Multimodal MR/PET imaging for characterization of hypoxia in human glioblastoma

Christine Preibisch[1,2], Mathias Lukas[3], Anne Kluge[1], Severin Keinath[3], Vivien Tóth[1,4], Kuangyu Shi[3], Thomas Pyka[3], and Stefan Förster[3]

[1]Department of Neuroradiology, Klinikum rechts der Isar der TU München, Munich, Germany, [2]Clinic for Neurology, Klinikum rechts der Isar der TU München, Munich, Germany, [3]Department of Nuclear Medicine, Klinikum rechts der Isar der TU München, Munich, Germany, [4]Department of Radiology, Klinikum rechts der Isar der TU München, Munich, Germany

Introduction: Glioblastoma (GBM) is one of the most malignant brain tumors. Even though hypoxia is assumed to play an important role in its high prevalence of therapy resistance and dismal prognosis [1], hypoxia imaging is not contained in clinical protocols because a robust, clinically useful method is still missing. Recently, a BOLD based method was proposed, which was shown to be clinically feasible in a pilot study of patients with glioma [2,3]. A semiquantitative parameter, termed relative oxygen extraction fraction (rOEF), was shown to correlate with tumor grade [3]. Even though, preliminary correlation with immuno-histochemistry yielded encouraging results, a number of confounding influences impede straightforward application, and a compelling validation is still missing. PET tracers like ^{18}F-FET or ^{18}F-FMISO have been shown to be valuable for detecting highly malignant [4] and hypoxic [5, 6] tumor tissue, respectively. Therefore, combined MR and PET studies are expected to achieve major contributions in elucidating GBM pathophysiology. Here, we present preliminary multimodal MR/PET data from 18 patients with glioblastoma which were obtained with the aim of a comprehensive characterization of these supposedly hypoxic brain tumors.

Materials and Methods: 20 patients (60.3±13.6y, 13 men) with histologically confirmed glioblastoma underwent a simultaneous ^{18}F-FET-PET (dynamic acquisition for 1h after injection of 185 MBq) and MRI examination on a clinical 3 T Biograph mMR scanner (Siemens Medical Solutions) equipped with a 16-channel head/neck coil. In four patients, additional ^{18}F-FMISO-PET was acquired. PET images were attenuation corrected using the DIXON MR sequence and reconstructed iteratively using OSEM (3x21 subsets, 172x172 matrix, Hann filter 4,9mm). The advanced clinical MRI protocol, acquired simultaneously to the FET acquisition, comprised R2' mapping (voxel size 2x2x3 mm^3, matrix 128x128, 30 slices) by separate acquisition of a multi-gradient echo (12 echoes, TE_1 = 5ms, ΔTE = 5ms, TR = 1950ms, α = 30°, rapid flyback, acq. time 4:08min; repeated with half spatial resolution for motion correction [7]) and a multi-echo TSE sequence (8 echoes, TE_1 = 16ms, ΔTE = 16ms, TR = 4040ms, acq. time 5:04 min). Before mono-exponential fitting for T2* multi-GE data were corrected for magnetic background gradients [8] and motion [7]. For T2, only even echoes were fitted to eliminate influences of imperfect RF pulses [2]. Maps of relative cerebral blood volume (rCBV) were obtained by dynamic susceptibility contrast (DSC) using a bolus injection of 15 ml Gd-DTPA during dynamic single-shot GE EPI (TR = 1500 ms, TE = 30 ms, α=90°, 60-80 dynamics), a prebolus of 7.5 ml was employed to mitigate leakage effects [9]. Data coregistration, fitting, rCBV evaluation and calculation of rOEF = R2‘/(c·rCBV) with R2‘ = (1/T2*) - (1/T2) and $c = 4/3 \cdot \pi \cdot \gamma \cdot \Delta\chi \cdot B_0 = 317$Hz at 3 T [2] were performed with SPM8 (www.fil.ion.ucl.ac.uk/spm) and custom programs in Matlab (The MathWorks, Natick, MA, USA). Using Vinci (http://www.nf.mpg.de/vinci3), quantitative values were extracted in different volumes of interest (VOIs; control: unaffected contralateral tissue; FLAIR: tumor tissue with T2 alterations; CET: tumor tissue with T1 contrast enhancement; FET: standardized uptake values (SUV) > 1.4· TBR (tumor-to-background ratio); $FET_{90\%}$: SUV > 0.9·FET_{max})

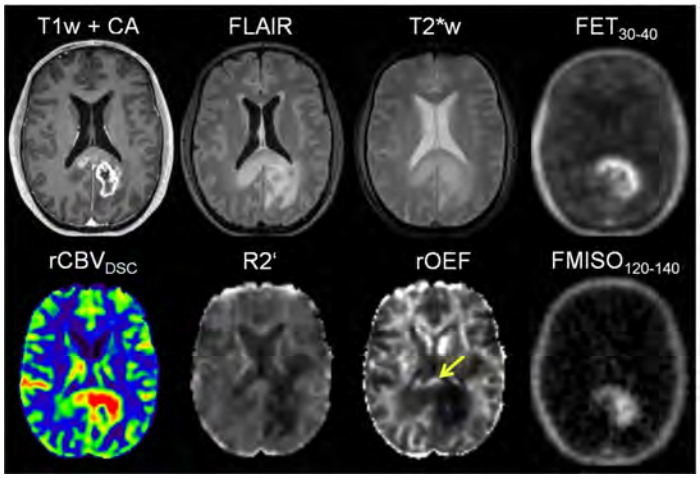

Figure 1. Selected slice of a male patient (56y) with GBM. Anatomical MRI (T1w with CA, FLAIR, T2*w), ^{18}F-FET PET, rCBV, R2', rOEF, and ^{18}F-FMISO images. Please note that the border of the brain and ventricles appear bright in the rOEF map because of magnetic susceptibility artifacts and low rCBV.

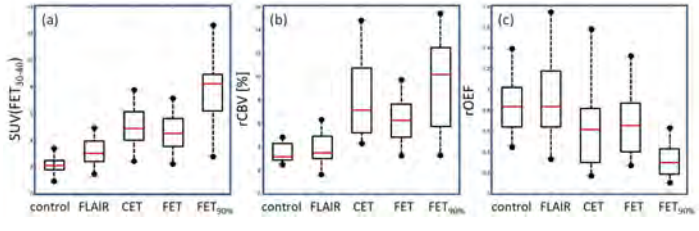

Figure 2. Patient averages (n=18) of standardized ^{18}F-FET uptake (SUV), rCBV and rOEF in selected VOIs: unaffected brain tissue (control), tumor tissue with T2 signal alterations (FLAIR), T1w contrast enhanced tumor (CET), ^{18}F-FET (tumor volume and 90% isocontour of maximum FET SUV).

Results : rOEF maps with diagnostic quality could be obtained in 18 of 20 patients. Figure 1 exemplary shows a selection of multimodal images from one (of four) patients where ^{18}F-FMISO data were available. Figures 2a and 2b demonstrate that ^{18}F-FET SUV as well as rCBV values are high in malignant tumor areas (VOIs: CET, FET, $FET_{90\%}$), indicating metabolically highly active tumor tissue. As could be expected from high rCBV, rOEF (~R2'/rCBV) values in the same VOIs are rather low. In addition to that general characteristic, there are focal spots of high rOEF values within contrast enhancing and non-enhancing tumor tissue. This is illustrated in Figure 1 where a small area of high rOEF values in the T2-FLAIR-hyperintense tumor periphery (splenium: yellow arrow) most likely indicates an area with increased vascular deoxygenation.

Discussion and Conclusion: These preliminary data of rOEF measurements in GBM acquired on a integrated MR/PET scanner confirm previous results obtained on a stand-alone MR system [3]. In addition to that, a strong positive correlation between rCBV values and ^{18}F-FET SUV ($R = 0.55$, $p < 0.0001$) supports the utility of these two markers as representatives for viable malignant tumor tissue. With respect to hypoxia, a first qualitative impression (see Figure 1) rather suggests disparity between vascular deoxygenation and tissue hypoxia as revealed by rOEF [2,3] and 18F-FMISO [5,6]. However, definite statements are not yet possible due to the small number of only four patients where ^{18}F-FMISO data are available. Moreover, a more sophisticated evaluation of dynamic data is supposed to allow a more reliable delineation of hypoxic tumor areas [10]. Thus, more patient data and more sophisticated analyses are clearly needed before any definite conclusions can be drawn with regard to this issue.

References:[1] Heddleston JM et al, Cell Cycle 15;8(20): 3274-84, 2009. [2] Hirsch N et al. NMR Biomed 27(7):853-62, 2014. [3] Tóth VJ et al. Neurooncol. 115(2): 197-207, 2013. [4] Piroth MD, et al. RadiotherOncol. 99(2): 218-24, 2011. [5] Rasey JS et al. Int J Radiat Oncol Biol Phys 36(2) 417-428, 1996. [6] Tochon-Danguy HJ et al. Nucl Med Biol. 29(2):191-197, 2002. [7] Magerkurth J et al. MRM 66(4):989-97, 2011. [8] Baudrexel S et al. MRM 62(1):263-8, 2009. [9] Boxerman JL et al. AJNR 33:1081-7, 2012. [10] Cheng X. et al. Phys Med Biol. 20;59(2):347-62, 2014.