

## Article

# Quantitative Analysis of the *MGMT* Methylation Status of Glioblastomas in Light of the 2021 WHO Classification

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**Simple Summary:** The status of a DNA repair protein called *MGMT* is a prognostic marker in patients with glioblastomas, the most frequent malignant brain tumor. Epigenetic silencing of this gene predicts increased sensitivity to chemotherapy. Silencing is assessed by analyzing modifications, so-called methylation, of a certain gene region. Whereas most studies report such information only in a qualitative manner, quantitative testing might provide additional information. The aim of our study was to determine a quantitative threshold for better survival among patients with glioblastomas. Among 321 patients suffering from glioblastoma, we found better survival in patients with glioblastomas that have  $\geq 16\%$  methylation of a particular region of the *MGMT* gene. Above 16% methylation, we found no additional benefit with increasing degree of methylation. We suggest using this threshold for selection in clinical trials and for patient counseling.

**Abstract:** Background: Glioblastomas with methylation of the promoter region of the O(6)-methylguanine-DNA methyltransferase (*MGMT*) gene exhibit increased sensitivity to alkylating chemotherapy. Quantitative assessment of the *MGMT* promoter methylation status might provide additional prognostic information. The aim of our study was to determine a quantitative methylation threshold for better survival among patients with glioblastomas. Methods: We included consecutive patients  $\geq 18$  years treated at our department between 11/2010 and 08/2018 for a glioblastoma, IDH wildtype, undergoing quantitative *MGMT* promoter methylation analysis. The primary endpoint was overall survival. Results: A total of 321 patients were included. Median overall survival was 12.6 months. Kaplan-Meier and adjusted Cox regression analysis showed better survival for the groups with 16–30%, 31–60%, and 61–100% methylation. In contrast, survival in the group with 1–15% methylation was similar to those with unmethylated promoter regions. A secondary analysis confirmed this threshold. Conclusions: Better survival is observed in patients with glioblastomas with  $\geq 16\%$  methylation of the *MGMT* promoter region than with  $<16\%$  methylation. Survival with tumors with 1–15% methylation is similar to with unmethylated tumors. Above 16% methylation, we found no additional benefit with increasing methylation.

**Keywords:** glioblastoma; temozolomide; O(6)-methylguanine-DNA methyltransferase

## 1. Introduction

Glioblastoma is the most common malignant primary tumor of the brain, with an incidence of 3.23/100,000 [1]. The standard of care consists of maximal safe resection followed by radiotherapy combined with temozolomide (TMZ) chemotherapy [2]. Despite



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# Quantitative Analysis Mgmt

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