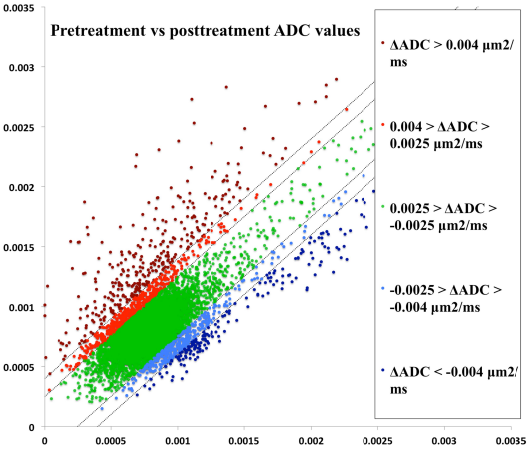
Early Serial Functional Diffusion Mapping in Patients with Newly Diagnosed Glioblastoma During Combined Chemoradiation and Anti-angiogenic Treatment

Pavlina Polaskova[1], Marco C. Pinho[1], Kyrre E. Emblem[1], Jayashree Kalpathy-Cramer[1], Dominique Jennings[1], Elizabeth Gerstner[2], A. Gregory Sorensen[3], Alexander S.R. Guimaraes[1], and Tracy T. Batchelor[2]

[1]A.A. Martinos Center for Biomedical Imaging / Massachusetts General Hospital, Charlestown, Massachusetts, United States, [2]Massachusetts General Hospital Cancer Center / Harvard Medical School, Boston, Massachusetts, [3]Radiology, Harvard Medical School

Purpose

Functional diffusion mapping (fDM) is a promising new technique for monitoring glioblastoma (GBM) therapy [1,2]. Traditionally, functional diffusion maps are derived using diffusion magnetic resonance imaging at two imaging time points - one before therapy onset and one intra- or post-therapy (typically 4-6 weeks). From these, treatment response is assessed by quantifying changes in the apparent diffusion coefficient (ADC) values between the two time points. In our study, we have extended the fDM analysis to assess *early longitudinal* changes in ADC using multiple early time points instead of the previous "snapshot".



Methods

Eighteen patients with newly diagnosed GBMs (aged: 22–74 years, mean: 56 years, 27 males, 13 females) were included after signing informed consent. In addition to standard radiation therapy (60 Gray over 6 weeks) and concurrent temozolomide, all patients received daily anti-angiogenic therapy (cediranib, oral VEGF signaling inhibitor [4]). Imaging consisted of two baseline scans prior to treatment onset and then follow-up scans on day +1, +8, +15, +22, +29, +36, +43, +50. In addition to standard anatomical MRI, ADC maps were calculated from diffusion-weighted images with repetition-time TR=7500 ms, echo-time TE=84 ms and b-values of 0 and 700 s/mm^2 in 42 directions. Functional diffusion maps were obtained by coregistering all images to a baseline image by normalized mutual information coregistration, followed by a voxel-wise subtraction of the pre-treatment ADC map from that of post-treatment. The analysis was limited to baseline contrast enhancing regions (CE-T1 ROIs) and FLAIR abnormality regions (FLAIR ROIs). Using the magnitude and direction of the changes each voxel was assigned to a color-coded group (Figure 1) that represented an increased ADC (light red and red), stable ADC (green) or decreased ADC (light blue and blue). The thresholds determining the groups have been previously shown to reflect the changes in tissue cellularity. [1,2]. The patients were split into two groups based on overall survival (A = OS<12 months, B = OS>12 months) and the differences in the relative volumes of the color-coded voxels between the two groups were assessed using linear mixed model and Mann-Whitney test with a significance level of P=0.05.

Figure 1: Example of pre and post-treatment pixel distribution (FLAIR ROI)

Results

Figure 2 shows resulting relative color-coded ADC regions from CE-T1 for the short (Fig 2A) and long (Fig 2B) survival groups. Here, compared to group B, the relative amount of green voxels (voxels with no change in ADC) in group A *decreased* significantly over time (P<0.01; at week 5 and onwards). Correspondingly, the relative amount of light blue voxels for group A *increased* significantly over time (P<0.01; at week 4 and onwards) as well as the amount of blue voxels (P<0.001; all visits included). We found similar results for FLAIR ROIs; the relative amount of green voxels in group A decreased significantly compared to group B (P<0.05; all visits included) and the relative amount of blue voxels increased significantly (P<0.01; all visits included).

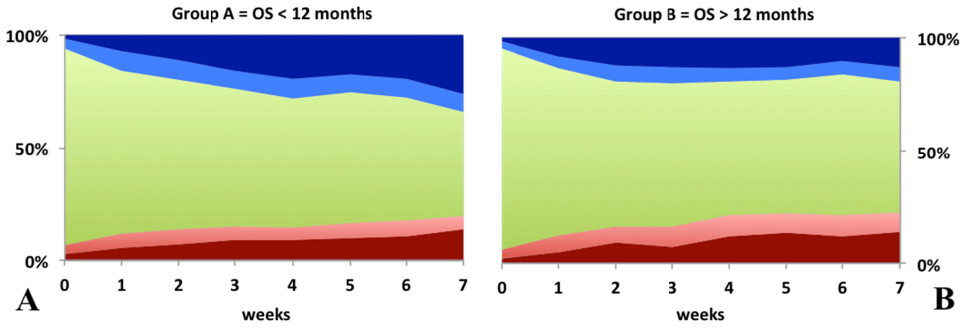


Figure 2: CE T1 ROI results shown. The individual color groups follow the same trend until week 4, after which the relative amount of light blue voxels and dark blue voxels, representing regions with decreasing ADC, increase over time. Group A also experienced a significant decrease in the relative amount of green voxels.

Discussion

Serial graded functional diffusion maps provide a new insight into a glioblastoma patient's response to therapy. It is challenging to choose one early time-point that would accurately predict the response to therapy, because the timing of significant changes (anti-vascular effect vs anti-tumor effect) is strongly dependent on the type of therapy. By looking at multiple time-points, our longitudinal assessment allows us to show early trends rather than one-time imaging changes. We observed that the continuous relative decrease in ADC (light blue and blue regions) as shown by longitudinal fDM is associated with shorter survival (possibly reflecting infiltrative tumor growth). Also, as confirmed by others, a relative higher number of voxels that change group status (i.e. green to blue) seem to be associated with shorter survival [2,3]. This work demonstrates that these trends can be distinguished as early as 4 weeks after treatment onset. We acknowledge the limitation of traditional automated registration algorithms for registering voxels from different time points in a brain experiencing substantial anatomical changes (either from tumor/edema shrinkage or expansion), and in fact, visual interpretation of these fDM reveals that a percentage of the changing voxels in the population occur in the periphery of the tumor, suggesting that this technique may be directly sensitive to volumetric changes in the tumor. We find this to be a positive discovery, potentially providing a method that is capable of sensitively extracting this feature. In fact, future work such as evaluation of the spatial relationships of the graded fDM maps might highlight these effects and provide yet a more robust and specific feature for volumetric tumor changes.

References

1. Moffat BA et al. Natl Acad Sci USA 2005;102:5524-5529
2. Ellingson BM et al. Neuro-Oncology 2011 Oct; 13(10):1151-1161.
3. Ellingson BM et al. J Magn Reson Imaging 2010 Mar; 31(3):538-548
4. Batchelor TT at al. Cancer Cell 2007 Jan;11(1):83-95.