Evaluation of diffusion parameters as early biomarkers of response to therapy in high-grade gliomas

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Introduction: The apparent diffusion coefficient [1] and the fDM analysis [2] have been reported as providing early predictors of response to therapy. Key to the interpretation of these parameters is a comparison between parameters in similar regions of tissue in the pre-treatment and follow-up scans. This can be problematic when there is an extensive surgical resection, which leaves a relatively small region of residual tumor and which may lead to substantial tissue shift in the follow-up examinations. The goal of this study was to evaluate the differences in diffusion parameters for patients showing clinical progression or short term radiographic response using pre-, mid- and post-RT scans for patients who had their initial surgery and adjuvant therapy at UCSF. The parameters being assessed were differences in the values of median ADC, median FA, V_R, V_B and V_T (from fDM analyses) for patients who were classified as having clinical progression or radiographic response versus those that had stable disease.

Methods: A cohort of 44 patients with newly diagnosed grade IV glioma who received surgical resection and are being treated with the same radiation and chemotherapy schedule have been recruited to a study that includes imaging prior to treatment (pre-RT), halfway through radiation (mid-RT – 1 month) and shortly after the end of radiation (post-RT – 2 months), as well as follow-up scans every 2 months thereafter. At the current time 18 of these patients have long enough follow-up to assess clinical progression and are presented below. The MRI protocol that is being used includes pre and post-gadolinium (Gd) T1-weighted images, axial T2-weighted images, and 6 directional axial diffusion imaging with (TR/TE=1000/108ms), voxel size = 1.7×1.7×3mm, b=1000s/mm^2. Diffusion images were analyzed using in-house software to calculate the ADC and FA. A semi-automated segmentation method was applied to define the contrast-enhancing lesion (CEL) from post-Gd T1-weighted images, T2 hyperintense lesion (T2All) from T2-weighted images and the non-enhancing lesion (NEL=T2All-CEL). Diffusion images were aligned to the anatomical images from the same time point. The mid and post-RT anatomical and diffusion images were then aligned to the pre-RT anatomical images. This was performed by aligning the individual mid and post-RT pre-Gd T1-images to the pre-RT pre-Gd T1-image and applying the transformation to the other anatomical and the diffusion images. The median nADC value was calculated for each time point (pre, mid, post) within the CEL, NEL and T2ALL. Functional Diffusion Maps were calculated as described in [3] using overlapping regions of the pre and mid-RT scans within the CEL, NEL and T2ALL lesions to generate V_R, V_B and V_T (V_R+V_B) percentages. Radiographic response was determined by applying the modified Macdonald criteria [4] for changes in the CEL volume from pre to post-RT on the post-Gd T1-weighted images. Progression free survival was determined based on a cutoff time of 5 months.

Results and Discussion: Seven out of the 18 patients studied so far have shown evidence of clinical progression. Applying the modified volumetric MacDonald criteria to assess radiographic response at the post-RT scan, patients were classified as 9 partial responders (PR), 8 stable disease (SD), and 1 progressive disease (PD). The volumes at pre-, mid- and post-RT within the CEL, NEL, T2ALL were as follows. CEL: 10.2[1.99-44.7], 4.67[0.99-13.04], 4.03[0.28-20.36] cc; NEL: 18.1[0.48-97.1], 15.45[0.94-77.12], 16.99[1.81-151.44]cc; and T2ALL: 26.98[12.07-114.89], 22.63[2.92-78.11], 22.15[5.75-155.82]cc. Note that although 10 of these 18 patients has been classified as having a GTR and 8 as STR at the post-surgical scan, all of them showed at least a small CEL on the pre-RT scan. Volume changes: Patients who did not show subsequent clinical progression had a decrease in CEL volume from pre to mid ($p<0.0830$), mid to post ($p<0.001$) and pre to post ($p<0.001$) RT scans. Patients that progressed showed a significant CEL volume decrease ($p<0.0156$) in 7/7 scans from pre to mid-RT followed by a CEL volume increase ($p<0.0781$) in 6/7 scans from mid to post-RT (see Figure 1A). fDM Analysis: The fDM parameters V_R, V_B or V_T in the overlapping anatomic volumes did now show a significant difference between the 11 patients that were classified as having clinical progression and the 7 who did not. There was also no significant difference in V_R, V_B or V_T between the 9 partial responders and the 9 with stable or progressive disease based upon radiographic response. Median ADC: There were no significant differences in ADC values for patients that progressed relative to patients that did not. The data showed significant changes in ADC within the CEL between pre & post ($p<0.0156$) and between mid & post ($p<0.0156$) RT scans for patients that progressed (see Figure 1). Patients who did not progress showed changes in ADC within CEL between pre & mid ($p<0.0566$) and pre & post ($p<0.0049$) RT scans. This suggests that the greatest ADC changes for patients who did not progress appear between the pre & mid RT scans. There did not appear to be differences in ADC within any of the regions based on radiographic response. Median FA: There was a significantly lower median FA within the CEL for patients that progressed versus those that did not at the post-RT scan ($p<0.0083$). There was no significant change in the median FA between scans within any of the regions. There did not appear to be differences in FA within any of the regions based on radiographic response.

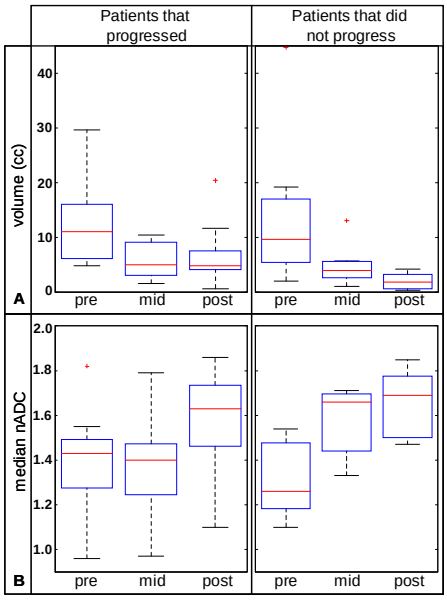

Figure 1. CEL volume (**A**) and median normalized ADC within the CEL (**B**) for pre, mid and post-RT scans separated by clinical progression. CEL volume from mid to post RT increased for patients that progressed and decreased for patients that did not progress. Median nADC shows the largest change from mid to post and pre to mid-RT scans for patients that progressed and those that did not, respectively.

Conclusion: Patients that progressed in 4 months or less tended to show a decrease in CEL from pre to mid-RT followed by an increase from mid to post-RT scans. The data that have been analyzed so far have not identified an fDM parameter that distinguished patients who exhibited clinical progression or radiographic response. Patients that progressed tended to show the greatest median ADC changes from mid to post-RT scans, whereas patients that did not progress tended to show the greatest ADC changes from pre to mid-RT scans. Median FA or changes in median FA did not show significant differences based on radiographic response or clinical progression. In conclusion, diffusion parameter values may aid in determining response to therapy but further analysis is required to determine which are the most valuable parameters for assessing these effects. More patients will be included in this analysis as the additional scans required to determine progression become available.

References: [1] Mardor et al. J Clin Oncol 21: 1094-1100 (2003). [2] Hamstra et al. PNAS, 102(46):16759-16764 (2005). [3] Moffat et al. PNAS, 102(15) 5524-5529 (2005). [4] Henson et al. AJNR Am J Neuroradiol, 29(3):419-424 (2008).

This study was supported by the NIH Grant P50CA97257, UC Discovery Grant LSIT-01-10107 and ITL-Bio-04-10148, in conjunction with GE Healthcare.