Correlation of DTI Metrics with Proliferation Index and Survival Analysis in Glioblastomas

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Introduction:

Glioblastoma is the most common primary intracranial tumor; however, despite the use of aggressive combinations of surgery, radiation and chemotherapy, the prognosis of these patients remains poor[1,2]. Tumor cellularity and proliferation index has been associated with patient prognosis and survival. MIB-1 labeling index has been used for the evaluation of tumor proliferation and has been correlated with aggressiveness of brain tumors[3,4]. However, in vivo imaging techniques providing information about tumor proliferation and microstructure pre-operatively are limited, mostly due to the resolution of most of the clinically available imaging tools. Diffusion tensor imaging (DTI) provides quantitative information about the magnitude and directionality of water diffusion along a vector in a 3-dimensional space[5]. Although DTI has been shown to be useful in pre-operative grading and postoperative assessment of gliomas[6,7], its value for predicting survival has not been fully discussed. The purpose of this study was to retrospectively correlate various DTI metrics [fractional anisotropy (FA) and apparent diffusion coefficient (ADC)] in patients with glioblastomas with the degree of tumor proliferation index determined histologically and also with patient survival analysis.

Materials and Methods:

Subjects: Thirty-four patients (22 males, 12 females; age: 62.24±13.89 yrs) with treatment naïve glioblastomas were retrospectively studied. ***Imaging protocol:*** Conventional MRI and DTI data were acquired on a 3.0 Tesla MR imaging system (Excite HD, GE Medical Systems, Milwaukee, WI) using a 8-channel head coil. DTI was performed in the axial plane with single-shot spin-echo-echo-planar imaging with the following parameters: TR=17000 ms; TE=84.3 ms; diffusion gradient encoding in 26 directions; b=0, 1000 s/mm^2; field of view=250 mm^2; image matrix of 96×96; slice thickness of 2.6 mm with no gap and NEX=1. The DTI data was processed and evaluated using DTI Studio (Version 2.5, H. Jiang, S. Mori, John Hopkins University). The region-of-interest (ROIs) was determined on a slice demonstrating the maximum tumor size on post-contrast T1-weighted images. In each patient, ROIs were manually drawn over the contrast enhancing lesion (CEL) and non-enhancing lesion (NEL) of tumor. Another ROI was drawn as an internal control in the normal appearing white matter (NAWM) in the contralateral hemisphere. For all these ROIs, care was taken to avoid cystic, necrotic or haemorrahagic components of the tumor with reference to conventional MR images. ***Statistical analysis:*** In the following analyses, the endpoint of interest was progression free survival (PFS), which was computed as the time between the pre-operative MRI and progression or death. Patients without progression and still alive were censored at their last follow-up. Kaplan-Meier estimates and Cox proportional hazards regression methods were used to assess the relationship of FA, ADC (× 10^{-3} mm^2/s) and MIB-1 (%) with PFS. For FA and ADC, minimum values (FA_{min}, ADC_{min}) as well as the mean values (FA_{mean}, ADC_{mean}) were considered. Various cutpoints for FA, ADC and MIB-1 were evaluated to determine which were most associated with the endpoint (i.e. had p-values less than 0.10). All data analysis was conducted using SAS (SAS version 9.2, SAS Institute Inc., Cary, NC).

Results: FA_{mean} values of glioblastoma CEL (0.212±0.064) and NEL (0.199±0.053) were significantly lower than that of NAWM (0.493±0.052) while no significant difference was observed between CEL and NEL ($p<0.05$, one way ANOVA with Bonferroni multiple comparison). The various cutpoints which were considered for FA, ADC and MIB-1 along with the corresponding p-values for PFS are shown in Table. For FA_{min}, no cutpoints were found to be associated with PFS. For FA_{mean}, the cutpoint of 0.2 was statistically significant for PFS (p=0.035). For ADC_{min}, the cutpoint of 0.6 was associated with PFS (p=0.106) and for ADC_{mean}, the cutpoint of 1.5 was associated with PFS (p=0.074). For MIB-1, the cutpoint of 30% was associated with PFS (p=0.011). Correlation between MIB-1 and ADC_{min} was not statistically significant (r=-0.162, p=0.266). Correlations between MIB-1 and FA_{min} (r=-0.152, p=0.397) and FA_{mean} (r=-0.105, p=0.562) were not also statistically significant.

Discussion: Our results suggest that pre-treatment tumoral ADC values could be used as a prognostic indicator in patients with glioblastomas. ADC_{min} was used to calculate PFS in these patients based on the hypothesis that this value reflects the sites of highest cellularity within heterogeneous tumors and that these sites are of prognostic importance. Tissues with high cellularity have a low ADC because the mobility of water protons is impeded whereas cystic regions have a high ADC owing to the rapid diffusion of water protons[8]. Our observation of low ADC associated with poorer survival rate is similar to what has been reported in previous studies[9,10]; however the cutoff values used for ADC_{min} were different, most likely due to the 3T MR scanner used for all the cases in our study.

In our study, the cutpoint of 0.2 in FA_{mean} was considered for the prediction of prognosis. Patients with the lower FA_{mean} had a significantly lower PFS rate or worse outcome than those with favorable prognosis. No significant positive correlation between FA_{mean} and MIB-1 indicates that cellularity is not the only factor that affects the directionality of water diffusion. We speculate that FA value in glioblastomas is largely affected by the lack of neuron or axon destruction rather than cellularity. Lower mean FA values in glioblastomas compared to contralateral NAWM may be due to the destruction or infiltration of WM fibers resulting in a decrease in directionality of water diffusion and reduced FA. More the destruction or infiltration of fibers due to tumor aggressiveness, the patients will have lower survival rate or poorer prognosis.

We conclude that, various DTI metrics can be used as a sensitive and early indicator for disease free survival in patients with glioblastomas. This could be useful for treatment planning as high-grade gliomas with lower ADC and FA values can be treated more aggressively.

Table: Various cutpoints for fractional anisotropy (FA), apparent diffusion coefficient (ADC) and MIB-1proliferation index associated with progression free survival (PFS) in patients with glioblastomas

Variable	Cutpoint	PFS rate (6 month)	p-value*
FA_{mean}	≤0.02	48.6% (n=17)	0.035
	>0.2	73.7% (n=17)	
ADC_{min}	≤0.6	23% (n=8)	0.106
	>0.6	68% (n=26)	
ADC_{mean}	≤1.5	64.2% (n=25)	0.074
	>1.5	66.7% (n=9)	
MIB-1	≤30%	72.7% (n=23)	0.011
	>30%	28% (n=10)	

* p-value from Cox proportional hazards model.

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