Evaluation of non-invasive MRI based measurement of blood oxygenation in malignant glioma

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Introduction

Hypoxia has been linked to tumor progression and therapeutic resistance. New studies show that a hypoxic microenvironment promotes the self-renewal and development of tumor stem cells within malignant glioma, suggesting that these cells may contribute to tumor maintenance and recurrence [1]. Emerging MRI techniques for non-invasive measurement of blood oxygenation [2] might allow in vivo detection of hypoxic areas within malignant glioma and may help to improve therapeutic strategies in the future. In our study, we seek to evaluate measurements of blood oxygenation levels within malignant tumors based on the theory of Yablonski & Haake [3].

Methods

The fractional cerebral blood oxygenation Y is related to the transverse relaxation rates $R_2 = 1/T_2$ and $R_2^* = 1/T_2^*$:

$$Y = 1 - \frac{R_2'}{C \cdot CBV}; \qquad R_2' = \frac{1}{T_2^*} - \frac{1}{T_2}$$

(CBV: cerebral blood volume; $C \propto \Delta\chi \cdot \gamma B_0 = \text{const.}$)

Quantitative maps of transverse relaxation times T_2 and T_2^* were obtained from exponential fits of multi-echo signals of spin and gradient echo sequences (Fig. 1).

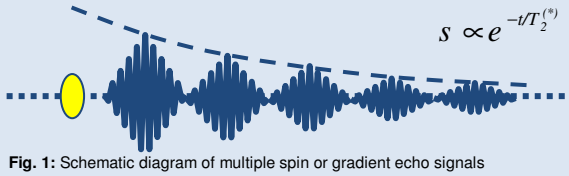

Fig. 1: Schematic diagram of multiple spin or gradient echo signals

Subjects: Quantitative T_2 and T_2^* maps were obtained from 6 patients with malignant glioma (4 male, 2 female, 61±9 a).

Instrumentation: 3 T whole body scanner (Philips Achieva): body coil for transmit; 8-channel head coil for receive

Imaging Parameters:

- Spatial resolution for all measurements: 10 slices, matrix 112x106, voxel size 2x2x3 mm³
- T2 measurement: GRASE with EPI factor 7 and SENSE factor 2, 6 echoes,TE = [20,120] ms, TR = 2146 ms, α = 90°, duration 34 s
- T2* measurement: multi-GE: 8 echoes, TE = [6, 51.5], TR = 1000 ms, α = 30°, duration 94 s

Postprocessing:

Evaluation was performed with custom programs written in MATLAB und SPM8 [5] and comprised exponential fit for T2 and T2*, spatial coregistration and calculation of R_2'.

Results and Conclusion

Fig. 2 summarizes preliminary results in 4 patients. Increased R_2' values indicate areas with low blood oxygenation levels within viable tumor tissue. These results indicate that a non-invasive measurement of oxygen saturation within malignant glioma might be feasible in a clinical setting.

However, further effort is needed to validate these results:

- Inclusion of quantitative CBV measurement [4] to control for blood volume effects and enable calculation of Y
- Correlation with immunohistochemical analyses of biopsy specimen to validate hypoxic areas
- Higher spatial resolution for better delineation of anatomical features
- Correlation with clinical outcome of R_2' positive and negative patients could identify R_2' as a prognostic factor

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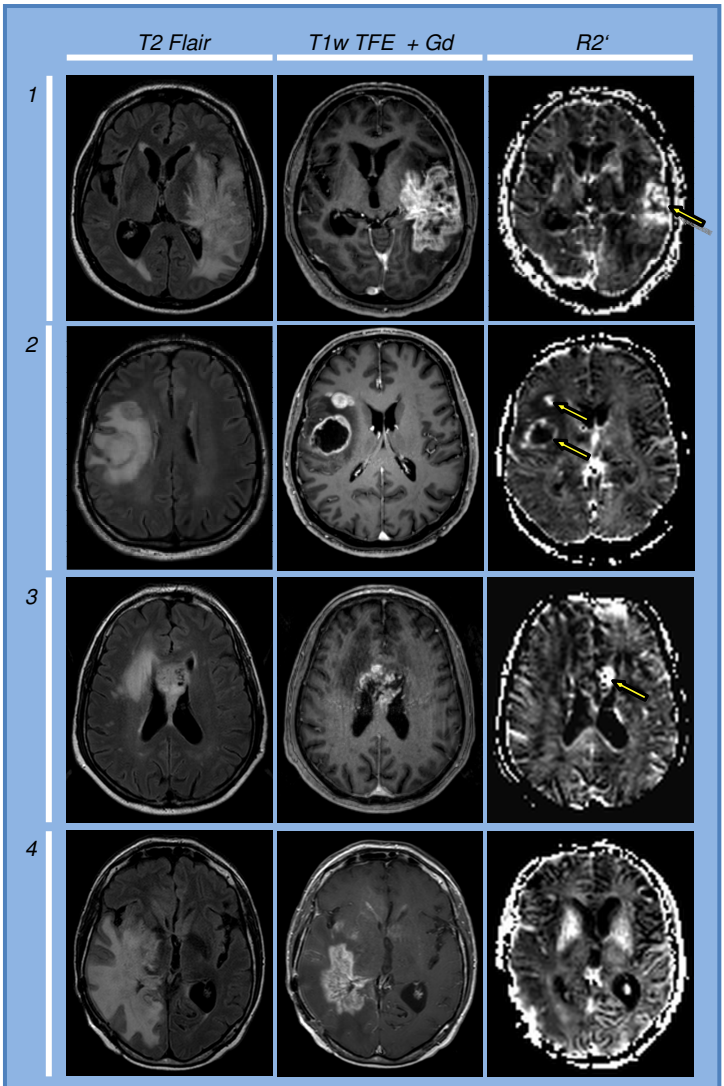

Fig. 2: Examples of 4 patients with malignant glioma (n = 6). MRI sequences: T2 FLAIR, 3D-T1w-TFE with gadolinium (Gd) and R2' maps. Patients 1 - 3 showed areas with high R_2' values, indicating low oxygenation levels, mainly within the solid, Gd-enhancing tumor mass. Even though patient 4 showed a large Gd-enhancing tumor mass, there were no areas with high values in R2' measurements.

References: [1] Heddleston JM, Li ZZ, McLendon RE, Hjelmeland AB, Rich JN. The hypoxic microenvironment maintains glioblastoma stem cells and promotes reprogramming towards a cancer stem cell phenotype. Cell Cycle. 2009;8(20):3274-84; [2] An HY, Lin WL. Quantitative measurements of cerebral blood oxygen saturation using magnetic resonance imaging. Journal of Cerebral Blood Flow and Metabolism. 2000;20(8):1225-36; [3]Yablonskiy DA, Haacke EM. Theory of NMR signal behavior in magnetically inhomogeneous tissues- the static dephasing regime. Magnetic Resonance in Medicine. 1994;32(6):749-63; [4] Uh J, Lewis-Amezcua K, Varghese R, Lu HZ. On the Measurement of Absolute Cerebral Blood Volume (CBV) Using Vascular-Space-Occupancy (VASO) MRI. Magnetic Resonance in Medicine. 2009;61(3):659-67; [5] http://www.fil.ion.ucl.ac.uk/spm.