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BIOM-07. QUANTITATIVE MGMT PROMOTER METHYLATION INDEX INDICATES A NON-LINEAR PROGNOSTIC EFFECT IN GLIOBLASTOMA, SUGGESTING THAT USE OF OPTIMAL CUTOFF POINTS MAY BE CLINICALLY DISADVANTAGEOUS

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transcriptomic signatures. RESULTS: Local recurrence was the most prominent failure pattern (62.9%), followed by combined recurrence (22.8%). Multivariate Cox regression analysis confirmed failure pattern as one of the independent prognostic factors. Patients with combined failure patterns exhibited the worst prognoses, whereas patients with remote recurrence exhibited the most favorable outcomes (median overall survival = 11.4 and 25.2 months, respectively). In IDH1-wild type glioblastoma (GBM) patients, TERT and PIK3CA mutation were significantly associated with the development of combined failure pattern and leptomeningeal seeding, respectively (p-value=0.015 & p-value=0.004, respectively). Transcriptomic analysis exhibited that inter-neuronal synaptic transmission was enriched in GBMs with combined failure pattern and this finding was further validated in proteomic analysis; neuronal myelination and synaptic transmission-related pathways were upregulated in GBMs which exhibited combined failure pattern. CONCLUSIONS: Collectively, we demonstrated that the inherent molecular characteristics of the tumors might contribute to the eventual relapse patterns; tracking their evolutionary pathways may unravel novel therapeutic vulnerabilities of these tumors.

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BACKGROUND: Epigenetic inhibition of the O6-methylguanine-DNA-methyltransferase (MGMT) gene has emerged as a clinically relevant prognostic marker in glioblastoma (GBM). Methylation of the MGMT promoter has been shown to increase chemotherapy efficacy. While traditionally reported as a binary marker, recent methodological advancements have led to quantitative approaches that measure methylation, providing clearer insights into methylation's functional relationship with survival. METHODS: A CLIA assay and bisulfite sequencing was utilized to develop a quantitative, 17-point MGMT promoter methylation index derived from the number of methylated CpG sites. Retrospective review of 240 newly diagnosed GBM patients was performed in order to discern how risk for mortality transforms as promoter methylation increases. Non-linearities were captured by fitting splines to Cox proportional hazard models, plotting smoothed residuals, and creating survival plots. Covariates included age, KPS, IDH1 mutation, and extent of resection. RESULTS: Median follow-up time and progression free survival were 16 and 9 months, respectively. 176 subjects experienced death. A one-unit increase in CpG methylation on a scale of 1-17 resulted in a 4% reduction in hazard (95% CI 0.93–0.99, P< 0.005). Moreover, GBM patients with low-levels of methylation (1-6 CpG sites) fared markedly worse (HR=1.62, 95% CI 1.03-2.54, P< 0.036) than individuals who were unmethylated (reference group). Subjects with medium-levels of methylation (7-12 CpG sites) had the greatest reduction in hazard (HR=0.48, 95% CI 0.29-0.80, P< 0.004), followed by individuals in the highest methylation tertile (HR=0.62, 95% CI 0.40-0.97, P< 0.035). CONCLUSION: This novel approach offers greater bisulfite conversion efficiency when compared to alternative methods, reducing the likelihood of false positives. Analysis of the resulting methylation index scores demonstrates a non-linear relationship between MGMT methylation and survival, suggesting conformation of the marker's protective effect. These findings challenge the current understanding of MGMT's functional form and underline why implementing an "optimal cutoff point" may be disadvantageous.

BIOM-08. DNA METHYLATION-BASED SUBGROUPING PREDICTS SURVIVAL BENEFIT FROM LOMUSTINE/TEMOZOLOMID COMBINATION THERAPY IN MGMT PROMOTOR-METHYLATED GLIOBLASTOMA

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BACKGROUND: The CeTeG/NOA-09 trial showed that lomustine/temozolomide chemotherapy prolongs survival for newly diagnosed MGMT-methylated glioblastoma patients. Previous reports on temozolomide monotherapy suggested, that the survival benefit of temozolomide in MGMT-methylated tumors may be restricted to the RTK II methylation subgroup and absent in RTK I and MES subgroups. To identify patients with a particularly strong benefit from CCNU/TMZ, we explored the association of methylation subgroups with outcome after lomustine/temozolomide therapy. METHODS: All patients from the CeTeG/NOA-09 trial with sufficiently available tumor tissue (n = 98) underwent 850K methylation array analysis of their tumor and methylation subgroup annotation (Heidelberg brain tumor methylation classifier v11b4; calibrated score > 0.5 required). Overall survival (OS) was compared between a pooled cohort of tumors of the RTK I/MES subgroups and RTK II tumors. RESULTS: In the CCNU/TMZ arm of CeTeG/NOA-09, OS was prolonged in RTK I/MES (n = 16; median not reached, 4-year OS 69%) as compared to RTK II patients (n = 14; median 20.6 months, 4-year OS 23%; p = 0.004 logrank test). In the standard temozolomide arm of CeTeG/NOA-09, OS tended to be shorter in RTK I/MES (n = 7; median 23.7 months, 4-year OS 17%) as compared to RTK II patients (n = 17; median 35.2 months; 4-year OS 38%, p = 0.15). CONCLUSION: The CCNU/TMZ-dependent survival prolongation in patients with RTK I/MES tumors as opposed to RTK II seen in CeTeG/NOA-09 suggests that methylation-based subgrouping could be predictive for CCNU/TMZ efficacy in newly diagnosed MGMT-methylated glioblastoma.

BIOM-09. MYO-INOSITOL LEVELS ON MR SPECTROSCOPY CAN PREDICT FAILURE OF ANTI-ANGIOGENIC TREATMENT IN RECURRENT GLIOBLASTOMA

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BACKGROUND: Recurrent glioblastoma (rGBM) patients are often treated with anti-angiogenic agents such as bevacizumab (BEV). Despite therapeutic promise, conventional MR methods fail to determine which patients may not benefit. PURPOSE: The purpose of this study was to utilize magnetic resonance spectroscopic imaging (MRSI) with intermediate and short echo time to generate corrected Myo-inositol normalized by contralateral creatine (mI/c-Cr) in patients with rGBM treated with BEV and