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## **MGMT expression and promoter methylation status may depend on the site of surgical sample collection within glioblastoma: a possible pitfall in stratification of patients?**

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### **Abstract**

We recently described a three-layer concentric model of a glioblastoma (GBM) related to a specific distribution of molecular and phenotypic characteristics driven by the intratumoral hypoxic gradient in which the cancer stem cells niche is located in the hypoxic necrotic core of the tumour. The purpose of this study was to investigate the relationship between O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation status and MGMT expression in GBM samples collected according to the three-layer concentric model. Multiple tissue samples were obtained, by means of image-guided surgery, from the three concentric layers of newly diagnosed GBM. Two samples from each layer were collected from 12 patients (total 72 samples). Immunohistochemical analysis was performed on formalin-fixed paraffin-embedded tissue samples. The methylation status of the MGMT promoter was determined by methylation-specific polymerase-chain-reaction analysis. In all tumours, MGMT protein expression decreased progressively from the inner to the outer layer, and methylation of the MGMT promoter was unrelated to tumour layer. In particular, the MGMT promoter was unmethylated in all layers in 41.7% of tumours, methylated in all layers in 25%, and variably methylated in the three layers in 33.3%. We recorded concordance between MGMT expression and MGMT promoter methylation status within the GBM in only 58.8% of the samples collected. Our data suggest that both MGMT expression and promoter methylation data may be variable throughout GBM and that they may, consequently, depend on the site of surgical sample collection, even in the same patient. However, whereas MGMT expression is pre-operatively predictable when sampling is performed according to the three-layer concentric model, MGMT promoter methylation is not. These results must be considered when sample collection is performed for assessment of MGMT data.

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