Diffusion tensor and magnetization transfer imaging of tumor margin in a rat C6 Glioma Model

Monika Huhndorf[1], Olga Will[2], Rolf Mentlein[3], Olav Jansen[1], and Susann Boretius[2]

[1]*Department of Radiology and Neuroradiology, University Medical Center Schleswig-Holstein, Kiel, Germany,* [2]*Section Biomedical Imaging, Department of Radiology and Neuroradiology, Christian-Albrechts-University, Kiel, Germany,* [3]*Anatomical Institute, Christian-Albrechts-University, Kiel, Germany*

Introduction: Annual incidence of glioblastoma is about 3 per 100,000 [1]. Current clinical diagnostic is performed with contrast enhanced MRI, utilizing the areas of contrast agent accumulation to identify the presumed boundaries of the tumor. However, as shown by histology this method often underestimates the area of tumor-cell-infiltration [2]. Diffusion tensor imaging is assumed to reflect changes in tissue microstructure. Within gliomas the fractional anisotropy (FA) has been shown to correlate with cell density and proliferation [3]. However the findings are in part contradictory and little has been reported about DTI parameters at the tumor margin. In the present study we performed DTI and magnetization transfer (MT) imaging on rats inoculated with C6 glioma cells in order to evaluate the potential of DTI and MT for characterization of the tumor margin and tumor-cell-infiltration.

Methods: 5 µl suspensions with different cell numbers were stereotactically injected into the basal ganglia of 5 male Wistar rats (6-10 weeks). On days 5, 9, 14, 21, and additionally on days 25 or 27 and 35 for low cell counts, MRI was performed at 7 T (ClinScan, Bruker Biospin). MRI measurements of anesthetized rats (0.4 mg/kg medetomidine/ 70mg/kg ketamine (10%), 0.5-1.0% isoflurane via endotracheal tube) comprised T2-weighted images (2D FSE, TR/TE=3150/41 ms), Diffusion-weighted images (2D EPI, TR/TE= 7000/30 ms, 12 directions, b= 0/1000 s/mm²), 3 differently weighted 3D FLASH based datasets (TR/TE=30/1 ms, flip angle=25° for proton weighted data sets one without and one with additional MT-weighting by Gaussian-shaped off-resonance irradiation. The latter two yielded maps of the MT ratio. The MT saturation (δMT) correcting for signal amplitude and T1 ($T1_{app}$) was calculated as detailed in [4]. After the last scan rats were sacrificed and prepared for histology. Diffusion weighted images were post-processed using Matlab (Mathworks Natick, USA) to calculate FA-, ADC- Axial-Diffusivity- and Radial-Diffusivity maps. Data analysis was performed using Amira 5.4. Based on the T2-weighted image 4 different ROIs were defined, describing tumor center, tumor border, normal appearing peritumoral tissue and normal contralateral tissue. These ROIs were transferred to the co-registered maps of diffusion parameters and magnetization transfer.

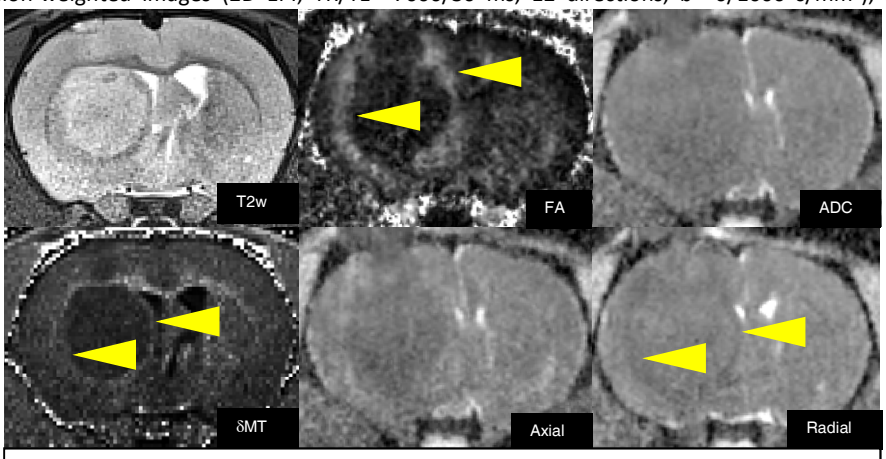

Fig.1: C6-Tumor at day 21 after initial injection of 100,000 cells

Results: By the end of the investigation period the peritumoral rim exhibited an increased FA compared to normal contralateral tissue, whereas the central tumor tissue showed unchanged or even reduced FA values (Fig 1). Interestingly, the ADC did not reveal a delineation of the tumor at all. The axial diffusivity was only marginally reduced in the tumor center whereas the radial diffusivity was slightly reduced at the tumor margin, contributing mainly to the observed increase in FA. Changes in FA were correlated with tumor volume and became manifest only at the end of the observation period. The increase in FA at the tumor margin was accompanied by an increase in δMT (Fig. 1) whereas the tumor center exhibited a reduced δMT compared to the normal contralateral tissue. Fig. 2 shows the corresponding results of the ROI analysis.

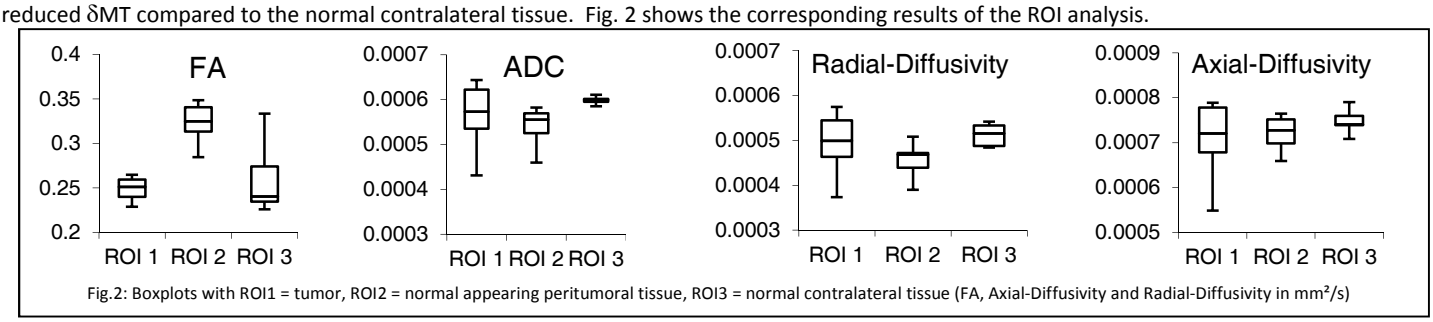

Fig.2: Boxplots with ROI1 = tumor, ROI2 = normal appearing peritumoral tissue, ROI3 = normal contralateral tissue (FA, Axial-Diffusivity and Radial-Diffusivity in mm²/s)

Discussion and Conclusion: The observed higher FA value and its correlation with tumor volume may reflect tissue compression with increased tumor size as reported previously[5]. However, in this case a general reduction of the diffusivity, that is the ADC, would be expected rather than a reduction in radial diffusivity only. Together with the increased δMT there is evidence for an increased cellularity and gliosis at the tumor margin beyond the tumor region visible on T2-weighted images. However, δMT did not appear as a sufficiently sensitive parameter for the detection of early tumor cell infiltration.

References: [1] Dolecek et al, Neuro Oncol. Suppl 5:v1-v49 (2012), [2] Scherer, Brain 63:1-35 (1940), [3] Beppu et al, Surg Neurol 2005;63:56–61, [4] Helms et al, MRM 60:1396 (2008), [5] Lope-Piedrafita et al, Proc Intl Soc Mag Reson Med 13:246 (2005)