Towards Improving Tumor Boundary Identification in Murine Models of Glioma using Cerebral Blood Volume Maps

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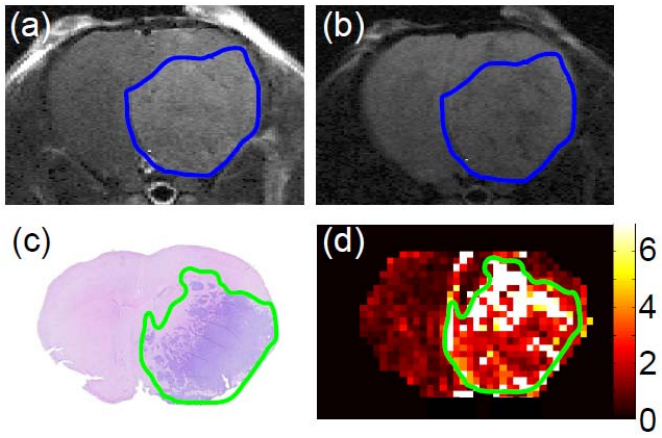

Fig. 1. Axial (a) postcontrast T_1-weighted, (b) T_2-weighted MRI images of a 3 week tumor. H&E stained whole mount brain slice (c); and CBV map (d). T_1-weighted contrast enhanced ROI in blue, actual tumor boundary ROI in green.

Introduction: Accurate determination of brain-tumor margins is a challenging problem, with important implications for patient management. MR contrast enhancement (breakdown of the blood brain barrier), often serves as a surrogate marker for actively growing tumor. However, many tumors, including glioblastoma multiforme, are highly infiltrative, often exhibiting tumor cells well beyond the margins of contrast enhancement. For such tumors, contrast enhancement is a poor measure of tumor boundary. Clinically, dynamic susceptibility contrast (DSC) perfusion MRI is an established technique in the evaluation and grading of brain tumors (1). Resulting cerebral blood volume (CBV) measurements have been shown to correlate with tumor grade and increased vascularity (2), with high-grade gliomas generally having higher rCBV value than low-grade tumors. However, a clear role for perfusion measurements in delineating tumor margins has not been established. The goal of this work is to determine whether elevated CBV, as measured in mice by the recently described local arterial input function (LAIF) DSC method (3), provides a better measure of 'extent' of tumor, than contrast enhancement alone.

Materials and Methods: DBT glioblastoma cells were injected intracerebrally into brains of female Balb/c mice (n = 14) (4). Mice were imaged between 7 and 24 days post implantation. Experiments employed an 11.7-T Agilent/Varian INOVA scanner using an actively decoupled volume (transmit) / surface (receive) coil pair. For DSC MRI, a series of T_2*-weighted gradient-echo fast low-angle shot (FLASH) (TE = 10 ms; TR = 15.65 ms, FA = 20°; total imaging time = 2 minutes) images were acquired from a slice through the center of the tumor, as determined from a series of T_2-weighted spin-echo images (multislice; TE = 30 ms; TR = 2 s; 21 slices; NT = 4; total imaging time = 17 min), following a preloading bolus injection of contrast agent. Images were acquired every second for 100-s. A contrast bolus of Multihance (Gd-BOPTA) was injected at 0.2-mmol/kg via a jugular vein catheter after the 20th image acquisition. T_2*-weighted, DSC data sets were analyzed using the signal model (3) described below.

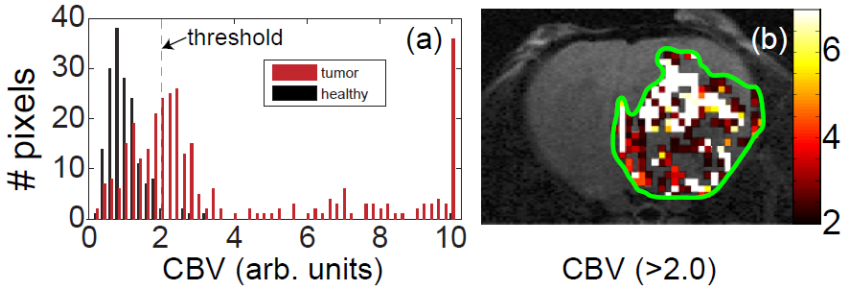

Fig. 2. (a) Histogram analysis of left (normal) and right (tumor) hemisphere CBV map; (b) CBV map (note different scale than in Fig. 1) of values above 2.0 overlaid onto a T_2-

Theory: In the standard tracer kinetic model (4,5) the tissue concentration $C_T(t)$ is represented as a convolution of the arterial input function (AIF) and the residue function: $C_T(t) = \text{CBF} \cdot C_A(t) \otimes R(t)$. In mice, accurate AIF measurements are particularly challenging due to partial volume effects and motion; further, the AIF is likely heterogeneous in tumor. Rather than attempting to measure the AIF directly, we used the LAIF DSC model (3), in which the residue function is modeled as an exponential: $R(t) = \exp[-(t-t_0)/\text{MTT}]$ and the LAIF as a gamma-variate: $C_A(t) = N(t-t_0)^{\alpha} \exp[-\beta(t-t_0)]$. These expressions were substituted into the tissue concentration equation ($C_T(t)$) and convolved analytically. Finally, the contrast agent concentration was converted to MR signal intensity as: $S(t) = S_0 \exp[-kC_T(t)]$, where k is a constant. The model parameters were estimated as in (3) employing algorithms based on Bayesian probability theory.

Results and Conclusions: Parametric maps of MTT, CBF, and CBV were generated from LAIF DSC model parameter estimates (a CBV map is shown in Fig. 1d) and histogram analyses were performed. The brain was segmented, based upon its midline, into left and right hemispheres. Histograms of CBV values for the right (tumor bearing) and left (healthy) brain were produced using in-house Matlab code (Fig. 2a). Fig. 2a clearly shows a shift in mean and a right-skew in the tumor-bearing hemisphere (red bars). Based upon the healthy tissue histogram (black bars), a CBV threshold of 2 was established for normal brain. After pixels with CBV < 2 were removed from the CBV parametric map, the remaining pixels (Fig 2b) correlated well with histology, as indicated by the green ROI in Figs. 1 and 2. These results suggest that histogram analysis of LAIF DSC model-derived CBV maps can accurately identify tumor boundaries based on tissue perfusion characteristics. We speculate that LAIF DSC-derived perfusion maps may aid in the identification of high-grade components of tumor, in guiding biopsy or treatment planning, and in differentiating between necrotic tissue and recurrent tumor.

References: (1) Law M et al., AJNR, 2007:28:761-766; (2) Law M et al., AJNR, 2003:24:1989-1998; (4) Lee J et al., MRM, 2009:63:1305-1314; (4) Jost et al., Neurosurgery, 2007:60:360-371; (5) Zierler K, Circ. Res., 1962:10:393-407.