# Characterization of tumor angiogenesis and microvascular leakage in high grade glioma patients using dynamic perfusion weighted MR imaging

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## Introduction

With the advent of new anti-angiogenic therapies for the treatment of high grade gliomas, it is becoming increasingly important to add specificity to the classification of high grade gliomas based upon vasculature characteristics. Quantification of parameters that can globally describe regions of angiogenesis and microvascular leakage is thus useful in planning and monitoring these anti-angiogenic therapies. Dynamic perfusion MRI measurements of regional cerebral blood volume (rCBV) and histology studies have confirmed that blood vessel density increases with tumor grade.[1,2] However, in order to estimate rCBV non-invasively in regions of microvascular leakage, it is necessary to make corrections that require assumptions regarding the shape of the perfusion time curve which have not yet been fully substantiated.[1] This study investigated non-parametric parameters corresponding to the peak height and percent recovery of the T2* relaxivity curve to independently characterize angiogenesis and microvascular leakage in regions of T2 abnormality and contrast enhancement in high grade gliomas.

## Methods

Thirty-three patients (17 female, 16 male, median age 52 years) with a diagnosis of grade III (10 patients) or IV (23 patients) gliomas were recruited for this study prior to receiving treatment. All grade IV and six out of ten grade III patients exhibited contrast enhancement on a T1-weighted SPGR image post gadolinium injection. MRI exams were performed on a 1.5 T Signa Echospeed scanner (GE Medical Systems, Milwaukee, WI). T2-FLAIR or FSE and post contrast T1-SPGR images were acquired and used to define regions of T2 or T1 enhancing abnormality. The perfusion imaging consisted of the injection of a bolus of 0.1 mmol/kg body weight of gadopentetate dimeglumine (Gd-DTPA) contrast agent at a rate of 5 mL/s. A series of 60 $T2^*$-weighted gradient-echo, echo-planar images were acquired during the first pass of the contrast agent bolus injection, with a TR/TE of 1000-1250/54 ms, $35^o$ flip angle, FOV of $26 \times 26$ cm$^2$, $128 \times 128$ acquisition matrix, and 3-6 mm slice thickness. The perfusion series was resampled to a $32 \times 32$ grid in-plane with a 16 x 16 cm$^2$ FOV so that the observed signal changes had sufficient signal to noise ratio to be analyzed reliably on a voxel by voxel basis. The T2* signal time curve, S(t), was converted to relative concentration using the relationship $C(t) \sim -\ln(S(t)/S_0)$, where $S_0$ is the average pre-contrast signal intensity baseline. Peak height and percent recovery of the post bolus signal from the peak were calculated for each voxel within the T2 and contrast enhancing (CE) lesions. Peak height values were normalized to the peak of a model curve function derived from normal appearing brain based on histogram analysis of the pre-contrast echo planar images. Voxels with peak height values greater than twice the model curve were classified as having abnormal peak height (aPH), while those whose post-bolus concentration recovered less than 75% from the peak concentration were considered to have abnormal recovery (aRec). Regions with no signal drop (NSD), as defined by a flat signal on the time series data, were excluded from the calculations.

## Results

The heterogeneity in the dynamic concentration curve shapes within a grade IV glioma and corresponding maps of aRec (red) and aPH (blue) overlaid on a post-contrast T1-SPGR image are displayed in figure 1. Figure 2 compares the normalized mean volumes within regions of NSD, CE, aPH, and aRec for grade III and IV patients. The averaged maximum and mean relative peak height values, as well as minimum and mean recovery values are shown in figure 3 for both the CE lesion (CEL) and the T2 lesion excluding the CEL (T2L-CEL). The statistical significance of the group comparisons observed in both figures, as denoted by an asterisk, was determined through the use of a Wilcoxon ranked sum test. As expected, grade IV gliomas showed significantly larger volumes of NSD and CE compared to grade III patients. The volume of aRec was also significantly greater for grade IV than grade III gliomas, supporting the idea that there is increased blood-brain-barrier breakdown in the microvasculature of grade IV gliomas. An increasing trend was observed in the volume of aPH with higher grade, but this difference was not significant. Only within the CEL did grade IV gliomas exhibit significantly higher mean and maximum peak height values than enhancing grade III patients. This was due to significantly higher maximum peak height values outside the CEL in the grade III cohort. Enhancing grade III patients demonstrated a higher minimum recovery within both the enhancing and the non-enhancing components of the T2 lesion compared to grade IV patients, but mean recovery values were similar between grades in both regions. Although the maximum peak height and minimum recovery lay outside the region of enhancement for enhancing grade III patients, 57% of grade IV patients showed maximum peak height and 22% exhibited minimum recovery within the CEL.

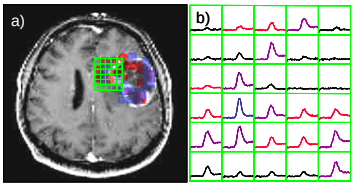


**Figure 1:** a) Grade IV enhancing glioma with abnormal peak height (blue) and recovery (red) overlays b) Concentration curves from which overlays were generated

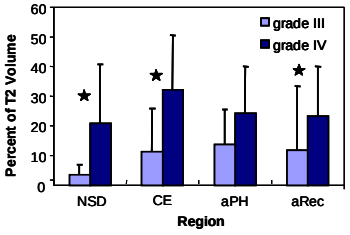


**Figure 2:** Normalized mean volumes for regions of no signal drop (NSD), contrast enhancement (CE), abnormal peak height (aPH), and abnormal recovery (aRec) in grade III and IV gliomas

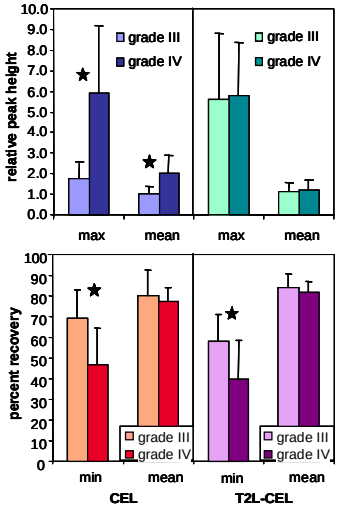


**Figure 3:** *Top:* Maximum and mean relative peak heights, and *Bottom:* Minimum and mean percent recovery, within the CEL *(left)* and T2L-CEL *(right)* for high grade gliomas

## Discussion and Conclusions

There was considerable heterogeneity in the characteristics of tumor microvasculature and their spatial distributions in grade III and grade IV glioma patients. That the maximum abnormal peak height values were lower within the CEL for enhancing grade III gliomas, suggested that there is increased angiogenesis in portions of tumor outside the CEL. In grade IV patients, it appears angiogenesis is more likely to be localized to the enhancing region. The lower recovery in the CEL is usually interpreted as being indicative of damage to the microvasculature, which leads to leakage of contrast agent into the extravascular space. However, our results showed an unexpected decrease in minimum recovery in the surrounding T2L. This may reflect that the mechanism behind the formation of vasogenic edema is that vessels are still functional but are beginning to breakdown and become leaky.[3] Further investigation is necessary to understand this phenomenon because there is no difference between the mean recovery values in these regions and the minimum recovery values are not all that different from the recovery pattern within the enhancement. Direct measurement of curve-shape parameters such as peak height and percent recovery clearly improves specificity in characterizing vascular changes in high grade gliomas compared to traditional rCBV calculations. Future studies will increase the number of patients to further assess the spatial distribution of these perfusion imaging parameters as well as their prognostic value in both predicting and evaluating tumor response to anti-angiogenic therapy within high grade gliomas.

## References

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