MR perfusions imaging of anti angiogenic (bevacizumab) treatment in patients with recurrent high grade gliomas

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Introduction: Perfusion MRI has become a powerful tool for evaluating brain tumors (1). Anti-angiogenic therapy using bevacizumab (Avastin) affects abnormal neovascularity which is a hallmark of high grade primary brain tumors. Alterations in neovascularity result in hemodynamic changes; therefore, perfusion imaging would be an ideal surrogate for assessing the effects of anti-angiogenic therapy. Evaluating such therapeutic effects can have significant clinical implications (2). DCE and DSE MR perfusion techniques provide several parameters of tumor vascularity, such as Ktrans and rCBV (3-6). We hypothesized that micro vascularity changes related to treatment with bevacizumab can be reliably detected with DCE and DSE and that vessel permeability (~Ktrans) and microvascularity (fraction blood volume: fBV or rCBV) of enhancing brain tumors decreases with treatment. In our study, we used DCE and DSE perfusion techniques on a group of patients with recurrent high grade gliomas before and after the first cycle of bevacizumab. Our aims were to evaluate the hypothesis and to seek out one of the most sensitive parameters from the perfusion data for demonstrating the changes in tumor vascularity and capillary integrity with treatment.

Materials and methods: 14 patients, 12 GBM's and 2 grade III/IV astrocytomas were studied. Among patients, 9 (7 GBM and 2 high grade astrocytoma) had DCE and DSE before and after the first cycle of the bevacizumab. The baseline perfusion images were performed within 2 weeks prior to the first dose. 10 mg of IV bevacizumab per kilogram of body weight were administered once every two weeks, on days 1 and 15 of the cycle, which was defined as 28 days. Post cycle 1 (i.e., after two doses of bevacizumab), the patients had their MR perfusion follow up (25-29 days; mean 27.3 days after the 1st dose). The perfusion imaging protocol included the following: first T_1 relaxation times were mapped by using a series of volume acquisitions (3D SPGR) with flip angles of 2°, 5°, 10°, 15°, and 26°, dynamic series for the contrast bolus tracking was performed by using the multi slice 2D SPGR with a 30° flip angle over a period of approximately 6 minutes for a total of 82 volumes. The contrast agent was administered through the antecubital vein. After the acquisition of the first five volumes of the dynamic series (20 seconds), 0.1 mmol of Gd/kg was injected at 2-4 mL/sec. After DCE, a SPGR T_1 weighted volume acquisition was performed to provide position matched high resolution images for comparison with the T_1 perfusion maps. After completions of the routine imaging sequences, DSE was performed. The rCBV maps were obtained by integrating the negative areas of the bolus tracking time course for each voxel using GE's "FuncTOOL" software. The averaged time courses for region of interest (ROI) areas in the tumors were fitted by applying the Tofts Model to obtain the bolus wash-in slopes (6). The DCE maps, including Ktrans and fBV maps, were obtained by using software (4) with in-housing modifications. The ratios of the Ktrans, fBV, and rCBV were calculated for ROIs in the tumors and corresponding areas in contralateral hemisphere. Mean values (M) with standard deviation (SD) for the wash in slopes and the ratios of Ktrans, fBV, and rCBV pre and post cycle 1 were calculated, and a paired or unpaired T-test for the ratios was performed. A "p" less than 0.05 for a ratio was considered as statistically significant.

Results: Before treatment, both the Ktrans, fBV and rCBV ratios for the 14 patients demonstrated high values, with means (M) of 1.85 (SD=0.80) 1.83 (SD=0.91), and 2.4 (SD=0.91), respectively. For the 9 patients who underwent T_1 (DCE) and T_2* (DSE) perfusions, the mean bolus wash-in slope, the mean ratios of Ktrans, fBV, and rCBV decreased after bevacizumab treatment. Figure 1 illustrates the decrease in the ratios and the slope for a GBM patient before and after treatment. Table 1 lists the mean bolus wash-in slopes, M ratios and SDs of Ktrans, fBV, and rCBV for the 9 patients during the first bevacizumab cycle.

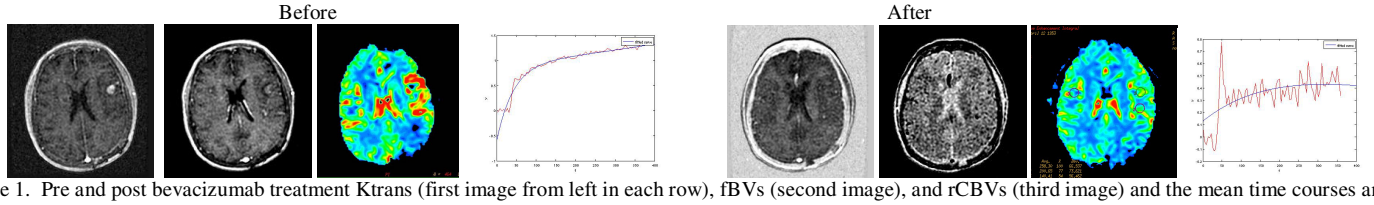

Figure 1. Pre and post bevacizumab treatment Ktrans (first image from left in each row), fBVs (second image), and rCBVs (third image) and the mean time courses and the fittings in the ROIs of the tumor areas (forth image) for a GBM patient with the tumor located in the left frontal lobe. Table 1: Mean (M) bolus wash-in slopes and standard deviations (SD), (M) ratios and (SD) of Ktrans, fBV, and rCBV before and after treatment for the 9 patients who had DCE and DSE perfusion data.

	Mean bolus wash-in slopes (M+SD)	Ktrans (M+SD)	fBV (M+SD)	rCBV (M+SD)
Before	2.03+1.77	1.86+0.80	1.83+0.85	1.92+0.99
After	0.84+0.85	1.26+0.21	1.36+0.71	1.20+0.28

Discussions and Conclusions: The approximately doubled values for Ktrans (1.85), fBV (1.83), and rCBV (2.4) of the 14 pretreatment-patients in the tumor side compared to the values of the contralateral side imply that blood vessels associated with tumors were leaky and vessel density was high. Considering the process of angiogenesis, the high values of the Ktrans, fBV, and rCBV are consistent with the characteristics of recurrent tumors' high vascularity and poor capillary integrity. Both DCE and DSE MR perfusions for the 9 patients in table 1 demonstrated decreased vascularity following the therapy. However, DCE perfusion imaging better demonstrated the decrease in capillary permeability that occurred in patients who treated with the bevacizumab. In fact, only Ktrans values and the mean bolus wash-in slopes before and after treatment for the 9 patients were significantly different with a p of 0.043 and 0.015, respectively. fBV and rCBV values before and after treatment were not significantly different, with a p of 0.22 and 0.051, respectively. These p values suggest that the mean bolus wash-in slope from DCE perfusion is the most sensitive parameter for tumor vessel changes during this treatment window. Our preliminary results on the reduction of the mean wash-in slope and Ktrans ratio suggest significantly less tumor vessel leakage after the first cycle of the Avastin treatment.

References: 1.Cha, S, AJNR, 2006, 27:409-417. 2, Batchelor, TT, Cancer Cell, 2007, 11:83-95. 3. Jackson, A., B JR, 2003, 76:S159-S173. 4. Barboriak, DP, ISMRM Workshop, McLean VA, April, 2004. 5. Hou, P JMRM 2007, 25:160-169. 6, Larsson HB, MRM 1992, 24:174-176.