Comparison of APT- and NOE-CEST in rat glioma at 7 T– Potentials for tumor characterization and detection of tumor cell infiltration

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Introduction Glioblastoma multiforme (GBM) is a highly aggressive brain cancer characterized by uncontrolled proliferation, resistance to cell death, extensive induction of angiogenesis, and vascular edema [1]. Chemical exchange saturation transfer (CEST) MRI [2] has emerged as an innovative technique generating contrasts dependent on the tissue content of small molecules such as glucose as well as mobile peptides and proteins. Previous CEST studies [3-6] particularly proposed the amide proton transfer (APT, 3.5 ppm) and the Nuclear Overhauser Enhancement (NOE) (in the range of -5 to -2 ppm) as new imaging contrasts. Especially the latter is sensitive to the tissue concentration of mobile macromolecules, such as lipids, proteins, peptides and various metabolites (e.g. lactate). Infiltration of glioma cell into the white and gray matter may be accomplished by a reduction of the myelin content per pixel which has been addressed by a variety of magnetization transfer techniques [7-9]. A recent 7 T study in humans reported a higher sensitivity of NOE for myelin content compared to less frequency-specific magnetization transfer techniques [10]. Thus, the purpose of this study was to compare APT- and NOE-CEST regarding tumor delineation and cellular infiltration in a rat glioma model *in vivo* over time.**Material and Methods** C6 glioma cells (100.000) were stereotactically injected into the right basal ganglia [11] of 6 male Wistar rats at the age of 6 weeks. The anesthetized rats (0.4 mg/kg medetomidine/ 70mg/kg ketamine (10%), 0.5-1.0% isoflurane via endotracheal tube) underwent MR measurements before and at days 7, 14, 28, 35 after tumor cell injection. All measurements were performed at 7 T (ClinScan^{TM}, Bruker Biospin, Ettlingen, Germany) using a volume resonator for RF excitation and a 4 channel rat surface coil for signal reception. During the *in vivo* MR measurements the temperature was kept constant at 36.0 ± 0.5°C. Single-slice chemical exchange saturation transfer (CEST) MR-imaging was performed using pulsed RF saturation followed by a 2D FLASH (Fast Low Angle SHot) readout [TR/TE: 123/4.8 ms, FOV: 31 mm, matrix: 128×128, slice thickness: 1 mm]. Z-spectra were acquired by the application of five repetitive (T_{sat} = 113 ms) RF Gaussian pulses of 180° at 41 frequency offsets between ± 5 ppm (total measurement time = 10.46 min). ROIs of the same size were selected inside the tumor and in the contralateral normal appearing brain region. Saturation transfer was quantified by magnetization transfer ratio: MTR=100× $[S_0\text{-}S_{sat}(\omega)]/S_0$ at frequency offsets of ω=±3.5ppm which corresponded to the maximum difference between the signal intensities in the tumor and healthy tissue. $S_{sat}(\omega)$ and S_0 are the signal intensities with and without frequency selective excitation, respectively. **Results** Figure 1 shows axially oriented T_2-weighted images and the corresponding maps of MTR at ± 3.5 ppm of a C6 rat glioma over time. Tumor growth went along with a signal enhancement on T2w (white arrow) and a clear reduction of MTR, both at +3.5 ppm and -3.5 ppm. Likewise, on both MTR maps regions of normal myelination (orange arrow) and tumor associated regions of reduced myelin (blue arrow) of the corpus callosum could be distinguished. However, the difference between tumor and healthy tissue as well as between regions of different myelin content was more pronounced in the MTR-maps at -3.5 ppm. Interestingly, in this animal model, a small rim surrounding the tumor (red arrow) reproducibly exhibited an increased MTR (-3.5 ppm).

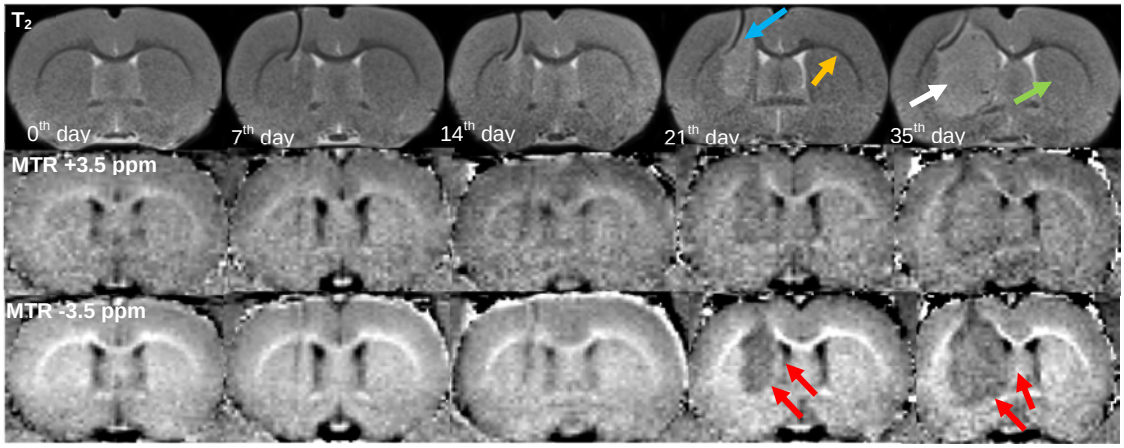

Fig. 1: *In vivo* MR measurements: Axial T_2-weighted images of a rat brain glioma *in vivo* (top) as well as the corresponding MTR at ±3.5 ppm maps. The maps are equally gray scaled. The white and green arrows point to tumor and normal brain tissue, the orange, blue, and red arrows show myelinated, unmyelinated region, and the tumor rim on the MTR maps, respectively.

Discussion and Conclusion The strongest contrast between glioma and normal appearing brain tissue could be achieved by an off-resonance frequency at -3.5 ppm (mainly NOE), rather than chemical exchange from mobile protons at +3.5 ppm. While the contrast alteration on the MTR map at +3.5 from 28th day was comparable to those of 35th day, the observed NOE-CEST effect revealed additional information about the tumor boundaries. These findings suggest a potential benefit of NOE-CEST MRI for the detection and characterization of glioblastoma in patients.

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