Evidence that Diffusion Tensor Imaging (Tractography) Predicts the Natural History of Regional Recurrence in Patients Irradiated Conformally for Primary Brain Tumors

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Purpose: Approximately 17,000 cases of primary brain tumor are diagnosed in the United Stated each year. Stereotactic Radiotherapy (SRT) treatment plans of malignant brain tumors typically incorporate a 4 – 30 mm isotropic margin to account for microscopic tumor spread, however, distant and/or recurrent tumors occur outside the treatment margin. Our hypothesis is that paths of elevated water diffusion provide a preferred route for transport or migration of cancer cells through an unknown mechanism. If our hypothesis is correct then future SRT treatment volumes would be modified to provide elongated treatment margins along the paths of elevated water diffusion leading from the primary tumor site, thereby reducing the incidence of recurrence and improving clinical outcomes.

Methods and Materials: We describe herein a method for applying magnetic resonance Diffusion Tensor Imaging (DTI) prospectively in patients with aggressive gliomas to predict the spread and recurrence of disease following SRT treatment. Patients treated with SRT were selected for whom DWI datasets were acquired either before the initial SRT treatment or at the first indication of tumor recurrence. Effort was made to select patients in whom existing tumor infiltration and/or radiation damage was absent at the time of DTI acquisition, to ensure these processes did not alter the measurement of the native diffusion environment present at the time of initial tumor cell migration. DTI was performed using an EPI sequence on a 1.5T clinical GE scanner using the following parameters: TR 10s; TE 89.4 ms; 20 serial axial slices; 25 diffusion gradient directions and 3 reference (b=0) scans; with voxel dimensions 0.98×0.98×6 mm. Following SRT, patients were given repeated MRI follow-ups at regular intervals to identify early tumor recurrence. When recurrent tumors were detected, either DTIstudio (Huang, Mori et al, MRM 52(3), 2004) and FSL (Behrens et al., MRM 50, 2003) software was used to compute paths of preferred water diffusion through the primary tumor site and the site of recurrence. Three categories of patients were found: Category 1 (Distant Secondary Tumor Group) included patients 1-3 who had secondary tumors located greater than 2 cm beyond the SRT treatment volume; Category 2 (Local Secondary Tumor Group) included patients 4-5 who had secondary tumors within 2 cm)or on the boundary of the treatment plan and had no sign of the recurrence in the DTI dataset; and Category 3 (Recurrence Group) included patients 6-7 who had surgical resection and recurrence on or near the margin of the primary tumor.

A random walk model of cell migration was used to calculate the probability of tumor spread from the tumor surface. Fractional Anisotropy (FA) and Principal Eigen Vectors were obtained from DTIStudio and brain masks were generated using FSL. The step size and uncertainty in the fiber direction in theta and phi were decided based on the FA values. At each step the direction of migration was decided randomly within the uncertainty range. Probability of cell migration was defined as the number of cells found/passed through each voxel after a fixed number of steps.

Results: In Category 1, two of three patients were found to have prominent fiber paths that predicted the subsequent spread of disease and the random walk model predicted that the cells traveled farther along these directions (Figure 1). In Category 2, both patients had prominent fiber paths that predicted within a 15-degree margin the location of the subsequent secondary tumor following ablative SRT to the primary tumor and a had high probability of cell migration in the computational model (Figure 2). The fiber architecture and computational model of cell migration were predictive of tumor spread for both patients in Category 3.

Conclusion: There exists an apparent correlation between patterns of tumor spread using both the predictions from our computational model and the paths of elevated water diffusion leading from the primary tumor in the brain.

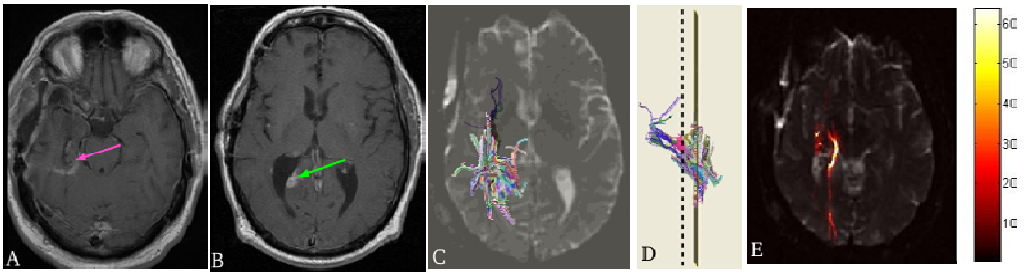

Figure 1: [A] T1 weighted post-contrast image in a patient from Category 1 showing the location of a primary hippocampal astrocytoma (pink arrow). [B] T1 weighted post-contrast image of a secondary tumor (green arrow) in the splenium of corpus callosum, two slices superior to the primary tumor. [C] DTI reference image (b=0) at the initial time point when the primary tumor was observed showing tracts from the primary tumor determined using DTIStudio projected onto the 2D plane of the secondary tumor. [D] Side view of the reconstructed fibers showing intersection of the slice corresponding to the location of primary tumor and the secondary tumor shown as a dotted line. [E] There exists a path of high probability from the primary to secondary tumor as seen in the probability map of cell migration (the colorbar illustrates probability from 0 to 60%).

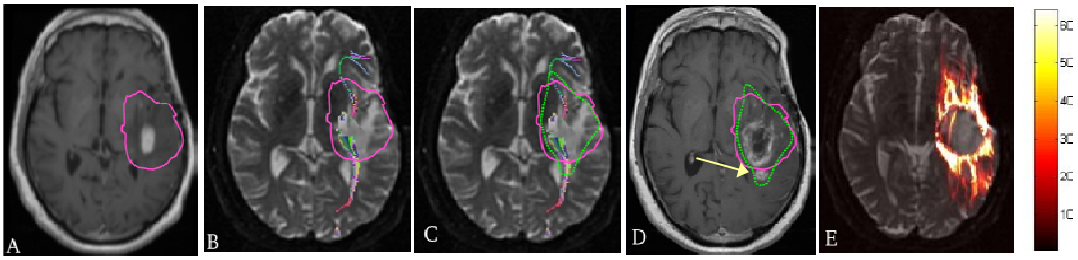

Figure 2: [A] T1 weighted post-contrast image in a patient from Category 2 showing glioma and treatment margins (pink line – 90% isodose), transferred from the CT treatment plan. [B] DTI reference image (b=0) taken at the same time point, showing all diffusion tracts passing through the tumor. Two major bundles pierce the treatment margin. [C] The treatment plan that was used for SRT (solid pink curve) and the proposed plan (dotted elongated green curve) with increased dose margins along the two prominent fibers emanating from the primary tumor [B] and reduced margins along other directions of normal tissue shown on the DTI reference image and [D] on the T1weighted post-contrast image. The new proposed treatment plan may have prevented the secondary tumor (yellow arrow in [D]) which indeed did occur along the prominent posterior fiber bundle. [E] The probability map of cell migration (the colorbar illustrates probability from 0 to 60%) showing higher probability of migration along the fibers in the anterior-posterior direction. The secondary tumor occurred in the region of high probability.