Quantitative Assessment of Glioma Therapy Efficacy based on Diffusion Isotropy and Anisotropy

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BACKGROUND

Novel therapeutic advances in neuro-oncology require non-invasive quantitative markers to assess their efficacy. Current methods rely mostly on anatomic MR imaging and occasionally, perfusion weighted techniques that use contrast agents. We present an approach using magnetic resonance Diffusion Tensor Imaging (DTI) that permits the longitudinal assessment of glioma response to therapy. This model utilizes a tensor decomposition technique[1] that was shown to allow in vivo measurement of spatio-temporal variations in isotropy and anisotropy of water diffusion, and by extension, the structural organization of tumor cells locally. A major challenge for such characterization of glioma is the inherent biological heterogeneity of this pathology. We demonstrate that the method used is applicable to both "local" forms of therapy, as well as, the more common "global" approaches such as chemo-therapy and radiation. The two therapy regimens evaluated here are a surgically injected genetically engineered oncolytic virus, and traditional chemo/radiation therapy, representing local and global strategies, respectively. Earlier, we reported success in evaluating G207[2] (MediGene , Munich, Germany), a derivative of the herpes virus (HSV-1) that replicates in dividing cells of the tumor, while not affecting the normal non-dividing cells of the brain, using DTI-methods. The virus therapy was administered as a part of a clinical trial undertaken by the UAB Brain Tumor SPORE and Medigene AG to evaluate the effects of G207 given in conjunction with radiation.

MATERIALS AND METHODS

Five patients undergoing G207 therapy and five on conventional chemo/radiation therapy were evaluated as a part of this study. MR Diffusion tensor imaging was performed on a 3T MRI scanner (Intera, Philips Medical Systems, Cleveland, OH) using a SENSE head coil. The diffusion single-shot EPI sequence was run with diffusion gradients applied in 15 directions (TR/TE = 3250ms/88ms, FOV 230 mm^2, slice thickness/gap = 4mm/1mm, 24 slices to cover the tumor, surrounding edema, and regions of possible infiltration, b-value = 1000s/mm^2, matrix size 256x256). Pre-contrast FLAIR and post-contrast T1 weighted images were also acquired for anatomic reference and visual compartmentalization of the tumor pathology. The G207 patients were imaged prior to G207 inoculation (baseline), at 4, and 8 weeks post-inoculation. Patients undergoing chemo/radiation therapy were imaged prior to commencement of therapy (baseline), and at 8, and 16 weeks following initiation of therapy. Diffusion tensor post-processing included eddy current correction, skull-stripping, and intra-subject registration, performed using FSL (Analysis Group, FMRIB, Oxford, UK). Parametric isotropy (**p**) and anisotropy (**q**) data were computed using a custom-written MATLAB (The MathWorks Inc, Natick, MA) program. The **p:q** data were analyzed using the following regions of interest (ROI): healthy contralateral brain, tumor, vasogenic edema and tumor-margins with possible infiltration, based on post-contrast T1 and FLAIR images. Additionally, **p** and **q** maps were used to perform a diffusion-based segmentation using custom-written MATLAB programs. These data were then statistically analyzed for longitudinal response patterns along with clinical outcomes. All studies were approved by the University of Alabama at Birmingham Institutional Review Board.

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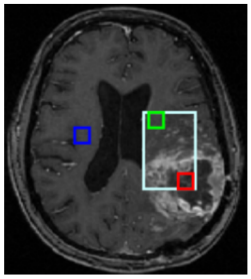
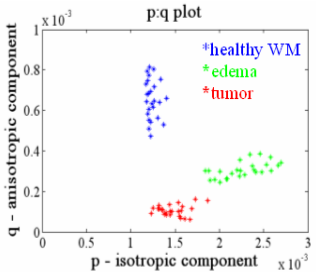
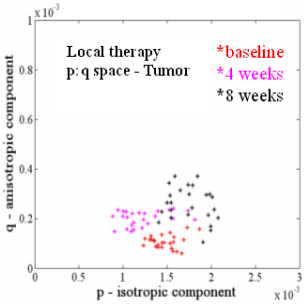
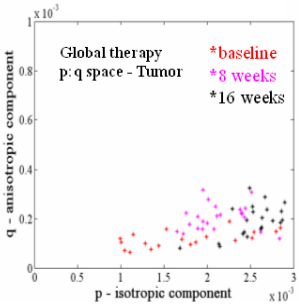
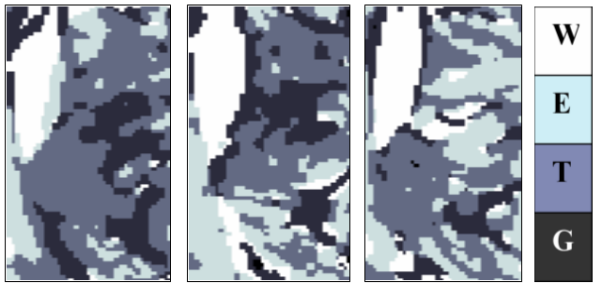
Figures 1: Baseline post-contrast T1w Image showing ROIs analyzed for **p**:**q** characteristics. **2**: **p**:**q** characteristics of tissue compartments showing the utility of this model for glioma evaluation. **3**: Longitudinal variation of tumor **p**:**q** space in a patient undergoing local therapy showing distinct temporal shift over the three time-points. **4**: Longitudinal variation of tumor **p**:**q** space in a global therapy patient showing less distinct **p**:**q** variations and greater overlap of isotropy/anisotropy characteristics. **5**: **p**:**q** weighted segmentation of the white ROI in fig.1 showing temporal redistribution of tissue (W: White matter, E: Edema, T: Tumor, G: Gray matter)











RESULTS

Figure 1 shows the baseline post-contrast T1-weighted image for one patient who underwent G207 therapy, and the ROIs from which longitudinal **p:q** data were generated. Figure 2 shows the **p:q** space for three compartments of the baseline study. The "tumor" region for this patient was positioned to be at the center of two virus inoculation sites. Tumor margins in all patients consistently demonstrate decreased anisotropy (**q**=0.16±0.19) and increased isotropy (**p**=2.38±0.31), suggesting white matter (WM) destruction. Our **p:q** data agree with earlier findings reported in literature[3]. Contralateral healthy tissue **p:q** data consistently demonstrate a narrow range of **p** values. Figures 3 and 4 show how the **p:q** space varies in tumor regions of the brain. For all studies, tumor regions showed increased isotropy (**p**=1.09±2.57) with a large variation. Under local therapy, the anisotropic component remained consistent for tumor margins (**q**=0.16±0.06) and for tumor (**q**=0.17±0.11), while under global therapy, the anisotropic component for tumor margins, (**q**=0.25±0.12) and tumor, (**q**=0.29±0.18) showed larger variations over time. All **p** and **q** units are in 10^{-3} mm^{2}s^{-1}. Local G207 therapy patients exhibited a narrower range of tumor tissue isotropy and anisotropy variation compared to patients undergoing chemo/radiation therapy. Finally, the **p**:**q**-segmented images in figure 5 allow local evaluation of changing tissue compartments as assessed by DTI.

CONCLUSION

The **p:q** approach to evaluating MR diffusion tensor data is quantitative and permits longitudinal evaluation of disease progression and treatment efficacy. It reveals a dimension, not directly available by inspecting parametric maps such as fractional anisotropy and diffusivity. The **p**:**q** weighted segmentation provides a method to longitudinally track tumor and surrounding tissue compartments. We observe white matter destruction in regions of tumor infiltration regardless of choice of therapy. Preliminary evaluation of the **p**:**q** diffusion model suggest that it could be used to evaluate and compare local and global therapy options, which, in turn, may assist in determining optimal treatment strategies for glioma.

REFERENCES

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