Spatially quantifying microscopic tumor invasion and proliferation using a voxel-wise analytical solution to a glioma growth model and serial diffusion MRI

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Introduction

Glioblastoma multiforme (GBM) is a particular type of infiltrative malignant brain tumor trademarked by a very poor patient prognosis. Despite advancements in surgical procedures, radiation therapy, and chemotherapy, mean survival time is only approximately 11 months for GBM patients, where the prognosis has not changed significantly in the last 30 years[1]. Microscopic invasion of tumor cells and otherwise undetected tumor proliferation is thought to be the primary reason for such a dismal prognosis. Identification of spatially-localized brain regions undergoing high rates of cell migration and cell proliferation is critical for improving patient survival; however, there are currently no non-invasive imaging biomarkers for estimating proliferation rates and migration rates of human gliomas *in vivo*.

A spatio-temporal mathematical model of glioma growth was developed based on the uncontrolled proliferation potential of gliomas, along with their ability to invade[2,3]. Since gliomas do not typically metastasize outside of the brain, a conservation-diffusion partial differential equation can be used to describe brain tumor growth. This model has led to a number of simulation studies meant to describe the *macroscopic* growth and invasion characteristics of gliomas under a variety of treatment conditions[2,3]. These simulations typically ascribe a singular value for "cell diffusion rate" and a singular value for "proliferation rate" to describe growth and invasion of the tumor as a whole. Based on the strong correlation between tumor cell density and ADC[4-6], we hypothesized that the glioma growth equation could be solved analytically and displayed, on a voxel-wise basis, for characterizing *microscopic* tumor growth and infiltration. The resulting CIMPLE (cell invasion, motility, and proliferation level estimates) image maps represent a new method of determining the level of aggressive malignant behavior, and quantifying the effects of treatment. In the current study, we describe the voxel-wise analytical solution to the glioma growth model using estimates of ADC and demonstrate their potential when applied to a group of patients with gliomas.

Eq. 1: Macroscopic Glioma Growth Model

$$\frac{dc}{dt} = \nabla\cdot(D\nabla c) + \rho\cdot c$$

(Rate of Change in Cell Density = Invasion + Proliferation)

Eq. 2: Microscopic Glioma Growth Model using DWI

$$\frac{d}{dt}ADC = D\nabla^2 ADC + \nabla D\cdot\nabla ADC + \rho\cdot ADC$$

Methods

The *macroscopic* glioma growth model (Eq.1)[2,3] suggests the rate of change in glioma cell density is equal to the net motility of glioma cells plus the net proliferation, where c is cell density, D is the diffusion coefficient for migrating cells, and ρ is the cell proliferation rate, and t is time. Substituting the correlative relationship between tumor cell density and ADC[4-6] into Eq.1 results in a differential equation that provides an estimate of tumor cell migration (diffusion) and proliferation rate using only the spatio-temporal characteristics of the ADC maps obtained on sequential scan days (Eq.2). Three-dimensional scalar fields for the variables D and ρ were solved directly by using Eq.2 applied to two different time series of ADC maps; however, since a *rate of change in ADC* is necessary in Eq.2, a minimum of three, 3D ADC image volumes are needed for a direct analytical solution to the microscopic glioma growth model using DWI. Using the *Method of Characteristics*[18], an analytic solution to the linear first-order partial differential equation with respect to D was obtained along the characteristic line described by dy/dx, which allowed for a direct estimate of ρ and a voxel-wise solution to the microscopic glioma growth model, thus enabling the creation of the CIMPLE maps. Analytical solutions were verified using Mathematica v7.01 (Wolfram Research, Inc, Champaign, IL).

Fifty-two patients with gliomas who were previously enrolled in a study of MR perfusion imaging at our Institution were enrolled in the current retrospective study. For all patients on all scan dates, ADC maps were collected using b = 1,000s/mm^2 and b=0s/mm^2 images. All images for each patient were registered to their own baseline 3D SPGR anatomical datasets using a mutual information algorithm and a 12-degree of freedom transformation using FSL (FMRIB, Oxford, UK). Single-voxel MR spectroscopy (MRS) or chemical shift imaging (CSI) was performed in 9/52 patients enrolled in the current study using a 1.5T MR scanner and either a PRESS (for MRS) or CHESS technique (for CSI). For validation, linear regression was performed between the mean proliferation rate (ρ) and the choline-to-N-Acetylaspartate (Cho/NAA) ratio obtained within similar image voxels on MRS/CSI.

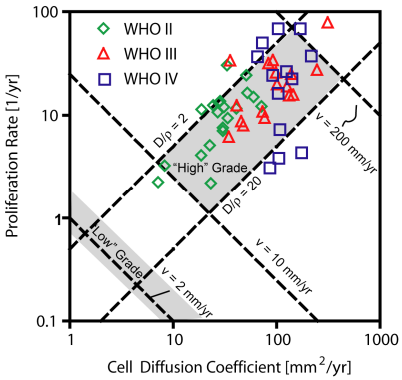

Fig.1: "Hot Spot" analysis showing proliferation rate and cell diffusion rate for different WHO grades

Results

In general, CIMPLE maps appeared to demonstrate increasing cell motility (diffusion) and proliferation rates with increasing malignancy (Fig.1). Regions of high Cho/NAA on MRS/CSI, suggestive of high cell turnover, appeared to have high estimates of cell proliferation rate (Fig.2). Quantitatively, a strong linear correlation was found between Cho/NAA and proliferation rate (R^2=0.9714,P<0.0001). CIMPLE map estimates of cell proliferation rate could also distinguish between contrast-enhancement due to radiation necrosis vs. recurrent tumor (Fig.3).

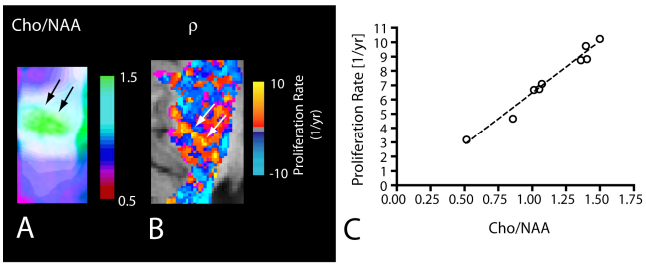

Fig.2: Strong correlation between Cho/NAA and Proliferation Rate.

Discussion

Although DWI estimates of ADC are known to reflect the underlying tumor cell density, to date, no efforts have been made to estimate the microscopic *cell* rather than water diffusion and proliferation rates on a voxel-wise basis using information collected in serial DWIs. The correlation between spatially matched regions on CIMPLE maps to MRS/CSI provides strong validation for this novel technique. As expected, cell turnover from rapidly dividing cell membranes resulted in a high Cho/NAA ratio in the same spatial locations exhibiting high cell proliferation on CIMPLE maps. Regions of high proliferation rates appeared to be isolated in regions of contrast enhancement, consistent with biopsy observations[7,8]. In summary, the current study presents a voxel-wise analytical solution to the glioma growth model, which allows for direct spatial quantification of microscopic tumor cell proliferation and migration based on serial DWIs in the same patient. This technique may be valuable for assessing tumor dynamics and predicting response to treatment in *all* types of cancers. ***Acknowledgements*** NIH/NCI R21-CA109820; MCW Advancing Healthier Wisconsin/Translational Brain Tumor Program; MCW Cancer Center Fellowship, NIH/NCI RO1 CA082500 ***References*** [1]Fine, *J Neurooncol*, 1994; [2]Swanson, *J Neurol Sci*, 2003; [3] Swanson, *Cell Prolif*, 2000; [4]Sugahara, *JMRI*, 1999; [5]Gauvain, *AJR*, 2001; [6]Kono, *AJNR*, 2001.[7]Kelly, *Mayo Clin Proc*, 1987; [8]Kelly, *J Neurosurg*, 1987.

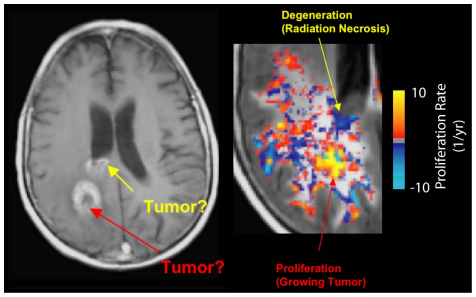

Fig.3: Maps of Proliferation Rate can distinguish between radiation necrosis vs. recurrent tumor.