

# Multi-exponential Diffusion Imaging: Clinically feasible Multiple B-value Diffusion Imaging for high grade gliomas

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**Introduction:** One of the greatest challenges in neuroimaging of high grade gliomas is the difficulty of differentiating active tumor, tumor related reactive edema, edema infiltrated with tumor cells, and treatment effect. The problem is compounded by the fact that high-grade gliomas are inherently heterogeneous lesions whose geographic heterogeneity become even more complex following therapy. It would be of paramount clinical importance if imaging can offer more specific information on biologic changes in tumor and its surrounding brain following therapy. In order to further characterize differences between tumor related edema and active tumor, the deviation from mono-exponential decay in multiple high b-value diffusion weighted imaging has been proposed to differentiate the 2 processes<sup>1</sup>. However, this requires a long imaging time, which is not clinically feasible. The goal of this study was to develop and validate a two b-value diffusion sequence that captures the deviation from mono-exponential decay signal (dS) in a time efficient clinical scan; and to test how well this signal can differentiate tumor (enhancing lesion, CEL) from edema (non-enhancing lesion, NEL) as compared to the conventional apparent diffusion coefficient (ADC) and fractional anisotropy (FA) in high grade gliomas.

**Methods:** The sequence consisted of 6 directional DTI with low ( $b=1000\text{s/mm}^2$ ) and high ( $b=2250\text{s/mm}^2$ ) b-values. The eigenvalues were calculated for both sequences. The main eigenvalue component was used to calculate (a) the measured high signal,  $S_{hm} = S_0 \cdot \exp(-b_{high} \cdot \lambda h)$  from the high b-value eigenvalue ( $\lambda h$ ) and (b) to extrapolate the expected high signal,  $S_{he} = S_0 \cdot \exp(-b_{high} \cdot \lambda l)$  from the low b-value eigenvalues ( $\lambda l$ ), assuming a mono-exponential decay. The difference in the signals,  $dS = S_{hm} - S_{he}$ , is the measured deviation from mono-exponential decay. Thirty-eight high grade glioma patients (36 GBM, 1 anaplastic astrocytoma, 1 anaplastic oligodendroglioma) were scanned on a 3T GE Scanner using this technique. The MRI protocol included pre and post-gadolinium (Gd) T1-weighted image, axial T2-weighted images, and six directional axial diffusion tensor imaging with (TR/TE( $b=1000, b=2250$ ))= 7000/61.9, 76.4ms), voxel size =  $1.7 \times 1.7 \times 3\text{mm}$ , NEX=4, Total scan time=7min. Diffusion images were analyzed using in-house software to calculate the ADC, FA and the main component eigenvalue ( $\lambda l$ ). The Signal Difference (dS) maps were generated as explained above. The contrast enhancing lesion (CEL) and the non-enhancing lesion (NEL) were defined on the post-Gd T1-weighted image and the pre-Gd T2-weighted image, respectively. Normal appearing white matter (NAWM) was defined using the pre-Gd T1-weighted image and the ADC, FA and dS were normalized by dividing by the median respective values within the NAWM to generate nADC, nFA and ndS maps. The absolute percent difference between the median NEL and CEL values per map were calculated,  $((\text{CEL}-\text{NEL})/\text{NEL} \cdot 100)$ , and compared between maps using the Wilcoxon signed rank test. Of the 38 patients, 15 patients had questionable tumor progression vs. treatment response, categorized into 8 recurrent and 7 non-recurrent based on changes in the CEL volume and/or follow-up information. The absolute percent difference between the max NEL and CEL values were calculated per map.

**Results and Discussion:** Figure 1 shows a boxplot of the percent difference between the the CEL and NEL values per patient with a median % difference for ndS, nADC and nFA of 25.7%, 10.2% and 14.2%, respectively. There was no significant percent differences between nADC and nFA ( $p=0.1296$ ), but a significant difference between ndS and both nADC and nFA ( $p<0.0001$  and  $0.0336$ , respectively). Figure 2 shows dS, ADC and FA maps with NEL and CEL ROIs for (a) recurrent and (b) non-recurrent patient. The recurrent patient shows much higher dS values within the CEL as compared to the NEL, while the non-recurrent patient shows no hyperintensity and similar values in both CEL and NEL. The % difference between CEL and NEL split into a recurrent (R) and non-recurrent (NR) group are shown in Figure 3. There was no significant difference between recurrent and non-recurrent nADC and nFA values ( $p=0.7789$  and  $0.8665$ , respectively). The p-value for the difference between the two groups for ndS was  $p=0.0541$ , with a median difference of 55% for recurrent and 18% for non-recurrent.

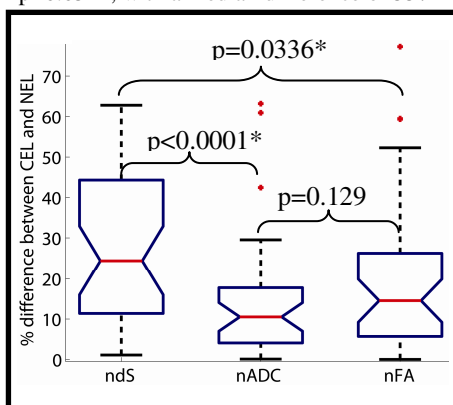


Figure 1. Percent difference between CEL and NEL for ndS, nADC and nFA maps showing a significantly larger difference in ndS compared to both nADC or nFA.

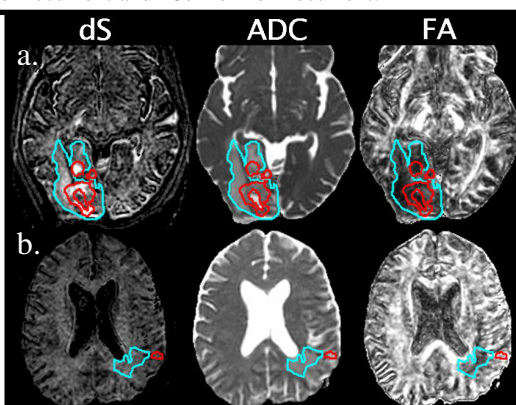


Figure 2. Maps of dS, ADC and FA for (a) recurrent GBM and (b) non-recurrent GBM within the non-enhancing lesion (cyan) and contrast enhancing lesion (red).

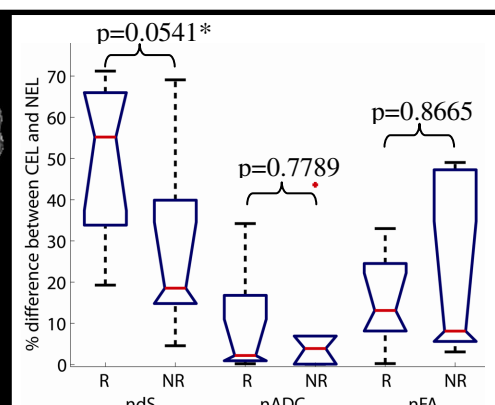


Figure 3. Recurrent and non-recurrent boxplots for ndS, nADC and nFA % differences, showing a significantly higher percent difference between NEL and CEL for ndS but not for nADC or nFA.

**Conclusion:** Multi-exponential diffusion imaging of high grade gliomas shows spatial variation within enhancing and non enhancing lesions, which may be helpful in characterizing active tumor and tumor related edema. This technique may also be utilized to distinguish progressive tumor from treatment response within the contrast enhancing lesion for recurrent patients. Further studies will verify this variation with image-guided biopsy.

References: [1] Maier SE et al. Radiology 2001; 219:842-9.

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