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Extent of MGMT promoter methylation correlates with outcome in glioblastomas given temozolomide and radiotherapy.

[Dunn J](#), [Baborie A](#), [Alam F](#), [Joyce K](#), [Moxham M](#), [Sibson R](#), [Crooks D](#), [Husband D](#), [Shenoy A](#), [Brodbeck A](#), [Wong H](#), [Liloglou T](#), [Haylock B](#), [Walker C](#).

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BACKGROUND: Epigenetic silencing of O(6)-methylguanine-DNA-methyltransferase (MGMT) by promoter methylation is associated with improved survival in glioblastomas treated with alkylating agents. In this study, we investigated MGMT promoter methylation in glioblastomas treated with temozolomide and radiotherapy in a single UK treatment centre. **METHODS:** Quantitative methylation data at individual CpG sites were obtained by pyrosequencing for 109 glioblastomas. **RESULTS:** Median overall survival (OS) was 12.4 months with 2-year survival of 17.9%. Pyrosequencing data were reproducible with archival samples yielding data for all glioblastomas. Variation in methylation patterns of discrete CpG sites and intratumoral methylation heterogeneity were observed. A total of 58 out of 109 glioblastomas showed average methylation >non-neoplastic brain in at least one clinical sample; 86% had homogeneous methylation status in multiple samples. Methylation was an independent prognostic factor associated with prolonged progression-free survival (PFS) and OS. Cases with methylation more than 35% had the longest survival (median PFS 19.2; OS 26.2 months, 2-year survival of 59.7%). Significant differences in PFS were seen between those with intermediate or high methylation and unmethylated cases, whereas cases with low, intermediate or high methylation all showed significantly different OS. **CONCLUSIONS:** These data indicate that MGMT methylation is prognostically significant in glioblastomas given chemoradiotherapy in the routine clinic; furthermore, the extent of methylation may be used to provide additional prognostic stratification.

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