Treatment effects of diffuse intrinsic pontine gliomas on tumor and normal appearing cortical gray matter assessed by arterial spin labeling perfusion and 3D volumetric measurements

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Introduction: Diffuse intrinsic pontine gliomas (DIPG) are amongst the most devastating neoplasms in children. No treatment benefits have been observed from chemotherapy and radiation therapy (RT) only postpones tumor progression by about six months [1]. It is believed that antiangiogenic therapy normalizes abnormal tumor vasculature thereby improving tumor perfusion and allowing a better delivery of radiation [2]. In a phase I trial of combined antiangiogenic and local RT in DIPGs [3] we closely monitored changes in tumor and cortical grey matter (GM) perfusion by arterial spin labeling (ASL) and volumetric MRI. Purpose of this study was to investigate if ASL is useful to detect tumor response to therapy and potential adverse effects of antiangiogenic treatment in normal appearing cortical GM.

Material and Methods: 35 patients (20f, 16m; age: 2-16y) with diagnosed DIPG were enrolled from 2007-2009 in an IRB approved phase I clinical trial. Patients received a combination of local RT (54Gy) for a period of six weeks and permanent oral administration of vandetanib. MRI (3T Siemens) was performed at baseline, 2, 4 and 8 weeks and every two months thereafter. In total, 203 ASL and 224 volumetric scans were available: 14 patients had 7-8 consecutive scans, 16 patients had 5-6 scans and 5 patients received less than 4 scans. Quantitative cerebral perfusion (CBF) maps were calculated [4] and co-registered with high-resolution 3D T2w (SPACE) and T1w (MPRAGE) images of the same time point. Figure 1 shows the approximate slice location for the ASL measurements. Tumors were manually segmented on T2w images assuming active tumor is T2-hyperintense by using MRIcro (Chris Rorden). Gray matter was automatically segmented on 3D T1 data using FAST (FSL). The segmented regions were then applied to the CBF maps and absolute CBF measures were evaluated with respect to treatment time. MatLab was used for data post-processing and Gnumeric for data plotting and correlation/regression analysis.

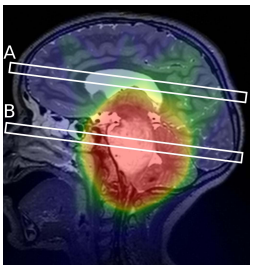

Figure 1: RT-dose deposition overlay on a T2w anatomical image showing the location of the ASL perfusion measurements for cortical GM (A) and tumor (B). Dose deposition was between 2-8 Gy for cortical GM and 54 Gy for the tumor.

Results: Median tumor perfusion was about 20ml/min/100g at baseline and stable during RT; it increased after RT (50ml/min/100g) and gradually decreased thereafter. In addition an increased inter subject variability of the post RT median tumor perfusion was observed (Fig. 2, left). Median perfusion of cortical GM was stable around 50ml/min/100g during the whole study except for the first two time points after baseline where it dropped below 40ml/min/100g (Fig. 2, right). Median tumor volume decreased shortly after onset of RT with a minimum at week 16 after baseline. Tumor relapsed thereafter and larger median tumor volume was measured at the end of study as compared to baseline (Fig. 3, left). Median volume of cortical GM dropped directly after baseline until week 4, but slowly increased thereafter (Fig. 3, right). Even though median perfusion and volume measurements seem highly correlated, correlation analysis of individual tumor perfusion and tumor volume revealed no statistical significance; Pearson correlation coefficient (R)= -0.19 and p=0.98. However, individual cortical GM perfusion and volume measures are statistically significantly correlated with R=0.47 and p<0.001.

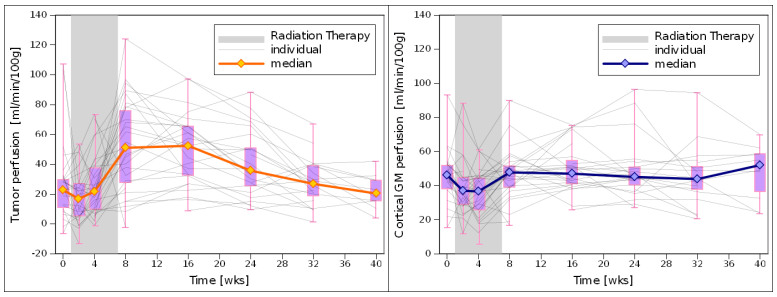

Figure 2: Median tumor (left) and cortical GM (right) perfusion over time. Duration of RT (week 1-7) is highlighted in gray.

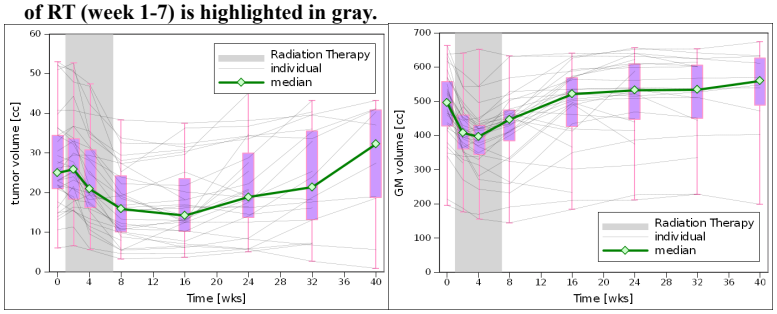

Figure 3: Median tumor (left) and cortical GM (right) volume over time.

Discussion and Conclusion: The fact that tumor perfusion did not decrease during RT and increased at the end of RT suggests that radiation was delivered under favorable conditions. However, we cannot ascribe this effect solely to vandetanib, RT, the combination of both, or other not yet controlled factors. The gradual decline of tumor perfusion at later time points suggests that vascular normalization had reached its climax right after RT. The higher variance in tumor perfusion directly after RT may suggest different tumor responses to treatment as compared to tumor volume which decreased, at least temporally, in all patients. The detected drop in cortical GM CBF and volume directly after baseline seems very interesting. We believe that steroids, given right at the beginning of therapy, dehydrate cortical GM causing a decrease in CBF. Since steroids were given as needed at an individual basis and were not controlled, further better controlled studies are necessary to prove this hypothesis. In summary, ASL seems to be a very promising tool for monitoring treatment strategies that affect tumor perfusion and for detecting potential adverse effects in normal appearing GM.

References: (1) Broniscer A and Gajjar A. Oncologist. 2004;9:197-206. (2) Jain RK. Science. 2005;307:58-62. (3) Broniscer A, et al. JClinOncol. 2010;28:4762-8 (4) Wang J, et al. MRM (2002);48:242-254.