PCR300

Overall Survival and Quality of Life of Glioblastoma Patients According to MGMT Methylation Status: Real-World Data Analysis

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Background

- Glioblastoma (GBM) is the most common primary malignant brain tumor in adults, accounting for 16% of primary brain and CNS neoplasms, with almost all patients facing tumor progression, a median survival of less than 15 months, and nearly universal mortality.[1]
- Standard therapy consists of surgical resection when feasible, followed by radiotherapy and treatment with temozolomide (TMZ), an alkylating agent with daily does of 150-200 mg/m^2 body surface area for 5 days in each 28-day cycle.[2]
- Methylation of the O6-methylguanine-DNA methyltransferase (MGMT) gene promoter in GBM leads to reduced expression of the MGMT protein, impairing the tumor's ability to repair DNA damage caused by TMZ. Patients with methylated MGMT typically respond better to alkylating agents like TMZ, showing improved survival rates compared to unmethylated cases.[3]
- As a disease with such a poor prognosis, treatment of GBM should go beyond improving overall survival (OS) and aim at preserving and even improving the quality of life (QoL) of patients.[1]

Objective

- To evaluate the relationship between QoL and OS in patients with GBM.
- To determine possible differences when stratified on their MGMT promoter methylation status.

Methods

Data Source and Methodology

- GBM patients were enrolled in the XCELSIOR master observational research protocol (NCT03793088).
- The 5-Level EuroQol 5-Dimension (EQ5D5L) survey is a standardized tool used to measure a person's health-related QoL, assessing five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[4,5]
- Participants with GBM were invited to complete the EQ5D5L questionnaire[5] on a weekly basis.
- Single-survey-entry per time interval per patient was achieved by taking the mean score of multiple surveys for the time interval.
- Among the overall patient cohort, two subgroups were identified:
  - Patients who completed at least two EQ5D5L surveys.
  - Patients who did not complete any surveys or completed only one survey.
- All patients received surgery within the first 3-months of diagnosis and majority of them also received another line of therapy such as chemotherapy and/or radiation.

Statistical analysis

- Based on our observations, we chose 9-months timepoint as a cut-off point for the analysis.
- The main analysis consisted of a univariate Cox Proportional Hazard (PH) regression analysis using the survival R package[6] to:
  - Examine the effects of MGMT methylation status on OS during the first 9-months after diagnosis and on OS beyond 9-months after diagnosis.
  - Examine the association between EQ5D5L domains and OS during the first 9-months and beyond 9-months after diagnosis.
- For all statistical analyses, p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

- There were 145 patients with primary diagnosis of GBM and known MGMT methylation status.
- The median age was 54 years and 55 years among methylated and unmethylated GBM patients, respectively. Among patients who completed a maximum of one questionnaire, the median age was 53 years (methylated) and 54.5 years (unmethylated).
- There were more unmethylated patients (n = 38) who received targeted therapy and immunotherapy than methylated patients (n = 16).

Overall Survival

- **KM curves for OS** were assessed among 145 GBM patients (n = 52, methylated and n = 93, unmethylated). Median OS of methylated and unmethylated GBM patients were 45.5 months and 29.6 months, respectively. Methylation status did not have any differential effects during the first 9 months after diagnosis **(Figure 1).**
- KM curves assessed 97 GBM patients who completed **at least two EQ5D5L surveys** (n = 36 methylated, and n = 61 unmethylated). Median OS of methylated and unmethylated GBM patients are 60.4 months and 29.6 months, respectively **(Figure 2).**
- KM curves were assessed among 48 GBM patients who completed **<2 surveys** (zero surveys: n = 4, or one survey: n = 44). Median OS of methylated and unmethylated GBM patients were similar at 21.4 and 24.4 months, respectively **(Figure 3).**

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Results

Figure 1: KM curves of overall survival in the overall GBM patient population by MGMT methylation status

No difference between methylated and unmethylated GBM during first 9-months after diagnosis.

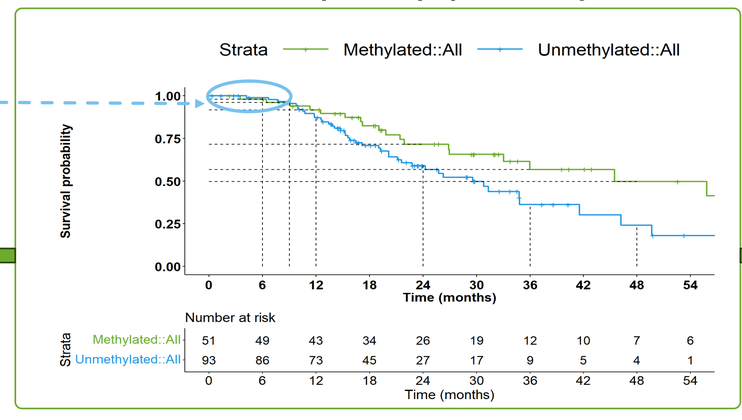


Figure 2: Patients who completed ≥2 EQ5D5L surveys show difference in OS when stratified by MGMT methylation

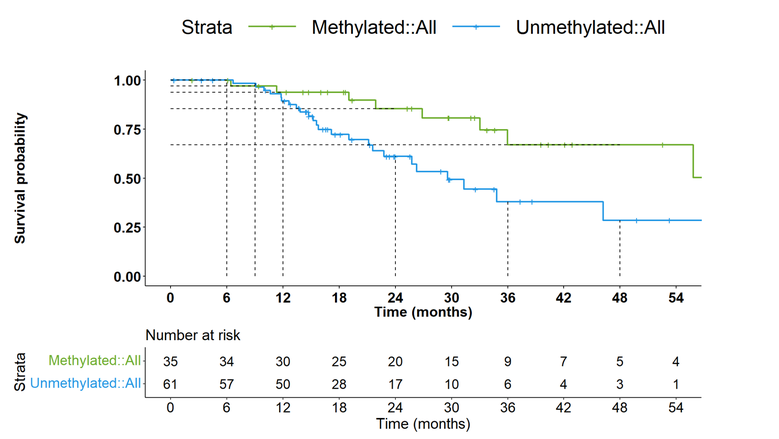
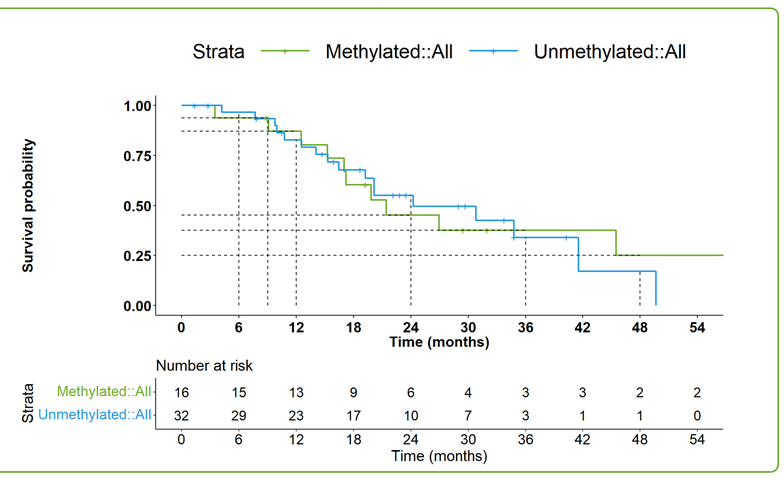


Figure 3: Patients who completed <2 EQ5D5L surveys show no difference in OS when stratified by MGMT methylation



EQ5D5L Quality of life

- Overall, methylated and unmethylated GBM patients provided scores indicating no problem (level = 1) to moderate problems (level = 3).
- Patients with methylated GBM generally provided a higher score (between slight to moderate problems) for each of the five EQ-dimensions than unmethylated GBM patients, although not statistically significant.
  - Larger mean score differences between methylated and unmethylated GBM in EQ5D: **mobility, self-care and usual activities** during the first 9-months after diagnosis.
  - There is minimal difference in mean score of pain/discomfort and anxiety/depression among methylated and unmethylated MGMT.
- The hazard ratios (HR) in **Table 1** shows the hazard (or instantaneous risk) of death increases with one-unit score increase in each EQ-dimension. For example, the hazard of death in methylated GBM patients ≤ 9-months after diagnosis is increased by a multiplicative factor of 1.84 compared to those patients with a one-unit lower score in the mobility dimension.
- A significant log-likelihood test (**Table 1**) of association is observed for 3 dimensions: mobility, self-care, and usual activity for both methylated and unmethylated GBM. The association with anxiety/depression is only seen in the unmethylated group; and pain/discomfort does not show any association in any group.

Table 1: Cox PH Regression Results for Overall Survival (OS) and EQ5D5L Dimensions – First 9 months vs. after 9 months

	Methylated		Unmethylated	
	HR (95% CI)	p-value	HR (95% CI)	p-value
≤ 9-months after diagnosis				
	n = 52		n = 93	
Mobility	1.84 (1.33, 2.55)	0.00	1.47 (1.23, 1.76)	0.00
Self-Care	1.88 (1.37, 2.59)	0.00	1.60 (1.31, 1.95)	0.00
Usual Activities	1.70 (1.25, 2.32)	0.00	1.79 (1.45, 2.20)	0.00
Pain/Discomfort	1.39 (0.80, 2.44)	0.26	1.29 (0.92, 1.79)	0.15
Anxiety/Depression	1.39 (0.95, 2.03)	0.11	1.51 (1.15, 1.97)	0.00
Health Scale	0.99 (0.96, 1.02)	0.37	0.98 (0.97, 0.99)	0.00
> 9-months after diagnosis				
	n = 47		n = 83	
Mobility	1.69 (1.19, 2.42)	0.00	1.49 (1.24, 1.79)	0.00
Self-Care	1.76 (1.23, 2.52)	0.00	1.61 (1.31, 1.97)	0.00
Usual Activities	1.54 (1.10, 2.17)	0.02	1.79 (1.44, 2.22)	0.00
Pain/Discomfort	0.96 (0.49, 1.89)	0.91	1.30 (0.92, 1.82)	0.15
Anxiety/Depression	1.20 (0.77, 1.88)	0.44	1.57 (1.19, 2.06)	0.00
Health Scale	0.97 (0.95, 0.98)	0.00	0.98 (0.97, 0.99)	0.00

A p-value of < 0.05 (highlighted in yellow) indicates mean score for an EQ-dimension is significantly associated with overall survival. For health domains (Mobility, Self-care, Usual Activities, Pain/Discomfort, Anxiety/Depression): higher scores indicate worsening. For Health Scale: higher scores indicate improvement.)

Discussion

- Our results are concordant with previous research that methylated GBM patients have a better survival than unmethylated GBM patients.[7]
- MGMT methylation status does not have an impact on OS during the first 9-months after diagnosis. This delay may be related to MGMT in relation to TMZ activity, and it deserves more research to understand their relationship.
- **Patients with methylated GBM** generally provided a higher score (between slight to moderate problems) for each of the five EQ-dimensions than unmethylated GBM patients. This difference, however, was not statistically significant. **In both methylated and unmethylated groups,** the absence of relationship between pain/discomfort and survival (**Table 1**) is expected because GBM is not a cancer associated with major pain besides initial headaches.[8] **Only in patients with unmethylated MGMT** was anxiety/depression related to survival.
- **Among patient who completed <2 surveys,** (i) there is no differential effects on OS according to methylation status, and (ii) median survival is much shorter than in patients with methylated tumor who completed at least two questionnaires. This absence of difference may be related to the treatments received by all patients.
- A limitation is concerning the small sample size and the possible effect of survivor bias, in which EQ5D5L questionnaires of individuals who survived or lived long enough to continue to participate and complete EQ5D5L surveys. This may result in an under-representation of patients who experienced worse outcomes or died early.

Conclusion

- This hypothesis-generating study suggests a relation between QoL and OS in GBM patients even when stratified by MGMT methylation status.
- It also highlights the need for more research to understand the relationship between QoL and survival in GBM patients.

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