounding T2-hyperintense tissue, the respective ROIs were placed in the AD map. For statistical analysis, one-way repeated measurements ANOVA was used including Bonferroni correction. Alpha level was 0.05. To determine the diagnostic value of the DTI-derived parameters considering the detection of an anaplastic transformation, a region of interest (ROI) defining the gross tumor volume including surrounding T2-hyperintense tissue and T1w contrast enhancement was placed in the b<sub>0</sub>-image. AD<sub>min</sub>, MD<sub>min</sub>, RD<sub>min</sub> and FA<sub>min</sub> within this region were extracted and used to perform an ROC analysis.

## Results

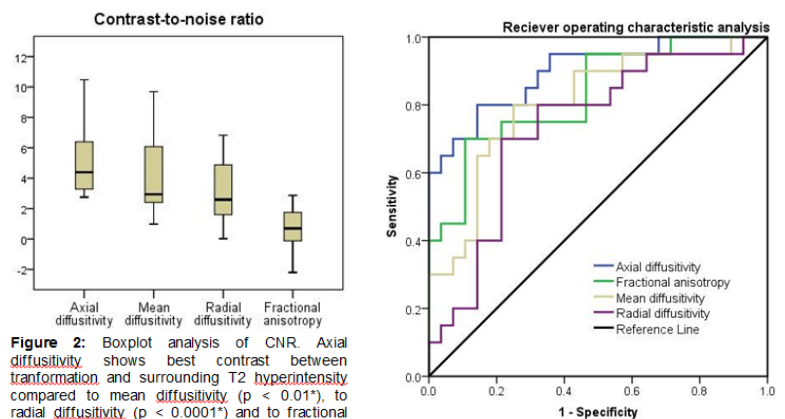
Focal and/or diffuse hypointense clusters were seen in every patient with anaplastic transformation in the AD and MD maps with best contrast in AD corresponding to the area of contrast enhancement, exemplarily demonstrated in Figure 1. In 13 of 20 patients with anaplastic transformation (65%), these clusters were noticed at the same time when compared to T1w contrast enhancement. In 7 patients (35%), hypointense changes were visible in AD maps in exams prior to the initial contrast enhancement. In the quantitative analysis, best CNR between the anaplastic transformation and surrounding T2-hyperintensity was found in the AD maps (Figure 2) compared to MD, RD and FA. Also, AD<sub>min</sub> showed best combined sensitivity/specificity compared to MD<sub>min</sub>, RD<sub>min</sub> and FA<sub>min</sub> to indicate transformation (Figure 3).

## Discussion

AD and MD maps provide additional essential information for anaplastic transformation of low-grade gliomas after resection and indicate the progress at the same time or earlier when compared to T1w-CE. We conclude that, since AD maps are tensor derived, it is advisable to use a DTI-protocol instead of isotropic diffusion weighted imaging for neuro-oncological exams. They could be integrated within a clinical multimodal MR protocol for tumor characterization, analogously and additionally to the currently used MD maps. Also, multi-parametrical DTI-based tumor characterization may be of special interest for patients with contraindications for contrast media.

## References

[1] Osborn A., *Diagnostic neuroradiology*, 1994 [2] Simon et al., *Cancer Imaging*, 2012 [3] Fritzsche et al., *Methods Inf Med.*, 2012



**Figure 2:** Boxplot analysis of CNR. Axial diffusivity shows best contrast between transformation and surrounding T2 hyperintensity compared to mean diffusivity ( $p < 0.01^*$ ), to radial diffusivity ( $p < 0.0001^*$ ) and to fractional anisotropy ( $p < 0.0001^*$ ). \*Bonferroni corrected.

**Figure 3:** ROC-analysis of AD<sub>min</sub>, MD<sub>min</sub>, RD<sub>min</sub> and FA<sub>min</sub> values in the gross tumor volume shows that AD<sub>min</sub> provides best combined sensitivity/specificity with area under the curve = 0.9. Best AD<sub>min</sub> threshold value was  $0.82 \times 10^{-3}$  mm<sup>2</sup>/s with 80% sensitivity and 86% specificity.