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Impact of weak MGMT promoter methylation on the prognosis of patients with newly diagnosed glioblastoma

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Abstract

Background: In most cases, routine neuropathological analysis can clearly distinguish between methylated and unmethylated MGMT promoters in glioblastoma (GBM). However, some GBMs display weak MGMT promoter methylation. This study aimed to evaluate its impact on disease progression and survival compared with fully methylated and unmethylated cases.

Methods: A quantitative analysis of MGMT promoter methylation was performed on 140 of 190 samples from a cohort of adult patients with newly diagnosed GBM. The MGMT promoter was stratified into three subgroups based on methylation status: unmethylated, weakly methylated (9-28%), and methylated (29-100%). These cut-off values were selected based on previously published data demonstrating significant differences in progression-free survival (PFS) and overall survival (OS) among patients with these categories. Clinical characteristics, treatment regimens, and survival outcomes were analyzed and compared. Cox proportional hazards regression was used to evaluate the impact of MGMT methylation status on progression-free interval (PFI) and overall survival (OS).

Results: The MGMT promoter was unmethylated in 57 (40.7%) samples, methylated in 66 (47.1%) samples, and weakly methylated in 17 (12.1%) samples. Compared to patients with methylated and unmethylated MGMT promoters, the PFI of patients with weak MGMT methylation was comparable (P=0.53) and the OS was slightly longer (P=0.08). After stratification following chemoradiotherapy consisting of TMZ, patients with weakly methylated MGMT have a longer PFI. The Cox proportional hazards regression model revealed that a weakly methylated MGMT promoter was a significant risk factor for longer OS (P=0.02), while older age remained an unfavorable prognostic factor for survival (P<0.001).

Conclusions: Weak MGMT promoter methylation may offer clinical benefits comparable to full methylation, including longer PFI and improved OS compared to unmethylated cases. This positive effect on PFI appears more pronounced in patients receiving concurrent chemoradiotherapy with TMZ. Advanced age continues to be associated with a less favorable prognosis.