Non-invasive MR oxygen mapping of primary central nervous system tumors

Marta M Safronova[1], Florence Colliez[2], Julie Magat[2], Bénédicte F Jordan[2], Bernard Gallez[2], and Thierry Duprez[3]

[1]*Service de Radiologie, Cliniques universitaires Saint-Luc, Brussels, Belgium,* [2]*Louvain Drug Research Institute, Biomedical Magnetic Resonance Research Group, University of Louvain, Brussels, Belgium,* [3]*Department of Radiology and Medical Imaging, Cliniques universitaires Saint-Luc, Brussels, Belgium*

Target audience: MR experts in mapping brain oxygenation and tumor hypoxia.

Purpose: Malignant tumors of the neuroepithelial tissue are the most frequent primary central nervous system tumors still with a very short survival rate[1]. Aberrant and spatially disorganized neovasculature and increased oxygen demands lead concomitantly to intratumoral hypoxia which is a predictor for chemo-radiotherapy failure and poor patient outcome[2-3]. Quantitative monitoring of tumor oxygenation can thereby be relevant in radiation therapy planning[4] and in antiangiogenic and antivascular treatment optimization[5]. Magnetic resonance (MR) using blood level oxygen-dependent (BOLD) contrast has up to now appeared as promising non-invasive technique to map brain hypoxia despite significant limitations[3]. Non-invasive measurements of tissue oxygen level variations can also be obtained using oxygen itself as an endogenous paramagnetic contrast (T_1-shortening agent), a method which has been coined *'Oxygen enhanced MRI'* [6]. This technique provides T_1 measurements influenced by O_2-related relaxation of the water protons but with low sensitivity. Based on higher solubility of oxygen in lipids than in water, a better performing MR method for mapping variations in oxygenation was recently developed and acronymized '*MOBILE*' for Mapping of Oxygen By Imaging Lipids relaxation Enhancement[7]. The aim of this study was to assess the clinical applicability of MOBILE for mapping oxygenation of primary central nervous system tumors, mainly of astrocytic lineage.

Methods:

Recruitment: 25 patients with neuroepithelial tumors (23 astrocytic tumours, 1 mixed glioma and 1 mixed neuronal-glial tumor), underwent a standardized MR brain tumor protocol on a clinical 3T MR system (Achieva; Philips Medical System, Best, the Netherlands), combining morphologic imaging with sequences aimed at measuring water relaxation rate R_1 (with $R_1=1/T_1$), lipids R_1 (MOBILE) and R_2* (=$1/T_2$*), these three lasting for a total acquisition time (AT) of 5 min.

Methods: Water T_1 measurements were obtained using a Look Locker sequence (T1 TFE, T1 Turbo Field Echo sequence) applied during 10 seconds with TR/TE/flip angle/TFE/NSA= 3.467ms/1.45 ms/5°/10/1 to acquire one 20mm-thick slice covering a FOV of 183x230 mm with a matrix size of 80^2 resulting in a voxel size of 3.91x5.08x20 mm. For MOBILE measurements, the same sequence was used with the addition of a 90° SPIR pre-pulse (Spectral saturation by Inversion recovery) to spoil water signal with a BW of 300Hz centred on the water peak. 38 images averaged 30 times with similar metrics and slice location than previous acquisition were obtained for total AT of 4 min. Regions of interest (ROIs) contouring the different areas including enhanced tumor (C+) (presumptively of histological high grade), unenhanced tumor (C-) (presumptively of low grade), peritumoral edema, and normal appearing white matter (NAWM) were manually drawn on post-contrast FLAIR images and overlaid on water R_1, lipids R_1, and R_2* mapped images. Comparison of the means of the water R_1, lipids R_1 and R_2* values was performed using paired t test.

Results: 28 primary central nervous system tumors were analyzed. Examples of ROIs of R_1 lipids overlaid on FLAIR images are presented on Figure 1 (b and d). Lower **water R_1** values were recorded within both tumoral and edematous areas, when compared to NAWM ($p<0.0001$) (Fig. 2c). When C+ and C-tumors were separately analyzed, a progressive but not significant increase in water R_1 values was found from C+ to C- to edema and finally to NAWM. A significant difference raised when C+ tumors were compared to edema ($p=0,0328$) (Fig. 2a). For **R_1 lipids**, pooled (C+ and C-) mean R_1 values within tumors were significantly higher than in edema and NAWM ($p=0.0003$ and $p=0.0005$ respectively). However, no statistically significant difference could be shown between ROIs within edema and NAWM (Fig. 2d). R1 lipids measurements increased statistical power when compared to water R_1 measurements for all comparisons between the four groups except that between C+ and C- gliomas (Fig. 2b). **R_2*** values within edema were significantly lower to those within tumors and NAWM ($p=0.0051$ and $p=0.0001$, respectively) (Fig. 2e).

Figure 1

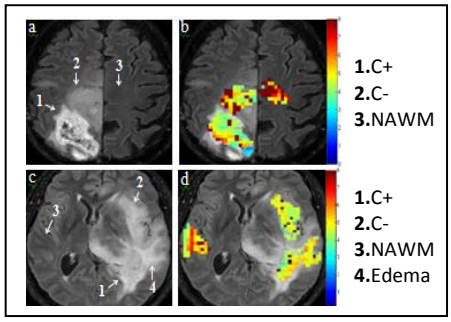
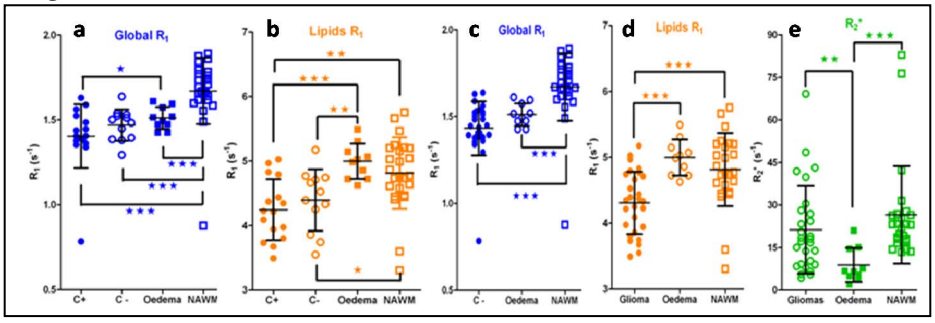


Figure 2



Discussion: The MOBILE sequence enables discrimination between tumoral C+ and C- areas, and peri-tumoral edema, presumptively because of lipids preservation within edema contrasting with lipids breakdown within tumor. Also, the water R_1 of NAWM is significantly different from that of both tumor and edema, presumptively because of lower content in free water of the healthy brain tissue, the hypothesis being supported by the progressive increase of water R_1 from C+ tumors to C- tumors to edema and ultimately to NAWM. Statistical differences between R_2* of edema, tumor and NAWM could be due to the T_2 effect of free water. None of the measurements allowed differentiation between C+ and C- tumors.

Conclusions: robust delineation of tumor from surrounding edema by water and lipids R1 mapping techniques using molecular oxygen as endogeneous contrast agent in brain gliomas suggests the potential value of the techniques for radiation therapy planning. Selective analysis of lipids R1 (MOBILE) performed better than water R1 in the purpose.

References: **(1)** Dubrow and Darefsky *BMC Cancer* 2011, 11:325. **(2)** Wilson WR, et al. *Nat Rev Cancer* 2011;11:393–410 **(3)**Pacheco-Torres J, et al. *NMR Biomed* 2011; 24:1–16 **(4)** Jordan BF, et al. *Contrast Media Mol Imaging* 2010;5:323–332 **(5)** Li SP et al.*J Natl Cancer Inst Monogr* 2011;2011:103–107 **(6)** O'Connor JP, et al. *Magn Reson Med.* 2007; 58:490-496 **(7)** Jordan BF, et al. *Magn Reson Med.* 2013; 70:732–744