Random walk model for predicting patterns of microscopic glioma spread using DTI: A prospective study

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Purpose: The current methods of determining treatment margins needed to encompass microscopic tumor spread for Stereotactic Radiotherapy (SRT) are often inadequate as recurrences/secondary tumors often occur at the boundary of the treatment margin. We hypothesize that paths of elevated water diffusion along the white matter tracts provide a preferred path for migration of glioma cells. If our hypothesis is true, then future SRT plans would be modified to provide elongated margins along white matter tracts from the primary tumor, thereby targeting tissue with unseen, microscopic spread of tumor cells and hence reducing the incidence of recurrence/secondary tumors. In the current study we present the pattern of glioma spread observed in follow-up MR images and compare it with the results of anticipated tumor spread from our predictive random walk model of cell migration based on DTI obtained prospectively.

Methods and Materials: Having established that there is a higher correlation between the location of recurrence/secondary tumors and the presence of white matter tracts retrospectively [1], we acquired high resolution DTI datasets of glioma patients in a prospective study to validate the predictive power of our hypothesis. As per standard of care the primary tumor was surgically resected followed by SRT. For our protocol the patients were then imaged either pre-surgically or post-surgically before SRT after the reduction of edema. DTI was performed using an EPI sequence on a 3.0T Siemens scanner with 70 serial axial images of voxel dimensions: 2.0×2.0×2.0 mm; TR 10.1s; TE 100 ms; 60 diffusion gradient directions and 10 reference (b=0) scans. Three volunteers and thirteen patients with gliomas were imaged. Following SRT, patients were given repeated clinical MRI follow-ups at regular intervals to identify early incidence of tumor recurrence.

Our method involved DTI acquisition and processing, followed by the application of a constrained random walk model for cell migration. Previously we showed that our random walk model based on one-tensor reconstruction is successful in areas of fiber crossing having a low intersection angle, where the inherent greater uncertainty in the direction of cell migration compensated for the presence of crossing fibers. The assumptions of our random walk model were: 1) Initially there were an equal number of cells in all surface voxels of the tumor; 2) In the initial state, all cells were in the surface voxels; and 3) The migration was constrained by the Principal Diffusion Direction (PDD). The tumors were segmented manually using FSLView and the brain masks were generated using FSL. The algorithm of our random walk model is described below. 1) The DTI datasets were reconstructed with Camino/DTIStudio and PDD and Fractional Anisotropy (FA) were obtained. 2) The migration of each cell from the surface voxel was simulated independently. The uncertainty in the direction of cell migration about the PDD was determined based on the FA value of the voxel. The PDD was given by the in-plane and out-of-plane solid angles. The uncertainty in cell migration was ±35°, ±20° and ±10° about the PDD when the FA was 0-0.3, 0.3-0.6 and 0.6-1, respectively. 3) At each step the direction of migration was decided randomly within the uncertainty range. 4) When the cell was on the tumor surface it was constrained to move away from the center of the tumor. 5) The probability of cell migration was defined as the number of cells found in or passing through each voxel after a fixed number of steps.

Results and Conclusions: Of the 13 patients recruited to date, six have had recurrence/secondary tumors. Two patients had secondary tumors outside the treatment margin and in both of these patients there was a high correlation between the areas of high cell concentration predicted by our random walk model and the location of secondary tumors (Figure 1). Four patients had recurrences within the treatment margin. In one of these patients the areas of high cell concentration from the random walk model predicted the direction of tumor spread (Figure 2). For recurrences outside the treatment margin our hypothesis appears to be valid.

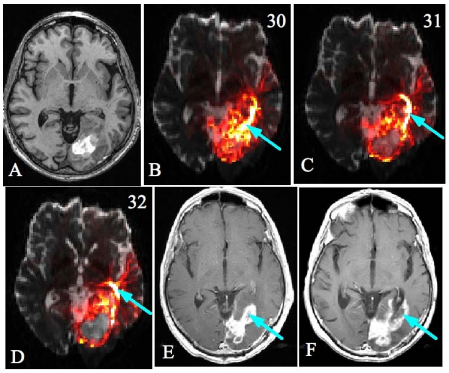

Figure 1: The primary tumor of patient 1; a Glioblastoma Multiforme in the left occipital lobe, is shown in the MR T1 weighted post-contrast image A. Images A-D were obtained at the same initial time point, image E was obtained 4 months later and image F was obtained 11 months later. The spread of the primary tumor is shown in the follow-up post-contrast T1 weighted images and is indicated by blue arrows [E-F]. The results of our random walk model are shown in B-D with the voxels in yellow predicting higher cell concentration (blue arrows) and red predicting lower concentration. The slice number is shown in top right corner. The area of predicted high cell concentration ([B-D]; blue arrows) anterior to the primary tumor foretold the observed spread of tumor seen in the follow-up images.

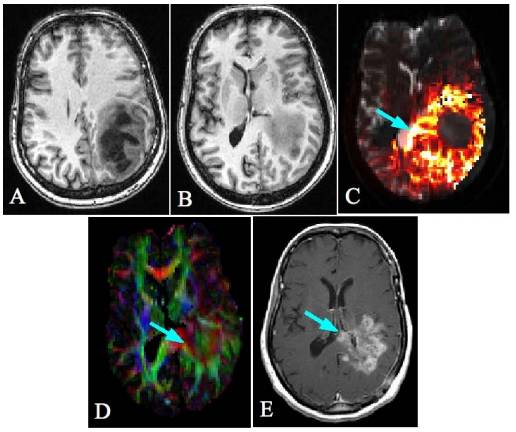

Figure 2: The primary tumor of patient 2, an anaplastic oligoastrocytoma in the left parietal lobe is shown in the T1 weighted images [A-B]. The images in A-D were obtained at the same initial time point and image E was acquired 8 months later illustrating spread of the primary tumor. The slice corresponding to image A was acquired 1.5cm superior to the location of slice B. The spread of the tumor along the splenium of the corpus callosum was observed in the 8-month follow-up T1 weighted image [E] and is indicated by the blue arrow. The results of our cell migration model are shown in image C with voxels in yellow predicting a higher cell concentration and red predicting a lower cell concentration. Note that the high cell concentration surrounding the tumor for this slice is due to the larger size of the tumor in the immediate surrounding slices [A-B], as well as some edema. Most of the voxels with a predicted higher cell concentration in the vicinity of the primary tumor fall within the 2cm high dose radiation treatment margin used for treating gliomas. However in C, outside the 2cm margin there is predicted high cell concentration along the corpus callosum (blue arrow) foretelling the primary tumor spread observed in the follow-up image [E; blue arrow]. The color-coded fractional diffusion anisotropy map [D] also shows the disruption of fibers in the splenium of the corpus callosum (blue arrow) indicating the possibility of detecting active tumor spread 8 months prior to the observation of spread using conventional imaging [E].

[1] Krishnan AP, Asher MI, Davis DD, Okunieff P, O'Dell WG. Evidence that MR Diffusion Tensor Imaging (Tractography) Predicts the Natural History of Regional Progression in Patients Irradiated Conformally for Primary Brain Tumors Int. J. Radiation Oncol. Biol. Phys, (Aug) 71(5):1553-1562, 2008