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### Determination of the methylation status of MGMT in different regions within glioblastoma multiforme.

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#### Abstract

Epigenetic silencing of the MGMT gene through promoter methylation correlates with improved survival in Glioblastoma Multiforme (GBM) patients receiving concurrent chemoradiotherapy. Although the clinical benefit is primarily seen in patients with methylated MGMT promoter, some unmethylated patients also respond to Temozolomide. One possible explanation may be intratumoral heterogeneity. This study was designed to assess the methylation status of the MGMT promoter in different areas of GBM and determine if methylation status varied depending on the fixation technique (paraffin-embedding versus fresh frozen) used to store tissue. Using intraoperative navigation, biopsies were obtained from three distinct regions: the enhancing outer area, the non-enhancing inner core, and an area immediately outside the enhancing region. Only patients with GBM were included for evaluation and analysis. Samples taken from each area were divided with half stored by flash freezing and the other half stored using paraffin fixation. Methylation Specific-PCR (MS-PCR) was used for analysis of MGMT promoter methylation. Thirteen patients were included. Ten were male with a median age of 62 years. In each patient, samples were taken from the enhancing rim and the necrotic centre. However, it was not considered safe or feasible to obtain samples from the area immediately adjacent to the enhancing tumor rim in one case. All patients were homogeneous for methylation status throughout their tumor and tissue taken adjacent to it when frozen tissue was used. However, four patients had discrepancies in the MGMT promoter status between the frozen and paraffin-embedded blocks and one patient was not homogeneous within the tumor when paraffin-embedded tissue was used. MGMT promoter methylation status was homogeneous in all GBM tumors. Our observation that methylation status varied depending if the DNA was extracted from paraffin-embedded versus frozen tissue is concerning. Although the reason for this is unclear, we postulate that the timing from resection to fixation or the process of fixation itself may potentially alter methylation status in paraffin-embedded tumors.

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