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Prognostic Significance of MGMT Promoter Methylation Status in IDH-mutant Glioma

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Abstract

Background: The prognostic and predictive value of O6-methylguanine-DNA methyltransferase promoter (MGMTp) methylation is not well established in isocitrate dehydrogenase (IDH)-mutant gliomas. This study evaluates the survival impact of MGMTp and other clinical, molecular, and radiologic variables in low-grade and high-grade IDH-mutant gliomas.

Methods: We retrospectively evaluated 520 consecutive adult patients treated for an initial diagnosis of IDH-mutant glioma, of any histological grade, at two large academic institutions. MGMTp methylation was evaluated by methylation-specific polymerase chain reaction (PCR) analysis. Log-rank test and Cox proportional hazards model were applied to evaluate the association of clinical, molecular, and radiological characteristics with overall survival (OS) and progression-free survival (PFS).

Results: Median age was 36.6 years; MGMTp was methylated in 70% and unmethylated in 30%. MGMTp methylation was not significantly associated with PFS (p = 0.74) but trended towards significance for OS (p = 0.11) on multivariate analyses. Cyclin dependent kinase inhibitor 2A/B (CDKN2A/B) homozygous deletion [HR = 3.26 (1.47, 7.23, p = 0.006] and an integrated grade 4 classification [HR = 2.08 (1.06, 4.67), p = 0.048] were strong predictors of OS in astrocytoma, whereas maximal resection [HR = 0.06 (0.01, 0.57), p = 0.016] and radiation [HR = 0.41 (0.18, 0.91), p = 0.03] were strong prognosticators for PFS in the entire cohort. Maximal resection of the enhancing disease [HR = 0.17 (0.05, 0.96), p = 0.014] and radiation [HR = 0.47 (0.19, 0.65), p = 0.046] were strongly associated with PFS in grade 2 and 3 gliomas.

Conclusion: MGMTp methylation was not associated with a prognostic or predictive value in our IDH-mutant glioma cohort. CDKN2A/B status and extent of resection were strong predictors of outcomes.

Keywords: IDH-mutant glioma; MGMT promoter methylation; prognosis.