Article published online: 2023-03-02



Brain Tumour

# Prognosis of *MGMT*-Positive Gene in Patients with Brain Tumors of Grade III and Grade IV

Ishitaa Rajendra[1] Shikha Dhal[1] Sumit Goyal[1] Surabhi Tyagi[2] B. S. Sharma[3] Ajay Yadav[4] Dinesh Yadav[5]

[1] Department of Radiation Oncology, Sri Ram Cancer and Superspeciality Centre, Jaipur, Rajasthan, India
[2] Department of Pathology, Sri Ram Cancer and Superspeciality Centre, Jaipur, Rajasthan, India
[3] Department of Head Neurosurgery, Sri Ram Cancer and Superspeciality Centre, Jaipur, Rajasthan, India
[4] Department of Medical Oncology, Sri Ram Cancer and Superspeciality Centre, Jaipur, Rajasthan, India
[5] Department of Surgical Oncology, Sri Ram Cancer and Superspeciality Centre, Jaipur, Rajasthan, India

Address for correspondence Sumit Goyal, MBBS, DNB, Radiation Oncologist, Department of Radiation Oncology, Sri Ram Cancer and Superspeciality Centre, 53 New Raja Park, Shanti Path, Jaipur 302004, Rajasthan, India (e-mail: sumit_goyal012@yahoo.com).

South Asian J Cancer 2024;13(2):146–149.

## Abstract

Sumit Goyal

**Objective** To evaluate *MGMT* gene positivity is associated with better survival in patients diagnosed with brain tumor World Health Organization (WHO) grades III and IV

**Material and Methods** Single-institute restrospective study. A total of 80 patients were enrolled, all underwent surgery either total or subtotal excision of the tumor and *MGMT* gene testing on tumor tissue by RT-PCR. All received adjuvant radiation (60 Gy/30 fractions, 5 fractions/week) with concurrent temozolomide (75 mg/m$^2$), followed by 12 cycles of adjuvant temozolomide (150 mg/m$^2$ 1st cycle followed by 200 mg/m$^2$) with regular follow-up.

**Results** A total of 80 patients, 75 underwent subtotal excision, 27 were WHO grade III vs. 48 WHO grade IV. Five underwent total excision 1 was WHO grade III vs. 4 WHO grade IV. The median PFS and OS in five patients in total excision in grade III patient was 9.0 and 20 compared with Grade IV, where the median PFS and OS was 8.8 and 17.8 months. Out of 75 patients in the subtotal group median PFS and OS, respectively, in Grade III group was 9.1 and 19.3 and, WHO grade IV with median PFS of 8.8 and OS of 18.8.

**Conclusion** *MGMT* gene positivity is a prognostic factor in grade III and IV brain tumor.

**Keywords**

- brain tumor
- excision
- grade III and IV
- *MGMT*
- temozolomide

## Introduction

Glioblastoma multiforme (GBM) is the most aggressive type of brain cancers. Diagnosis is often delayed because initial signs and symptoms of glioblastoma are non-specific, including headaches, personality changes, nausea, and symptoms, similar to those of a stroke. Symptoms often worsen rapidly and may progress to unconsciousness. Genetic risk factors include neurofibromatosis and Li–Fraumeni

DOI https://doi.org/10.1055/s-0042-1759771 ISSN 2278-330X

**How to cite this article:** Rajendra I, Dhal S, Goyal S, et al. Prognosis of MGMT-Positive Gene in Patients with Brain Tumors of Grade III and Grade IV South Asian J Cancer 2024; (2):146–149.



Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

syndrome. Previous radiation therapy is also a risk factor.[1] The current WHO classification recognizes three variants of GBM including conventional glioblastoma, giant cell glioblastoma, and gliosarcoma.[2] Standard of care for newly diagnosed GBM is surgery followed by radiation therapy with the addition of temozolomide.[3,4]

Tumor markers are gaining importance in the era of targeted therapy. O6-methylguanine DNA methyl transferase (MGMT) is crucial for genome stability. It repairs the naturally occurring mutagenic DNA lesion O6-methyl guanine back to guanine and prevents mismatch and errors during DNA replication and transcription.[5] Epigenetic silencing of the *MGMT* gene by promoter methylation results in decreased MGMT protein expression, reduced DNA repair activity, and potential increased sensitivity to therapy. Epigenetic *MGMT* gene silencing by promoter methylation is associated with loss of *MGMT* expression and diminished DNA repair activity. This results in increased sensitivity to temozolomide and longer overall survival (OS).[4–6]

## Methods and Materials

We conducted a single-institute retrospective study between 2018 and 2021.

All patients with WHO Grade III and IV brain tumors confirmed on histopathology were included in the study. All patients below 18 years of age and those with low-grade brain tumor were excluded.

Our department policy is to offer MRI brain with contrast and *MGMT* gene testing (done by RT-PCR) in all patients. The objective of surgical therapy is to do surgical excision wherever possible.

All patients were given adjuvant external beam radiotherapy (EBRT) along with concurrent temozolomide. Individual cast formation and CT simulation images, and transferring to the programming system via DAICOM, where gross tumor volume (GTV) and contouring according to the initial size of the tumor, i.e., the size of the tumor before surgery and clinical tumor value (CTV) margin of 1.5 cm and planned tumor volume (PTV) margin of 0.5 cm is as per the standard guidelines adopted by our department.[7] PTV was planned to dose of 60 Gy in 30 fractions, 5 days a week with a coverage of 95%, and minimal allowed dose to organ at risk[7] along with concurrent temozolomide (75 mg/m$^2$) daily. Regular weekly follow-up schedule was for 6 weeks and routine hematological investigation was planned weekly.[8]

After completion of EBRT, the patients' schedule was adjuvant temozolomide for 12 monthly cycles. MRI brain with contrast was planned every 3rd, 6th, and 12th months of adjuvant cycle of temozolomide. Patients were advised anti-epileptics during entire treatment.[9]

Our objective was to evaluate whether *MGMT* gene positivity is associated with better survival in patients diagnosed with GBM treated in a single institution.

## Results

A total of 80 *MGMT*-positive patient were included in the analysis of this retrospective study. Of them, 56 were males and 24 were females. Age ranging from 32 to 64 years of age (median 49 years). Out of 80 patients, 75 underwent subtotal excision and 5 underwent total excision of tumor.

Out of 75 patients who underwent subtotal excision, 27 were of WHO Grade III and 48 were of WHO Grade IV. Also, out of 5 patients who underwent total excision, one patient was of WHO Grade III and four were of WHO Grade IV.

Out of 80 patients, isocitrate dehydrogenase 2 (*IDH2*) was lost in all patients. *ATRX* was lost in 52/80 patients, whereas it was present in 28 individuals.

The median PFS and OS in five patients in total excision in Grade III patient was 9.0 and 20 compared with Grade IV, where the median PFS and OS was 8.8 and 17.8 months. Out of 75 patients in the subtotal group, the median PFS and OS, respectively, in Grade III group was 9.1 and 19.3 and, WHO grade IV with median PFS of 8.8 and OS of 18.8. PFS and OS were measured from the time of surgery to disease progression or death, respectively (►Table 1).

## Discussion

Our data confirmed that *MGMT* gene positivity is associated with a favorable outcome after temozolomide chemotherapy in patients with newly diagnosed WHO Grade III and IV brain tumor. The methylation status of the *MGMT* promoter is therefore of prognostic value and predicts benefit from temozolomide chemotherapy.

In a meta-analysis of 30 studies with 2,986 patients across different countries, the frequency of *MGMT* promoter methylation was 44.27%. It showed that *MGMT* gene positivity was associated with better PFS and OS in patients with GBM, regardless of therapeutic intervention. Longer OS in GBM patients was also documented in patients treated with alkylating agents.[1]

When compared with the global literature, we found interesting geographical variations in *MGMT* gene methylation across different countries. The highest is of Switzerland

**Table 1** Outcome in MGMT positive cases

| | Grade III (*N*: 28) | | Grade IV (*N*: 52) | |
|---|---|---|---|---|
| | Total excision (*N*: 1/28) | Subtotal Excision (*N*: 27/28) | Total excision (*N*:4/52) | Subtotal excision (*N*: 48/52) |
| Median PFS | 9 months | 9.1 months | 8.8 months | 8.8 months |
| Median OS | 20 months | 19.3 months | 17.8 months | 18.8 months |

 

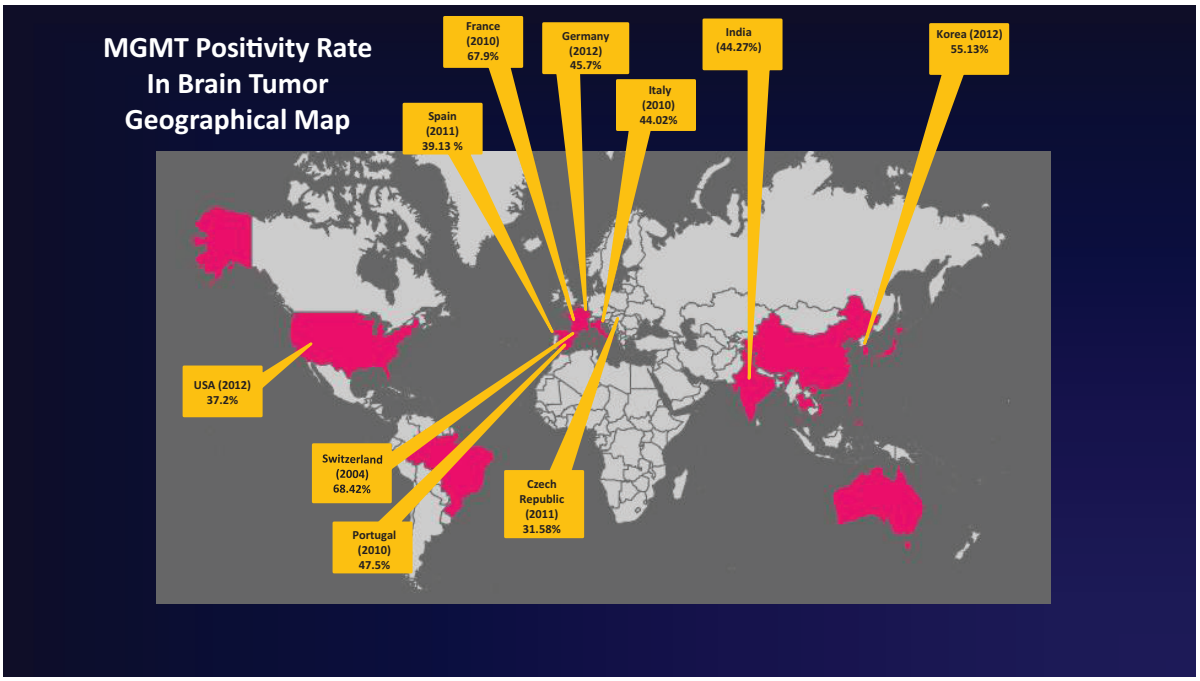


**Fig. 1** MGMT positivity rate in brain tumor geographical map.

(68.42%) and France (67.90%). The lowest incidence (31.58%) was reported from Czech Republic (►Fig. 1).[10–20]

Hegi et al also concluded that patients with glioblastoma containing a *MGMT* positivity benefited from temozolomide, conversely those who did not have a methylated *MGMT* promoter failed to benefit from temozolomide. They concluded that the median overall survival among patients with methylation was 18.2 months (95% confidence interval, 15.5 to 22.0), as compared with 12.2 months (95% confidence interval, 11.4 to 13.5) among those without methylation.[6]

Kim et al in study of 93 patients determined that the median OS was 29 months for the methylated group (*MGMT* positive) and 20 months for the unmethylated group (MGMT negative). In 35 patients with methylated *MGMT* genes, the 2-year and 5-year OS rates were 54% and 31%, respectively.[11]

Compared with above studies, we found the PFS and OS in grade IV tumor was 8.8 months and 17.8 months in the total excision group, while in the subtotal group, it was 8.8 months and 18.8 months. There was no difference because of small numbers.

Interestingly, CATNON, EORTC study 26053–22054 concluded that adjuvant temozolomide chemotherapy, was associated with a survival benefit in patients with 1p/19q non–co-deleted anaplastic glioma. However, they did not give concurrent temozolomide.[21]

Diagnostic *MGMT* testing requires sufficient and optimally preserved tumor tissue. The best results with methylation-specific PCR are obtained when cryopreserved tumor specimens are used. Fixation is known to result in the deterioration of tumor DNA, leading to false negativity. Other methods, such as immunohistochemistry, may not be reliable because *MGMT* expression is prone to induction by glucocorticoids, ionizing radiations, and genotoxic agents when the *MGMT* promoter is not methylated.[22,23]

Limitations of our study include being single-institute study, having a small number of patients and a few patients eligible for complete resection. We have also not studied other genetic alterations that could influence outcome.

## Conclusion

*MGMT* gene positivity is a prognostic factor in Grade III and IV brain tumors. Determination of *MGMT* gene positivity status by methylation-specific PCR may allow the selection of patients most likely to benefit from temozolomide treatment. Such patients are likely to have a longer PFS as well as overall survival.

### Conflict of Interest

None declared.

## References

1 Zhang K, Wang XQ, Zhou B, Zhang L. The prognostic value of MGMT promoter methylation in glioblastoma multiforme: a meta-analysis. Fam Cancer 2013;12(03):449–458
2 Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro-oncol 2021;23(08):1231–1251
3 Halperin EC, Wazer DE, Perez CA, Brady LW. Principles and Practice of Radiation Oncology. 6th ed. Wolters Kluwer/Lippincott Williams and Wilkins; 2013
4 Stupp R, Mason WP, van den Bent MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352(10):987–996
5 Yu W, Zhang L, Wei Q, Shao A. O$^6$-methylguanine-DNA methyltransferase (MGMT): challenges and new opportunities in glioma chemotherapy. Front Oncol 2020;9:1547

 

6 Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005; 352(10):997–1003

7 Kruser TJ, Bosch WR, Badiyan SN, et al. NRG brain tumor specialists consensus guidelines for glioblastoma contouring. J Neurooncol 2019;143(01):157–166

8 Armstrong TS, Cao Y, Scheurer ME, et al. Risk analysis of severe myelotoxicity with temozolomide: the effects of clinical and genetic factors. Neuro-oncol 2009;11(06):825–832. Doi: 10.1215/15228517-2008-120

9 Julie DAR, Ahmed Z, Karceski SC, et al. An overview of antiepileptic therapy management of patients with malignant tumors of the brain undergoing radiation therapy. Seizure 2019; 70:30–37. Doi: 10.1016/j.seizure.2019.06.019

10 Hegi ME, Diserens AC, Godard S, et al. Clinical trial substantiates the predictive value of O-6-methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide. Clin Cancer Res 2004;10(06):1871–1874

11 Karayan-Tapon L, Quillien V, Guilhot J, et al. Prognostic value of O6-methylguanine-DNA methyltransferase status in glioblastoma patients, assessed by five different methods. J Neurooncol 2010;97(03):311–322. Doi: 10.1007/s11060-009-0031-1

12 Sonoda Y, Yokosawa M, Saito R, et al. O(6)-Methylguanine DNA methyltransferase determined by promoter hypermethylation and immunohistochemical expression is correlated with progression-free survival in patients with glioblastoma. Int J Clin Oncol 2010;15(04):352–358. Doi: 10.1007/s10147-010-0065-6

13 Lechapt-Zalcman E, Levallet G, Dugué AE, et al. O(6) -methylguanine-DNA methyltransferase (MGMT) promoter methylation and low MGMT-encoded protein expression as prognostic markers in glioblastoma patients treated with biodegradable carmustine wafer implants after initial surgery followed by radiotherapy with concomitant and adjuvant temozolomide. Cancer 2012; 118(18):4545–4554. Doi: 10.1002/cncr.27441

14 Kim YS, Kim SH, Cho J, et al. MGMT gene promoter methylation as a potent prognostic factor in glioblastoma treated with temozolomide-based chemoradiotherapy: a single-institution study. Int J Radiat Oncol Biol Phys 2012;84(03):661–667

15 Costa BM, Caeiro C, Guimarães I, et al. Prognostic value of MGMT promoter methylation in glioblastoma patients treated with temozolomide-based chemoradiation: a Portuguese multicentre study. Oncol Rep 2010;23(06):1655–1662

16 Christians A, Hartmann C, Benner A, et al. Prognostic value of three different methods of MGMT promoter methylation analysis in a prospective trial on newly diagnosed glioblastoma. PLoS One 2012;7(03):e33449. Doi: 10.1371/journal.pone.0033449

17 Morandi L, Franceschi E, de Biase D, et al. Promoter methylation analysis of O6-methylguanine-DNA methyltransferase in glioblastoma: detection by locked nucleic acid based quantitative PCR using an imprinted gene (SNURF) as a reference. BMC Cancer 2010;10:48. Doi: 10.1186/1471-2407-10-48

18 Balańa C, Carrato C, Ramírez JL, et al. Tumour and serum MGMT promoter methylation and protein expression in glioblastoma patients. Clin Transl Oncol 2011;13(09):677–685

19 Ellingson BM, Cloughesy TF, Pope WB, et al. Anatomic localization of O6-methylguanine DNA methyltransferase (MGMT) promoter methylated and unmethylated tumors: a radiographic study in 358 de novo human glioblastomas. Neuroimage 2012;59(02):908–916. Doi: 10.1016/j.neuroimage.2011.09.076

20 Lakomy R, Sana J, Hankeova S, et al. MiR-195, miR-196b, miR-181c, miR-21 expression levels and O-6-methylguanine-DNA methyltransferase methylation status are associated with clinical outcome in glioblastoma patients. Cancer Sci 2011;102(12): 2186–2190. Doi: 10.1111/j.1349-7006.2011.02092.x

21 van den Bent MJ, Tesileanu CMS, Wick W, et al. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. Lancet Oncol 2021;22(06):813–823. Doi: 10.1016/S1470-2045(21)00090-5

22 Mansouri A, Hachem LD, Mansouri S, et al. MGMT promoter methylation status testing to guide therapy for glioblastoma: refining the approach based on emerging evidence and current challenges. Neuro-oncol 2019;21(02):167–178

23 Cankovic M, Mikkelsen T, Rosenblum ML, Zarbo RJ. A simplified laboratory validated assay for MGMT promoter hypermethylation analysis of glioma specimens from formalin-fixed paraffin-embedded tissue. Lab Invest 2007;87(04):392–397


 