Predicting Grade of Cerebral Glioma using Vascular-Space-Occupancy (VASO) MRI

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INTRODUCTION: Reliable determination of brain tumor grades is critical in the selection of proper treatment procedures. Existing approachs use biopsy sampling and histopathologic assessment, which has the disadvantage of limited spatial coverage, and the results may be affected by the location of the sampling (1). MRI can cover a large field-of-view and has the advantage of high spatial resolution and relatively low invasiveness, providing a potentially more effective tool for determining the grade of tumors. Glioma is one of the most aggressive forms of brain tumor, and is characterized by rapid proliferation accompanied by neovascularization. Furthermore, the permeability of the vascular wall is significantly increased. The aggressiveness and the grade of the gliomas are known to be correlated with these changes. As a result, an MR method that can accurately detect these hemodynamic changes is expected to provide a useful indication of the tumor grade. Recently, we have developed a technique that uses pre- and post-contrast (Gd-DTPA) images to compute vascular parameters in the brain (2), termed Vascular-Space-Occupancy (VASO) MRI. In cases where the blood-brain-barrier (BBB) is intact or the leakage is negligible, VASO MRI has been shown to provide quantitative estimations of cerebral blood volume (CBV) in physiological units (ml blood/100ml brain tissue) (2). When the BBB is significantly comprised as in the case of gliomas, the VASO results reflect a combined effect of CBV and vascular permeability. Note that both effects are known to become more pronounced for higher grade gliomas, i.e. greater CBV (3) and higher permeability (4), rendering VASO MRI a unique advantage in its sensitivity of differentiating low grade tumors from high grade tumors. Here we apply VASO MRI in a group of glioma patients and examine the VASO parameters for different tumor grades. The differentiation results are compared to the histopathologic assessment. The sensitivity and specificity of using VASO MRI for glioma grading is evaluated.

METHODS Experiments were performed on a 1.5T MR system (Siemens Medical Solutions). A total of 39 patients diagnosed with primary intracranial glioma underwent pre- and post-contrast VASO scans (2). Written informed consent was obtained before enrollment into the study. The classification of gliomas was based on histopathologic assessment using a three-tiered Ringertz system after volumetric resection or stereotactic biopsy: grade 1 = low-grade glioma (n=10), grade 2 = anaplastic astrocytoma (n=20), and grade 3 = glioblastoma multiforme (GBM; n=9). The VASO parametric maps were computed using the CSF-referencing method as described previously (2). Regions-of-interest (ROIs) were drawn in the tumor regions and in the contralateral normal regions, giving two parameters: $VASO_{Tumor}$, $VASO_{Contra}$. The ratio of these two parameters were also calculated, i.e. $VASO_{Ratio}=VASO_{Tumor}/VASO_{Contra}$. Each of these parameters was compared to the histopathologic tumor grade data. Image parameters: FOV=230x230mm, matrix=128x128, 10 slices acquired with descending order, slice thickness=4 or 5mm, TR=6000ms, TI=920ms, segmented EPI acquisition with EPI factor=9, TE=6.3ms, Flip angle=90°, acquisitions=2. The scan duration for each VASO experiment was 2 minutes and 12 seconds.

RESULTS and DISCUSSION: Fig. 1 shows the T2-weighted images (top row) and VASO maps (bottom row) for grade 1, 2 and 3 gliomas, respectively. It can be seen that most of the regions in the VASO images have the contrast of a CBV map, because the BBB is intact and the contrast agent is restricted to the intravascular space. In the tumor regions, the higher signal intensities are attributed to a combined effect of greater CBV and increased vascular permeability. The VASO parameters from ROIs are summarized in Table 1. The VASO values from different tumor grades are compared pair-wise and the statistical significance is shown in Table 2. It can be seen that grade 2 and grade 3 tumors each had significantly higher $VASO_{Tumor}$ values than did grade 1 tumors, but they were not significantly different from each other. There were no significant differences among tumor grades with respect to $VASO_{Contra}$. With respect to the $VASO_{Ratio}$, all three tumor grades were significantly different. Specifically, $VASO_{Ratio}$ exhibited a significant increase from grade 1 to grade 2 and from grade 2 to grade 3. Logistic regression shows that both $VASO_{Tumor}$ ($p=0.0006$) and $VASO_{Ratio}$ ($p=0.0004$) can be used as a significant predictor of tumor grades. The classification summary using $VASO_{Ratio}$ is listed in Table 3. Binary logistic regression was also applied to discriminate grade 1 tumors from tumors of higher grade (i.e., grades 2 and 3 combined as "high grade"). Fig. 2 plots the receiver operating characteristic (ROC) curves using $VASO_{Tumor}$ and $VASO_{Ratio}$, respectively. The results using the $VASO_{Ratio}$ as the criterion appear to have slightly higher sensitivity and specificity compared to $VASO_{Tumor}$. A possible reason for this is that by calculating the ratio between the two regions, slight scaling errors introduced by the CSF referencing signal (2) is minimized. The increases in VASO values may be explained by two possible reasons: 1) neovascularization (tumor angiogenesis) results in an increase in vascular density in tumor regions, thereby a higher blood volume; 2) vascular permeability is increased in tumor regions due to local breakdown of blood-brain-barrier (BBB), which results in leakage of gadolinium contrast agent into the tissue space, giving higher VASO signals. Compared to the dynamic susceptibility contrast (DSC) method, the VASO technique does not require the estimation of arterial input function and the quantification is independent of the vascular network topology (i.e. T2* change is dependent on the vessel distribution while T1 change is not). These data suggest that VASO MRI is a useful technique in quantifying tumor hemodynamics, and can provide complementary information to the histopathologic assessment in the classification of cerebral gliomas.

REFERENCES: 1) Daumas-Duport C et al. Cancer 62: 2152 (1988); 2) Lu H et al. MRM 54: in-press (2005, December); 3) Aronen H et al. Radiology 191: 41 (1994); 4) Burger P et al. Semin Oncol 13: 16 (1986).

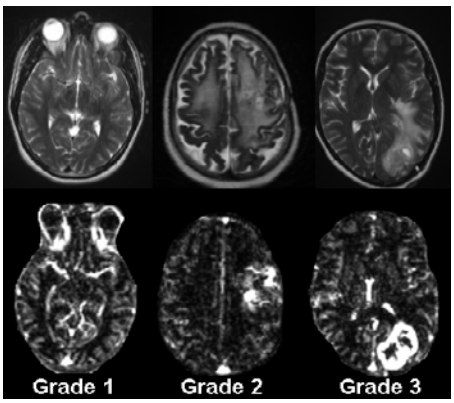

Fig. 1: T2W images and VASO maps for three patients with grade 1, 2 and 3 gliomas, respectively.

Grade	$VASO_{Tumor}$	$VASO_{Contra}$	$VASO_{Ratio}$
1	7.5 ± 3.2	5.4 ± 2.9	1.51 ± 0.54
2	41.3 ± 23.6	6.3 ± 4.2	8.16 ± 5.46
3	56.1 ± 32.7	4.8 ± 2.3	11.56 ± 3.66

Table 1: Mean ± standard deviation of each VASO parameter stratified by tumor grade. The units of $VASO_{Tumor}$ and $VASO_{Contra}$ are ml blood/100 ml tissue.

Comparison	$VASO_{Tumor}$	$VASO_{contra}$	$VASO_{Ratio}$
1 vs. 2	**0.0003**	0.685	**0.0002**
1 vs. 3	**0.00008**	0.508	**0.00002**
2 vs. 3	0.194	0.356	**0.0098**

Table 2: P values from a Mann-Whitney test for pair-wise comparison of tumor grades. Significant p values are labeled in bold.

True Grade	Predicted Grade			Sensitivity	Specificity
	1	2	3		
1	7	2	0	7/9 = 78%	28/30 = 93.3%
2	2	16	2	16/20 = 80%	12/19 = 63.2%
3	0	5	5	5/10 = 50%	27/29 = 93.1%

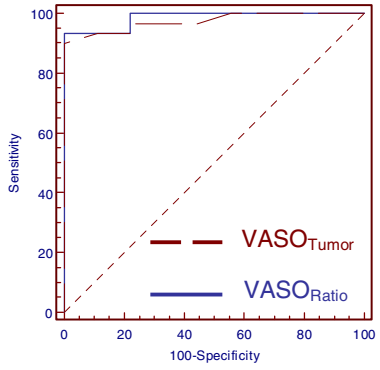

Fig. 2: Results of discriminating grade 1 from higher grades (grades 2 and 3 treated as same).

Table 3: Summary of results from ordinal logistic regression to predict tumor grade using $VASO_{Ratio}$.