Apparent Diffusion Coefficient is Higher in EGFR+ versus EGFR- Anaplastic Astrocytoma

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Introduction: Overexpression of the epidermal growth factor receptor (EGFR+) in high grade glioma has been associated with increased tumor aggressiveness and decreased patient survival[1]. A recently published diffusion tensor imaging (DTI) study of low grade glioma reported a higher apparent diffusion coefficient (ADC) in tumors with molecular markers of poor progonosis[2]. The association was so robust that the normalized median ADC within the T2-hyperintense lesion was able to classify tumors with poor and favorable markers with high accuracy[2]. Since EGFR overexpression is a prognostic marker for high grade astrocytoma, we questioned whether the ADC would differ in Grade 3 anaplastic astrocytoma (AA) that do not express EGFR (EGFR-) compared with those that overexpress EGFR (EGFR+). We also questioned whether the metabolic profile, assessed with three-dimensional magnetic resonance spectroscopic imaging (3D-MRSI), would differ for the two groups. Based on our previous studies we hypothesized that the more aggressive EGFR+ AA would have higher ADC, choline-containing compounds (CHO), and lipid (LIP) than the EGFR- AA.

Methods: Treatment-naïve patients harboring brain lesions that were subsequently determined to be AA underwent a pre-surgical MR exam on a 3T GE scanner. The exam included a T2-weighted fast low-angle inversion recovery (FLAIR) sequence (*PROPELLOR, TR/TE/TI = 9500/125/2375 ms, matrix = 256 × 256, FOV = 240x240mm, slice thickness = 5 mm, NEX = 1.5*), a six-direction DTI sequence (*echo-planar spin-echo, ASSET acceleration = 2, TR/TE = 7000 ms/ 63 ms, matrix = 256 × 256, FOV = 240x240mm, slice thickness = 3 mm, b = 1000 s/mm2, NEX = 4*) and 3D-MRSI (*lactate-edited flyback echo-planar spectroscopic imaging (EPSI), TR/TE = 1104/144, matrix = 16x16x16, FOV = 160x160 mm, slice thickness = 10mm, NEX = 1*). ADC and FA maps were calculated, resampled, and aligned to the FLAIR images. 3D-MRSI data were reconstructed and aligned to the FLAIR. Image maps of CHO, creatine (CRE), N-acetylaspartate (NAA), lactate (LAC), and LIP were generated by resampling the metabolite data to 128x128x128 using sinc interpolation. Regions-of-interest (ROIs) encompassing the T2-hyperintense lesion on the FLAIR and the normal-appearing white matter (NAWM) were generated using a semi-automated algorithm. Median normalized ADC and FA values were calculated by dividing the median value in the T2 lesion by the median value in the NAWM. Normalized CHO, CRE, and NAA values were calculated by dividing the mean value in the T2 lesion by the mean values in the NAWM. LAC and LIP content within the T2-lesion was normalized to the standard deviation of the noise within a non-peak region of the spectrum. The EGFR status of the tumors was determined by immunohistochemical assessment of tumor biopsies. A one-way ANOVA with a significance level of $p < 0.05$ was used to compare the MR values within EGFR+ and EGFR- AA.

Table 1. Mean +/- SD of MR parameters in the T2-hyperintense lesion of AA. (nmed = normalized median, nmean = normalized mean)

	EGFR neg	EGFR pos	P
nmedADC	1.8 ± 0.3	2.1 ± 0.2	0.004*
nmedFA	0.5 ± 0.2	0.4 ± 0.1	0.423
nmeanCHO	4.9 ± 2.4	5.5 ± 4.3	0.713
nmeanCRE	3.8 ± 1.9	2.7 ± 1.5	0.181
nmeanNAA	1.8 ± 0.6	1.4 ± 0.9	0.258
nmeanLAC	17.2 ±13.3	10.4 ± 13.9	0.288
nmeanLIP	12.7 ± 12.9	13.4 ± 17.4	0.910
CHO:CRE	1.3 ± 0.3	2.1 ± 1.7	0.170
CHO:NAA	2.9 ± 1.2	4.8 ± 4.9	0.266

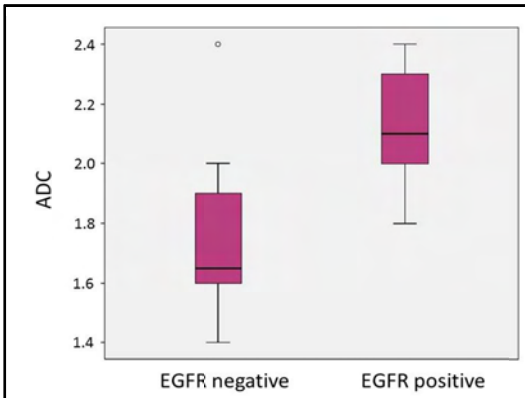

Fig 1. Normalized median ADC is higher in EGFR+ AA

Results: We studied 20 patients with AA, 10 of which were EGFR+ and 10 that were EGFR-. The ADC was the only parameter that differed between the EGFR+ and EGFR- AA (Table 1, Fig 1). The normalized median ADCs in the EGFR- AA were similar to ADCs observed in low grade glioma with favorable prognostic markers (Fig 2). Although there were trends towards lower Cre and higher Cho:Cre ratios in the EGFR+ AA they were not statistically significant.

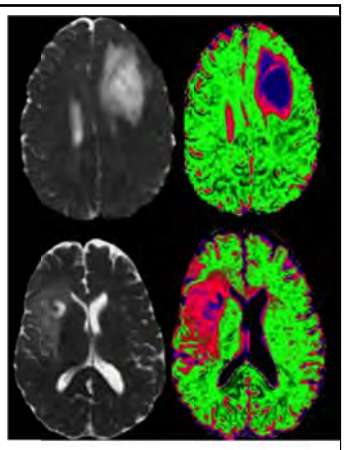

Fig 2. ADC maps (left) and colormaps (right) of EGFR+ (top) and EGFR- (bottom) AA. Pink are ADCs previously associated with favorable prognosis in low grade glioma while blue indicates ADCs associated with poor prognosis.

Discussion: The higher normalized median ADC in the EGFR+ AAs was consistent with our previous study that showed higher ADCs in low grade glioma that had molecular markers of poorer prognosis. The fact that none of the tumors had frank necrosis and that there was no difference in the CHO suggests that differences in cell density was not the primary reason for the difference in ADC, although this assertion needs to be verified. Histologic studies of biopsies from these patients are currently being performed to compare the cell density and microstructure of EGFR+ and EGFR- AA and the relationship to ADC. These results suggest that the ADC may be useful for identifying AA patients that have a less favorable prognosis, particularly in cases where the tumor is inaccessible for surgical diagnostic biopsy.

References: (1) Dehais, C., et al Cancer, 2006. 107(8): p. 1891-7. (2) Khayal,I et al Neuro Oncol 2011 13(11):1192-201.

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