Assessment of Diffusion Parameters in Scans Prior to Progression in GBM Patients following Anti-Angiogenic Therapy

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Introduction: For GBM patients, the introduction of new anti-angiogenic therapies, which act cytostatically rather than by directly killing tumor cells, has confounded the interpretation of post-treatment changes on standard post-gadolinium T1-weighted images. Diffusion-weighted Imaging (DWI) is a functional imaging technique that has the potential to become an important adjunct to standard anatomic imaging in the management of GBM patients receiving anti-angiogenic treatments in conjunction with radiation therapy and temozolomide. The apparent diffusion coefficient (ADC) has been reported as providing early biomarkers of response to therapy[1], but further study is needed in patients receiving anti-angiogenic treatments. The purpose of this study was twofold: a) to investigate if diffusion parameters on scans prior to progression act as early biomarkers for tumor progression in areas destined to become contrast-enhancing at progression, b) to investigate if diffusion parameters can elucidate the nature of new abnormal FLAIR lesions that arise following anti-angiogenic treatment.

Methods: 13 patients with newly diagnosed grade IV glioma were examined in this study. All underwent surgical resection and were treated with radio-, chemo- and anti-angiogenic therapy. Patients were imaged prior to the beginning of therapy (post surgical resection) and scanned serially at 1 month, 2 months, and every 2 months after therapy initiation on a 3T GE EXCITE scanner with 8- channel phased array receive coil. They were scanned with six directional diffusion tensor echo-planar imaging (EPI) sequence (TR = 7,000 ms, TE = 63 ms, matrix size = 256 x 256, slice thickness = 3 mm, b = 1000 s/mm^2, FOV = 220 x 220 mm^2, NEX=4). The apparent diffusion coefficient (ADC) was calculated on a pixel-by-pixel basis using software developed in-house. The ADC maps were registered to anatomical imaging by rigidly aligning the T2-weighted (b=0) diffusion image to the T2-weighted FLAIR and applying the transformation to the ADC maps. Anatomical T2-weighted FLAIR images and post-contrast T1-weighted SPGR images were used to define the contrast-enhancing lesion (CEL), T2 hyperintense lesion (T2ALL), and cavity (CAV) ROIs. The preprogression scans of this study included those that were one scan and two scans prior to the progression scan. The length of time between progression and the first preprogression scans varied from one month to two months, depending on whether a patient progressed early or later in the course of therapy. Individual preprogression pre-Gd T1-images were aligned to the progression pre-Gd T1-images and the transformation was applied to the other anatomical images. Preprogression diffusion scans were aligned to the newly aligned preprogression FLAIR images. Preprogression CAV and CEL ROIs were aligned to their newly aligned T1-image preprogression scans. Preprogression T2ALL ROIs were aligned to their newly aligned T2-weighted FLAIR images. **Figure 1** demonstrates creation of new contrast-enhancing lesion ROIs (NEW_CEL) and modified T2ALL ROIs (T2ALL_M). Statistical signrank tests were used to compare ADC values of NEW_CEL and T2ALL_M ROIs between scans and between CEL and T2ALL at individual scans.
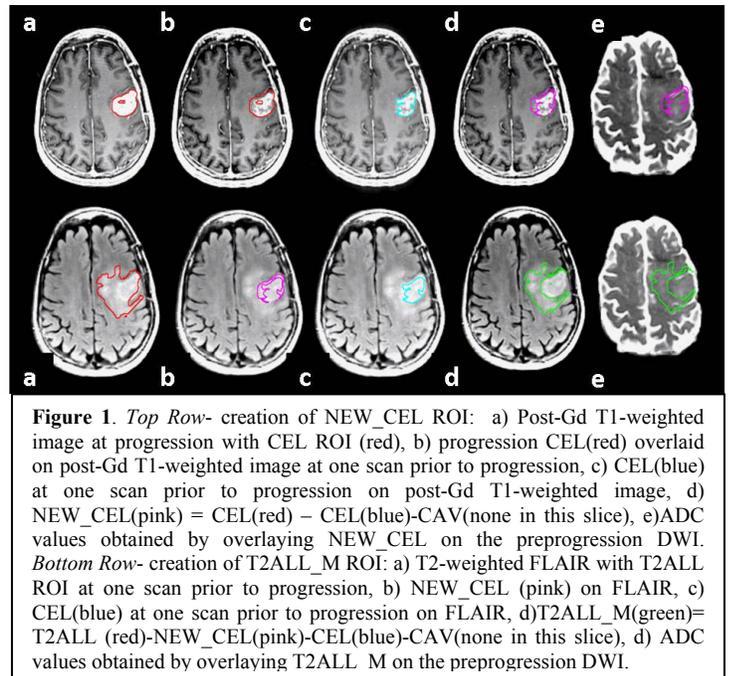

Figure 1. *Top Row*- creation of NEW_CEL ROI: a) Post-Gd T1-weighted image at progression with CEL ROI (red), b) progression CEL(red) overlaid on post-Gd T1-weighted image at one scan prior to progression, c) CEL(blue) at one scan prior to progression on post-Gd T1-weighted image, d) NEW_CEL(pink) = CEL(red) – CEL(blue)-CAV(none in this slice), e)ADC values obtained by overlaying NEW_CEL on the preprogression DWI. *Bottom Row*- creation of T2ALL_M ROI: a) T2-weighted FLAIR with T2ALL ROI at one scan prior to progression, b) NEW_CEL (pink) on FLAIR, c) CEL(blue) at one scan prior to progression on FLAIR, d)T2ALL_M(green)= T2ALL (red)-NEW_CEL(pink)-CEL(blue)-CAV(none in this slice), d) ADC values obtained by overlaying T2ALL_M on the preprogression DWI.

Results: *Median nADC NEW_CEL*- There is no significant difference in median nADC between the CEL and NEW_CEL at one scan prior to progression (p < 0.1465). There is a significant difference in median nADC between the CEL and NEW_CEL at two scans prior to progression (p < 0.0002) (see **Tables 1** and **2**). ADC median values increased in areas that later became contrast-enhancing on the progression scan. *nADC 10% NEW_CEL*- signrank tests performed on CEL and NEW_CEL values indicate a statistically significant difference at one scan and two scans prior to progression (p < 0.0266 and p < 0.006 respectively). *Median nADC T2ALL_M*- there is a significant difference in median nADC between CEL and T2ALL_M of the first and second scan prior to progression (p < 0.0171 and p < 0.0479). There is no significant difference between T2ALL_M at the first preprogression scan and T2ALL_M at the second preprogression scan (p < 0.3054). These results may demonstrate that new areas of FLAIR abnormality are secondary to

Parameter	NAWM	CEL	T2ALL	NEW_CEL	T2ALL_M
ADC median	788 ± 25	1415 ± 246	1251 ±153	1343 ± 316	1220 ± 151
ADC median 10%	665 ± 14	1008 ± 158	881± 144	930 ± 132	842 ± 192
nADC median	1.0 ± 0	1.80 ± 0.33	1.59 ± 0.19	1.70 ± 0.38	1.55 ± 0.19
nADC 10%	0.85 ± 0.02	1.28 ± 0.21	1.12 ± 0.17	1.18 ± 0.16	1.07 ± 0.24

Table 1. ADC Values at One Scan Prior to Progression

Parameter	NAWM	CEL	T2ALL	NEW_CEL	T2ALL_M
ADC median	792 ± 23	1416 ± 292	1289 ± 199	1239 ± 268	1239 ± 207
ADC median 10%	676 ± 23	978 ± 172	908 ± 101	864 ± 216	910 ± 106
nADC median	1.0 ± 0	1.79 ± 0.35	1.63 ± 0.26	1.56 ± 0.32	1.57 ± 0.27
nADC 10%	0.85 ± 0.02	1.23 ± 0.21	1.15 ± 0.12	1.09 ± 0.27	1.15 ± 0.14

Table 2. ADC Values at Two Scans Prior to Progression

the effects of anti-angiogenic therapy on surrounding areas of brain tissue and may not represent active tumor processes within this area. *nADC 10% T2ALL_M*-there is a statistically significant difference between T2ALL_M and CEL nADC 10% values at the first but not the second scan prior to progression (p < 0.0479 and p < 0.1909 respectively).

Conclusion: Increasing ADC values in scans prior to progression correlate with areas of new contrast-enhancement at progression. 10% nADC data supports that even areas that are putatively the most cellular develop higher ADC as they become enhancing. These new areas of enhancement in treated GBM patients likely contain areas of treatment-induced necrosis and tumor. New FLAIR abnormalities following initiation of anti-angiogenic therapy may represent anti-angiogenic treatment effect on the blood brain barrier rather than infiltrative tumor processes. ADC data from this study demonstrate that DWI parameter values may aid in assessing treatment effect prior to evident new contrast-enhancement and in assessing new FLAIR lesions in GBM patients receiving anti-angiogenic therapies. More patients will be included in this analysis as additional patients enrolled in the study undergo progression.

References: [1] Mardor et al. J Clin Oncol 21: 1094-1100 (2003). *This study was supported by the NIH Grant RO1CA127612-01A1 and NIH CA118816-01A2*