

Susceptibility weighted imaging (SWI) in children with brain stem glioma during combined antiangiogenic and radiation therapy.

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Introduction: The outcome of children with brainstem (BS) glioma remains dismal with long term survival <10% using standard treatment, i.e. local radiation therapy (RT) [1]. Diffuse BS gliomas correspond histologically to infiltrative gliomas, oftentimes harboring higher grade components, which are believed to be characterized by increased vascularization and due to intense angiogenesis. VEGFR-2 (vascular endothelial growth factor receptor-2) is believed to be the main pro-angiogenic receptor in gliomas [2]. Inhibition of this receptor through antiangiogenic therapy represents a promising target in the treatment of BS gliomas under the assumption that structurally and functionally abnormal tumor vasculature will then be normalized and tumor microenvironment improved for a better delivery of RT [3]. Tumor diminution as the conventional measure of antitumor treatment efficacy is likely inaccurate since inhibition of angiogenesis may affect tumor microvasculature without apparent changes in tumor size by conventional, anatomical imaging. In this study, we aim to assess indirectly and non-invasively changes in tumor vascularization by using the blood oxygenation level dependent (BOLD) MRI-sequence susceptibility weighted imaging (SWI) [4] which may prove to be useful as an early marker of treatment response to antiangiogenic therapy.

Methods: Twelve patients (8f, 4m; age 2-15y) with diagnosis of diffuse pontine glioma were enrolled in an ongoing IRB approved phase I clinical study. Patients received a combination of local RT for a period of 6 weeks and permanent oral administration of the VEGFR2 inhibitor Vandetanib (ZACTIMA, AstraZeneca). SWI was performed at multiple time points during therapy: at diagnosis (baseline), 2, 4 and 8 weeks and every two months thereafter. Six follow-up exams were available for all patients; four patients had a total of seven exams and two a total of eight. All MRI exams were performed under general anesthesia. The tumor was manually segmented on T2-weighted, 3D high resolution images thereby assuming that active tumor appears hyperintense on T2. White matter was segmented automatically on the same data set using the FAST tool in FSL [5]. To apply the segmented tumor and normal cerebellar parenchyma ROIs to SWI data, both 3D data sets (T2 and SWI) were spatially realigned by using the linear registration tool FLIRT in FSL [6].

The segmented regions are visualized in Fig. 1. Inter- and intrasubject variances were corrected by calculating the tumor SWI signal relative to cerebellar white matter.

Results: The mean relative signal of the tumor area averaged over all patients showed a drop two weeks after initiation of the treatment. Measurements during RT revealed an increase of the mean signal intensity that subsequently seemed to reach a plateau. However, the signal characteristic shows a high variance between the patients (Fig. 2).

Discussion/Conclusion: The variance of the signal-time course between the patients suggests a variety of possible individual responses of tumors to treatment. However, due to the low number of patients in our phase I study we are not yet able to distinguish between different response types, i.e. responders and non-responders. Nevertheless, the observed early treatment response of the tumor may indicate the impact of the combined antiangiogenic and radiation treatment used in our patient cohort. Following the underlying principles of the BOLD effect the observed overall signal response can be considered to be consistent with tissue hypoxia. The subsequent signal increase suggests that RT and the antiangiogenic therapy increases tissue oxygenation once it has caused a vascular normalization of the tumor. In summary SWI seems to be a promising tool for monitoring treatment strategies that affect tumor oxygenation.

Literature:

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Figure 1: Structural scan with T2 contrast used for tumor and normal cerebellar parenchyma segmentation (left). ROIs were transferred to the corresponding magnitude SWI image (right). The tumor region is highlighted in red and the normal cerebellar parenchyma in green.

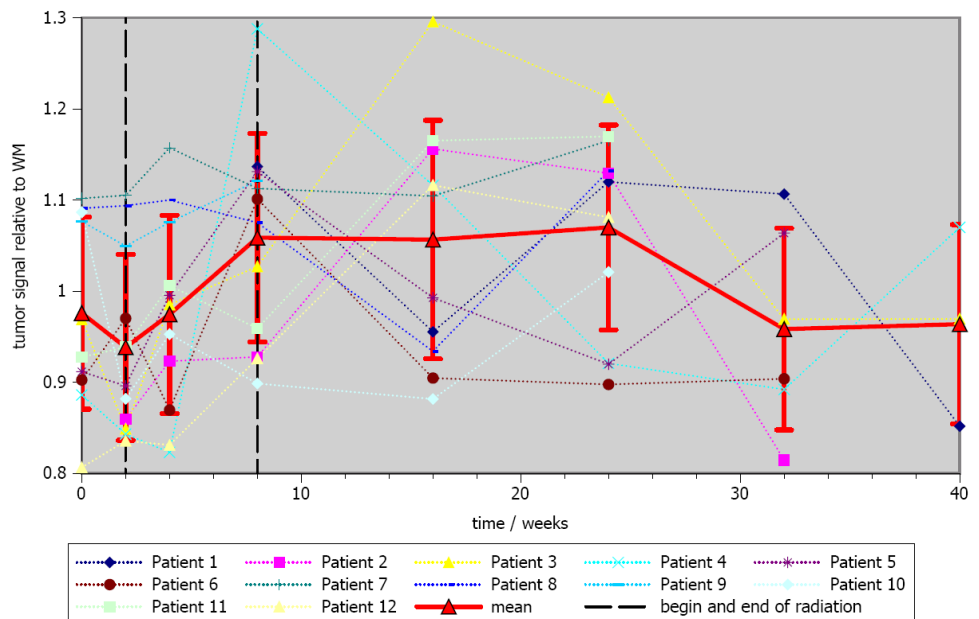
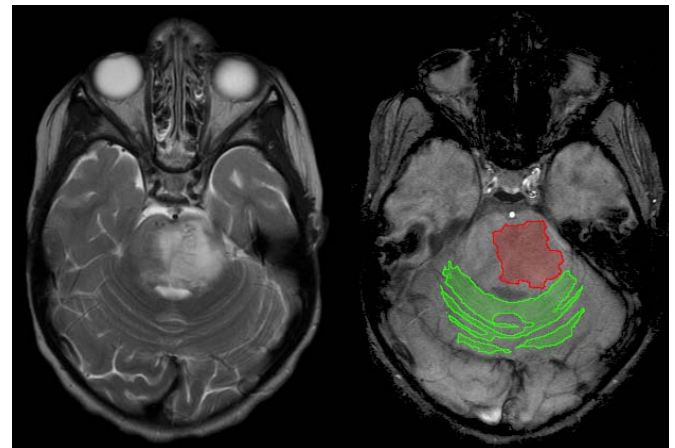


Figure 2: SWI signal in the tumor, measured relative to normal appearing cerebellar white matter, during the course of the therapy.