The Functional Diffusion Map (fDM) as an Early Imaging Biomarker for High-Grade Glioma: Correlation with Conventional Radiologic Response and Overall Survival

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Introduction: Standard assessment of radiologic response (RR) in patients with brain tumors utilizes the Macdonald Criteria applied to MRI 8-10 weeks from the start of treatment. Diffusion MRI, analyzed by the functional diffusion map (fDM), may provide an earlier measure of response to predict patient survival. In the present study, instead of just correlating fDM with later RR, which is itself a surrogate end-point, we instead ascertained if diffusion MRI could directly predict patient survival.

Methods and Materials:

Patient: Sixty patients were recruited for this study. Patients underwent scans 1 week before treatment, 1 and 3 weeks after the start of treatment, and 10 weeks after the end of treatment. Radiotherapy was administered using 3D-conformal therapy with ≥6-MV photons and was performed by using standard techniques. Chemotherapy was most often provided in the adjuvant setting and was at the discretion of the treating physician.

MRI: Imaging scans were performed on a 1.5T and 3T human MRI systems. Diffusion images were acquired using a single-shot, spin-echo, diffusion-sensitized, echo-planar sequence. Sequence parameters were: TR/TE=10000/100ms; FOV=22cm; matrix=128x128; 24 slices; and slice thickness = 6mm thick. Slices were contiguous with the slice package axial-oblique. Diffusion-weighting was performed with gradients applied along all orthogonal directions with b values of 0 and 1000 s/mm^2 (b0 and b1, respectively). Scan time was approximately 40 s. The diffusion-weighted images for the three orthogonal directions and b0 image were used for calculating an ADC map.

Image Registration and fDM: All MR images were coregisterd to the initial pretreatment MR images with an automated linear affine coregistration algorithm (MIAMI Fuse; University of Michigan, Ann Arbor, MI) to maximize mutual information between the two temporally distinct three-dimensional data sets. After coregistration, brain tumors were manually contoured on the images by radiologists who defined the regions of interest on the enhancing areas on the contrast-enhanced T1-weighted images. The ADC values of each voxel within the tumor at week 1, 3 and 10 were compared with the pretherapy values. fDM was performed by segmenting the tumor into three different categories: red voxels represent volumes within the tumor where ADC increased (>55x10-5 mm^2/s), blue voxels represent a decreased ADC (<55x10-5 mm^2/s) and green voxels represent regions within the tumor that were within these thresholds. Thresholds were empirically determined to be the 95% confidence intervals (CI) calculated from normal contralateral brain tissue, including white matter, gray matter and cerebrospinal fluid. The percentage of the tumor within the three categories was then calculated as volume increased (V_I), volume decreased (V_D) and volume unchanged (V_O). Mean ADC and tumor volume were also measured.

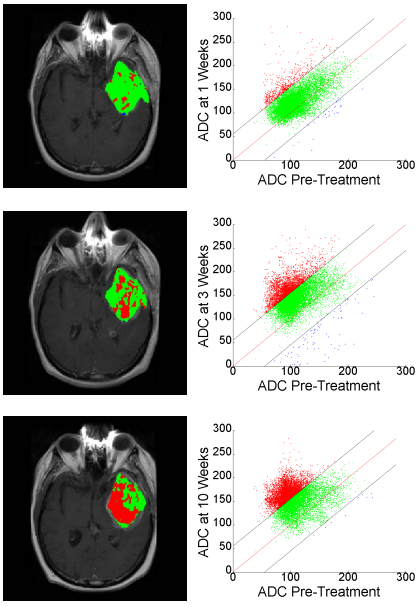

Figure 1. Functional diffusion maps for a patient treated with radiation therapy. Depicted images are single slices of the T1-post contrast scans at each time point (1, 3, and 10 weeks after radiation therapy, from top to bottom) with a color overlay of the fDM. Red voxels indicate regions with a significant rise in ADC at each time point as compared to pre-treatment, green regions had unchanged ADC, and blue voxels indicate areas of significant decline in ADC. Scatter plots display data for the entire tumor volume. The central red line represents unity while the flanking blue lines represent the 95% confidence intervals with those voxels that increased above the 95% confidence interval coded in red.

Statistical Analysis: The thresholds for determining if changes in volume, mean ADC, or fDM were correlated with patient survival were determined empirically using receiver operating characteristic (ROC) curve analysis. Survival analysis was performed by Log Rank analysis and Cox Proportional Hazards models were used for continuous or multivariable survival analyses. Statistical significance was set to P<0.05.

Results: Figure 1 is a representative fDM analysis over time for a single patient at week 1 (top), 3 (middle) and 10 (bottom). The patient scored as responsive by fDM but progressive disease by RR at week 10 and had OS of >33 months. In general, the volume of increased diffusion on fDM at 3 weeks was the strongest predictor of patient survival at one-year, with larger volume predicting longer median survival (Figure 2: 52.6 vs. 10.9 months, log-rank, p<0.003, HR 2.7(95% CI: 1.5-5.9)). The Macdonald criteria at 10 weeks were of similar prognostic value (median survival 31.6 vs. 10.9 months, log-rank, p<0.0007, HR 2.9(95% CI: 1.7-7.2)). Macdonald criteria and fDM agreed in their stratification for 75% of patients. A composite index of response including both fDM stratification at 3 weeks and RR at 10 weeks provided a more robust predictor of patient survival than either evaluation alone.

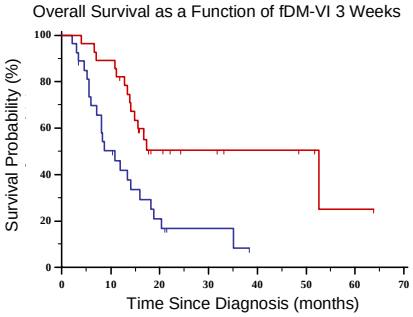

Figure 2. Overall survival as a function of fDM (V_I) stratification at 3 weeks. The Kaplan–Meier analysis of OS for patients stratified as SD/PR (*n* 31; red line) with a median survival of 52.6 months vs. those stratified as PD (*n* 29; blue line) with a median survival of 10.9 months [*P* 0.003; log-rank test; hazard ratio 2.7(95% CI: 1.5-5.9)].

Discussion: For glioma patients the current standard for determination of RR is the use of conventional MRI(1). In this study, RR based upon the Macdonald criteria at 10 weeks did correlate with one-year survival (77.8% PPV and 56.0% NPV). While this metric has been widely accepted, it does not allow for individualization of radiation treatment as the measurement is made well after the completion of therapy. Diffusion MR measures increasing movement of water molecules at the cellular level which result from changes in cellular density and precede volumetric changes(2). This information can provide rapid feedback as to the effectiveness of treatment for individual patients and may allow response adaptive therapy. The use of fDM-V_I provides a sensitive early biomarker for treatment response and was more predictive than mean changes in tumor ADC. In addition, the use of 3 week fDM-V_I as an early biomarker for one-year survival was at least as prognostic as the Macdonald criteria at 10 weeks (AUC for ROC analysis of 0.723 vs. 0.671, respectively), but was obtained 7-8 weeks earlier. Finally, combining fDM and RR into a composite provided the best response based prediction identifying 3 distinct groups of patients. This finding provides an additional application of the fDM wherein current clinical care is maintained with the addition of the 3 week fDM providing for a more accurate evaluation than either metric alone.

References:

1. Macdonald DR, Cascino TL, Schold SC, Jr., et al. J Clin Oncol 8:1277-80, 1990
2. Hamstra DA, Rehemtulla A, Ross BD. J Clin Oncol 25:4104-9, 2007