Diffusion-Weighted MR Imaging and MGMT Methylation Status in Glioblastoma: A Reappraisal of the Role of Preoperative Quantitative ADC Measurements

Methylation of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase (MGMT) has been well described as one the most significant biomarkers of glioblastoma (GBM) patient prognosis and response to standard first-line chemotherapy treatment with temozolomide.[1] As such, we read with great interest the recent study published in *AJNR* in May 2011 entitled "Apparent Diffusion Coefficient Histogram Analysis Stratifies Progression-Free Survival in Newly Diagnosed Bevacizumab-Treated Glioblastoma" by Dr. Pope and colleagues.[2]

A significant conclusion of this study was that "lower ADC is associated with tumor MGMT promoter methylation." This is a finding of significant interest to radiologists and oncologists alike as it suggests that ADC measures can potentially function as both a prognostic and predictive imaging biomarker and thereby act as a surrogate for the reference standard pathologic determination of MGMT methylation status. The authors arrived at this conclusion based on a pixel-by-pixel ADC histogram analysis with bimodal curve fitting of enhancing tumor in 89 patients with GBM with pathologically confirmed methylation status. This analysis showed a mean ADC of 1071 $\times$ 10^{-6}mm^2/s for 36 methylated tumors versus 1183 $\times$ 10^{-6}mm^2/s for 53 unmethylated tumors, with a *P* value of .01 between the groups.

To assess the applicability of these findings to our own patients, we retrospectively performed blinded quantitative ADC measurements in 105 treatment naïve, preoperative patients with GBM with pathologically confirmed MGMT promoter methylation status determined through real-time methylation specific polymerase chain reaction. Our goal was to build on the work of Pope et al[2] by using an ADC quantification technique readily available from a popular vendor and applicable to daily clinical practice. We performed region of interest analysis by using an off-line commercially available workstation (Advantage; GE Healthcare, Milwaukee, Wisconsin) and software (FuncTools 9.04b; GE Healthcare) to calculate quantititative ADC metrics. We drew ROIs around the contrast enhancing tumor and derived ADC_{mean}, ADC_{min}, and ADC_{max} values. In addition, by using a validated and commonly used standardized technique,[3,4] we manually placed 4 small circular ROIs (30–50 mm^2) in the enhancing tumor to select the region of maximal ADC hypointensity and recorded this minimum value as $ADC_{region\ of\ interest}$. We also obtained ADC_{ratios} by dividing $ADC_{region\ of\ interest}$ by ADC_{normal} with a region of interest placed in normal contralateral brain. Results after Wilcoxon rank-sum tests are summarized in the Table.

Unlike Pope et al,[2] in our slightly larger series (n = 105 versus n = 89) by using more widely available postprocessing tools (ADC region of interest analysis on commercially available software versus ADC histogram analysis), we were not able to find a correlation between ADC values and MGMT promoter status (*P* values >.12). Although our divergent conclusions may in part be related to differences in methods, we suggest that the role of DWI and ADC quantification to predict glioblastoma prognosis and MGMT promoter status requires more investigation and validation before wide adoption into routine clinical practice.

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Table 1: Relationship between ADC metrics and MGMT status

Diffusion MRI	MGMT Methylation Status (median, range)		*P* Value
	No (n = 66)	Yes (n = 39)	
ADC_{mean}	0.00120 (0.00012–0.00177)	0.00123 (0.00011–0.00197)	.48
ADC_{min}	0.00085 (0.00016–0.00838)	0.00084 (0.00054–0.00117)	.85
ADC_{max}	0.00184 (0.00102–0.00289)	0.00212 (0.00086–0.00328)	.12
ADC_{ROI}	0.00097 (0.00067–0.00159)	0.00099 (0.00068–0.00147)	.91
ADC_{ratio}	1.30144 (0.90670–1.90337)	1.23086 (0.18519–2.33216)	.29

ADC expressed as mm^2/s

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