Quantitative Characterization of Functional and Morphological Properties of Tumor Vasculature in High-Grade Gliomas

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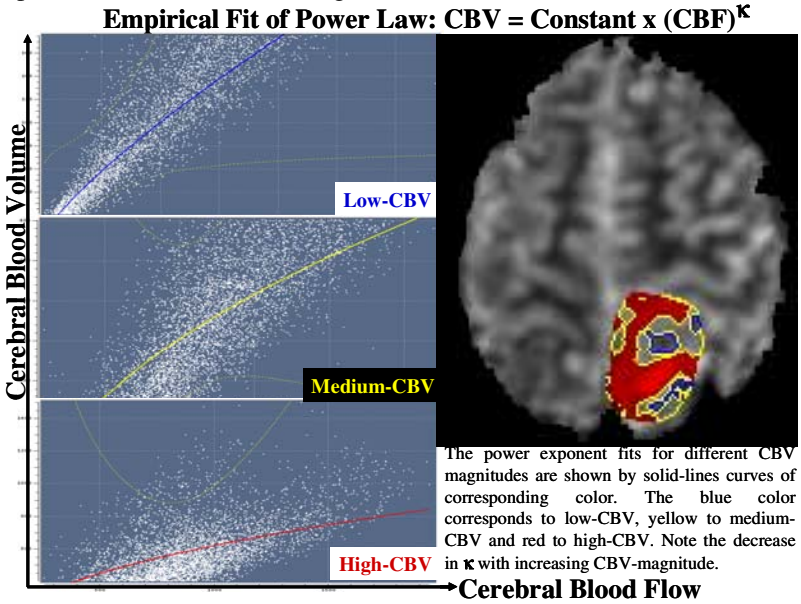
Introduction: Tumor vasculature plays a central role in therapy hence, an understanding of the structural and functional/dysfunctional characteristics of the vascular microenvironment of high-grade gliomas [HGG] is essential in design of therapeutic strategies. Typically, HGG can be classified into intratumor and peritumor which are likely to differ in angiogenic activity and expression of growth factors that are reflected by changes in the vascular properties. Alterations of the vascular properties in intratumor and peritumor may not be distinguishable by cerebral blood flow [CBF] or cerebral blood volume [CBV] alone. The objective was to examine the empirical and physiological relationships between CBF and CBV to estimate vasculature-specific hemodynamic characteristics in intratumor, peritumor and normal brain tissue. We hypothesize that the functional and morphological characteristics are significantly different in tumor and peritumoral tissue.

Materials/Methods: Twenty patients with Grade III or IV gliomas participated in an IRB approved clinical MRI study. The inclusion criterion was a minimum 4 cm^3 tumor volume [TV] after resection. The MRI protocol comprised of T1 pre- and post-contrast, FLAIR, and dynamic susceptibility contrast-enhanced imaging [DSCE] before radiotherapy [RT[. Quantitative CBF and CBV values were calculated from DSCE-MRI on a pixel-by-pixel basis. The relationship between CBV and CBF were evaluated by two different approaches: (1) The physiological measure of Mean Transit Time [MTT] = CBV/CBF; and (2) empirical fitting of CBV and CBF using the power law, expressed as CBV=Constant*$(CBF)^{\kappa}$. Three different tissue-types were assessed, namely: (i) post-Gd T1 TV [post-Gd-T1-TV], non-enhanced abnormal tissue located beyond post-Gd-T1-TV but within the abnormal hyperintense region on FLAIR images [NEA], and (iii) normal tissue in hemisphere contralateral to the tumor [CNT]. Effects of tissue-types on MTT and κ were analyzed by ANOVA. Also, the dependency of MTT and κ on CBV-magnitudes (low [L], medium [M] and high [H] CBV) were assessed.

Results: Both MTT and κ showed significant differences among the three different tissue-types ($p<0.009$), see Table. MTT increased in ascending order from CNT (1.60 s) to NEA (1.93 s) to post-Gd-T1-TV (2.28 s) ($p<0.0005$). The power exponent κ in post-Gd-T1-TV (0.50, averaged over the three CBV-magnitudes) was significantly greater than in NEA (0.45) and CNT (0.44), but κ in NEA and CNT were not significantly different. The power exponent κ decreased with increasing CBV-magnitude while MTT was independent of CBV-magnitude (Table).

Discussion: The sensitivity of MTT and κ to different set of variables used to assess tumor evolution and pathology suggest the diverse role of the two metrics. Prolongation of MTT in NEA and post-Gd-T1-TV compared with CNT suggests impaired autoregulation and increased vessel tortuosity. Increased κ in post-Gd-T1-TVcompared to normal tissue indicates that tumor vascular bed becomes severely disorganized, chaotic, tortuous and highly disordered in nature. In the NEA region, MTT was similar to that in post-Gd-T1 TV but not similar to that in CNT, indicating that developing functional abnormality precedes morphological changes.

Conclusions: Progressive abnormalities in functional and morphological characteristics of vascular bed were noted, with significant chaos and disorder in tumor, but mild abnormality in peritumoral tissue. MTT and power exponent κ provide information on different aspects of tumor vasculature in gliomas.



The power exponent fits for different CBV magnitudes are shown by solid-lines curves of corresponding color. The blue color corresponds to low-CBV, yellow to medium-CBV and red to high-CBV. Note the decrease in κ with increasing CBV-magnitude.

Table

ANOVA Analysis	MTT	κ
Tissue-Types	**p < 0.0005**	**p = 0.009**
CNT vs NEA	p<0.0005	n.s.
Post-Gd-T1-TV vs NEA	p<0.0005	p=0.027
Post-Gd-T1-TV vs CNT	p<0.0005	p=0.02
CBV-Magnitude	**p = 0.098**	**p < 0.0005**
Low vs Medium	n.s.	p<0.0005
Low vs High	n.s.	p<0.0005
Medium vs High	n.s.	p<0.0005

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