The significance of MGMT methylation in Glioblastoma Multiforme prognosis
Aaida Mumtaz Rao, Ayesha Quddusi, Muhammad Shahzad Shamim

Abstract
Methylation of O6-methylguanine-DNA methyltransferase (MGMT) has been extensively studied as a biomarker in predicting the prognosis of patients with GBM (Glioblastoma multiforme). Its significance has been studied in various subgroups, including age, gender and even race. Correlation between prognosis with MGMT methylation and different treatment regimens has also been studied in detail. There are multiple techniques to analyze MGMT methylation in tumour specimen. We review the current evidence for the importance of MGMT methylation as a biomarker for prognosis in GBM patients, the techniques to analyze it and the effect of epidemiologic factors on its significance.

Keywords: Glioblastoma multiforme, tumour markers, MGMT methylation.

Background
Glioblastoma is the most common primary brain tumour in adults. The standard treatment includes surgical resection, radiotherapy (RT) and chemotherapy, mostly with alkylating agent Temozolomide (TMZ). Despite these regimens, prognosis remains poor. Various biomarkers are used to predict prognosis of patients with GBM. Amongst these, methylation of O6-methylguanine-DNA methyltransferase (MGMT) is considered to be a biomarker for good prognosis. MGMT is a DNA repair protein, that repairs damage from alkylating agents. Methylation of MGMT gene can silence its expression, leading to cell death after damage from alkylating agents that can facilitate cell death of cancer cells in GBM.

Review of Evidence
One of the initial papers that showed MGMT methylation status as an independent prognostic factor in GBM patients was by Hegi et al. They demonstrated that MGMT methylation was associated with better overall survival in GBM patients treated with TMZ plus RT as well as patients receiving RT alone. A recent meta-analysis of 34 clinical trials concluded that MGMT methylation was significantly associated with better overall survival (OS) in patients with GBM. This is true even for tumours that are not suitable for resection. For recurrent GBM also not suitable for resection, a retrospective study by Kim et al., showed correlation of MGMT promoter methylation status with better progression free survival (PFS), and OS in patients who underwent gamma knife radiosurgery. MGMT methylation, and low MGMT expression were also identified as favourable prognostic markers in patients with newly diagnosed GBM, who underwent implantation of Carmustine releasing wafers (Gliadel) after surgery.

There are several different techniques available to analyze MGMT methylation status in GBM tumours. Christians et al., compared the use of methylation specific polymerase chain reaction (MSP), methylation specific multiplex ligation-dependent probe amplification (MS-MLPA) and pyrosequencing in methylation analysis of MGMT, and found that pyrosequencing was the most useful tool in analysis of...
MGMT methylation status in terms of predicting clinical outcome and cost effectiveness when a large number of samples have to be analyzed. However, MSP was useful for routine clinical diagnostics with a smaller number of samples.\textsuperscript{10}

The status of MGMT methylation as a predictive biomarker in prognosis may be effected by age, gender, and race. It is an important prognostic factor for OS, as well as PFS in elderly patients treated with TMZ and RT.\textsuperscript{11} In paediatric GBM studies, MGMT methylation has also been observed as a predictor of increased PFS, however these studies have a small sample size. Rizzo et al., showed that the presence of MGMT methylation in paediatric population is rare.\textsuperscript{12}

The importance of MGMT methylation also differs by area and continents. A recent systematic review and meta-analysis noted that while MGMT methylation remained a significant marker of PFS in patients in different parts of the world, it did not hold the same significance regarding OS in Asian patients with MGMT methylation compared to patients in US and Europe.\textsuperscript{13} Similarly, in another systematic review and meta-analysis MGMT promoter methylation had significant effect on OS in Asian population but not on PFS, while it had a significant effect on both OS and PFS in Caucasian population.\textsuperscript{14} Gender also appears to have an impact on the importance of MGMT methylation in predicting prognosis. In a recent study, Franceschi et al., observed that female patients with MGMT methylation had longer survival than male patients.\textsuperscript{15}

**Conclusion**

MGMT methylation has been shown to be significantly associated with PFS and OS in GBM patients and can be used as a prognostic marker. There are several ways to assess it and MSP as well as pyrosequencing appear to be good techniques to analyze MGMT methylation status. However, GBM biology is complex and MGMT methylation is not the only prognostic biomarker. The current evidence suggests that epidemiologic factors such as age, gender and race also appear to affect its importance as a marker. However, there are too few studies to establish a link here.

**References**


![Figure-2](a,b): MRI T1WI axial sections with and without contrast of the same patient, showing complete resection of tumor.
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