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Continuing the search for MR imaging biomarkers for MGMT promoter methylation status: conventional and perfusion MRI revisited

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Dear Sir:

It is with great interest that we read the recent investigation by Moon et al. [1] that assessed the value of preoperative imaging in the prediction of methyl-guanine methyl transferase (MGMT) promoter methylation status in 24 patients with high-grade gliomas. By evaluating preoperative computed tomography (CT), conventional magnetic resonance (MR) imaging, perfusion MR imaging, and diffusion tensor imaging (DTI), they found that MGMT

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promoter methylation was associated with ill-defined tumor margins, lower CT attenuation, higher apparent diffusion coefficient (ADC), and lower fractional anisotropy (FA). The remainder of the qualitative conventional MR imaging measures (ring versus nodular tumor enhancement, presence of a cystic portion, and heterogeneity of the signal intensity on the T2-weighted images) as well as perfusion MR imaging (as assessed by relative cerebral blood volume) were not found to be different between groups. Their results are relevant given the recently described prognostic significance of MGMT promoter methylation status in the survival of patients with high-grade gliomas [2, 3]. An imaging biomarker for MGMT methylation could serve as a surrogate for histopathology in those cases where pathology sampling is suboptimal, or could be of value if future preoperative treatment regimens are developed and based on presumed MGMT status. However, a major confounding factor in that study is the fact that both WHO grade III tumors and grade IV tumors were included, with a relatively small number of patients in each group. WHO grade III and IV tumors are a highly heterogeneous group in terms of histological findings, biological behavior, and radiographic characteristics. In that study, a total of 57.1% of grade III tumors were methylated versus only 41.1% in the grade IV tumors. Although this difference has not reached statistical significance, likely reflecting small sample sizes, the possibility that radiographic differences found between the methylated and unmethylated groups could at least in part reflect differences in histological grade cannot be excluded. The radiographic differences among the different types of malignant gliomas such as anaplastic oligodendrogliomas, grade III astrocytomas, and glioblastomas have been well described and cannot be ignored. The distribution of the different radiographic parameters according to tumor type and grade was not provided in that paper.

We would like to take this opportunity to report our experience with attempting to find MR imaging parameters that may predict MGMT promoter methylation status. We examined the preoperative MR imaging of patients with malignant glioma treated at our institution and who had the MGMT promoter methylation status determined. To improve the homogeneity of the sample, we restricted the analysis to patients with glioblastomas (WHO grade IV tumors). The cohort of 77 patients all underwent preoperative conventional MR imaging with standard sequences (axial diffusion, T1-weighted, T2-weighted, FLAIR, gradient-echo or susceptibility-weighted, and triplanar post-gadolinium T1-weighted images). We qualitatively assessed, by consensus of experienced neuroradiologists (6 and 11 years experience), the following signs: (1) enhancing border sharpness; (2) cystic/necrotic change; (3) hemorrhage; (4) T2-isointense signal; (5) diffusion restriction; (6) nodular enhancement; (7) subependymal enhancement; and (8) multifocal discontinuous enhancement. In addition, 49 of the 77 patients had T2* dynamic susceptibility contrast perfusion-weighted MR imaging, where rCBV was recorded using maximal region-of-interest (ROI) technique (in a fashion similar to the manner described by Moon et al. [1]) as well as additional perfusion metrics including peak height (PH), relative peak height (rPH), and percentage signal recovery (PSR).

Similar to Moon et al. [1], we found that 31 of our 77 patients (40.2%) had methylation of the MGMT promoter, compared with 46 (59.8%) with unmethylated MGMT promoter. Despite measuring additional perfusion metrics such as PH, rPH, and PSR, we also found

MR perfusion-weighted imaging to have no value in predicting MGMT promoter methylation, with p values ranging from 0.66 to 0.87 (Table 1).

However, none of our conventional MR imaging signs was significantly associated with MGMT methylation promoter status, with p values ranging from 0.14 to 0.97 (Table 2). Moon et al. [1] found that ill-defined tumor margins were associated with methylation of the MGMT promoter, which could be potentially explained by the fact that some lower-grade tumors tend to have ill-defined margins and have higher frequency of MGMT promoter methylation. Moon's findings also disagree with a study performed by Drabycz et al. [4] in 59 patients, which found that ring enhancement was highly associated with unmethylated MGMT promoter status ($p=0.006$) and in an elegant texture analysis found T2-weighted texture features to be important ($p<0.05$). Moreover, an additional study by Eoli et al. [5] in 86 patients found that ring enhancement was associated with unmethylated MGMT status ($p<0.005$). Clearly, additional studies are needed to settle this question.

We did not perform DTI in our patients. It is interesting that Moon et al. found that reduced FA is associated with methylation of the MGMT promoter. They performed DTI by applying six different directions of orthogonal diffusion gradients. They do not specify the number of excitations (NEX) used, but we estimate that at 3 T with a commonly applied NEX=6 that this sequence required approximately 2–3 min. We have considered adding DTI as a routine sequence for preoperative imaging at our institutions, but our standard DTI protocol prescribes 15 to 33 non-collinear gradient directions that may add 5–11 min to total scan time. The authors measured ROIs in the enhancing solid portions of the tumors and obtained ratios relative to ROIs in the contralateral homologous normal-appearing brain parenchyma. This technique helps mitigate but does not completely eliminate potentially dramatic regional and anatomy-specific variations in FA. Given these limitations, incorporating DTI into routine clinical practices in all preoperative imaging of high-grade gliomas may be challenging, and further validation would be needed.

Given the variability of these reports, we would urge caution in attempting to predict MGMT status based on preoperative MR imaging sequences. Our cohort of 77 patients showed no significant differences after qualitative assessment of MR imaging signs. It is therefore our opinion that, despite the interesting preliminary findings of Moon et al. and previous reports, additional studies are needed to address this critical clinical question. Although the potential role of DTI or quantitative ADC measurements in predicting MGMT status is important and warrants further investigation, qualitative measures performed at the picture archive and communication system (PACS) station that do not require sophisticated time-consuming post-processing are more likely to be adopted in standard clinical practice and are therefore more valuable to practicing radiologists. Clearly, more work is needed in this area before neuroradiologists can suggest with any reasonable degree of confidence the likely MGMT status of a high-grade glioma based on standard, conventional MR imaging sequences.

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Table 1

Relationship between perfusion metric and MGMT methylation status

Perfusion metric	MGMT methylation status, median (range)		<i>P</i> value ^a
	Unmethylated (<i>n</i> =32)	Methylated (<i>n</i> =19)	
rCBV	3.3 (1.2–7.7)	3.2 (1.4–6.5)	0.87
PH	712.5 (35.0–4,453.0)	1553.0 (72.0–2838.0)	0.79
PSR	0.8 (0.5–1.7)	0.8 (0.1–1.5)	0.70
rPH	3.2 (0.2–9.8)	3.5 (0.8–11.3)	0.66

^aBy Wilcoxon rank-sum test

Table 2

Relationship between MRI sign and MGMT methylation status

MRI sign	MGMT methylation status				P value ^a
	Unmethylated (n=46)		Methylated (n=31)		
	Number	%	Number	%	
Enhancing border sharpness					0.28
No	32	70	25	81	
Yes	14	30	6	19	
Cystic/necrotic change					0.26
No	3	7	5	16	
Yes	43	93	26	84	
Nodular enhancement					0.83
No	8	17	6	19	
Yes	38	83	25	81	
T2 isointense signal					0.37
No	21	46	11	35	
Yes	25	54	20	65	
Diffusion restriction					0.44
No	9	20	4	13	
Yes	37	80	27	87	
Hemorrhage					0.14
No	16	35	6	19	
Yes	30	65	25	81	
Subependymal enhancement					0.13
No	33	72	17	55	
Yes	13	28	14	45	
Multifocal discontinuous enhancement					0.97
No	31	67	21	68	
Yes	15	33	10	32	

^a By Chi-square or Fisher's exact test