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"Comprehensive Analysis of Factors Influencing Recurrence and Survival in Glioblastoma: Implications for Treatment Strategies": A Single Center Study †

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Abstract: Glioblastoma is a highly aggressive malignancy affecting the brain and central nervous system. It is the most common malignant primary brain tumor, yet its prognosis remains poor. Median survival typically ranges from around 13 months with standard treatment to up to 19.9 months in some recent clinical trials. Despite advances in treatment, the aggressive nature of glioblastoma continues to present significant challenges for improving patient outcomes. This study aimed to analyze various biological, radiological, and molecular factors associated with glioblastoma recurrence and to estimate survival outcomes. A total of 104 glioblastoma patients diagnosed between January 2017 and September 2022 were included. Patient demographics, treatment received, and molecular characteristics were obtained from the Electronic Patient Record (EPR). Tumor molecular characteristics were analyzed using the OnkoSight Advanced CNS NGS panel. Statistical analyses were performed to develop a prognostic model for glioblastoma recurrence and estimate survival rates. Among the patients, 65.4% had no recurrence, with a mean age of 63 years. No gender or BMI differences were observed, but ages <60 years were associated with recurrence. Radiological findings showed no significant differences in tumor size, necrosis, site, or focality. In multivariate analysis, the female gender, obesity, old age (>60 years), or bifocal tumors were associated with decreased glioblastoma recurrence. However, factors like tumor site, size, necrosis, *MGMT* promoter methylation, and *EGFR* alteration showed no significant association with recurrence. Median survival was 12 months, with older age significantly associated with shorter survival. Tumor sizes >4 cm showed shorter survival trends but not statistically significantly. Patients who lived longer experienced more tumor recurrence incidents. Standard or non-standard treatments were associated with longer median survival compared to no treatment. Our findings provide insights into factors influencing glioblastoma recurrence and survival. Age, gender, and tumor characteristics play pivotal roles in recurrence. Understanding these factors could aid in optimizing treatment strategies and improving patient outcomes. However, further multicentric investigations are needed to validate these findings. This study emphasizes the importance of considering biological and radiological factors in clinical decision-making for glioblastoma cases.

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1. Introduction

Glioblastoma is acknowledged as one of the most aggressive malignancies and the most prevalent malignant primary tumor affecting the brain and central nervous system. It accounts for 14.5% of all central nervous system tumors and 48.6% of malignant central nervous system tumors [1]. Glioblastoma is an astrocytic neoplasm characterized by the presence of microvascular proliferation and/or necrosis along with absence of isocitrate dehydrogenase (*IDH*) gene mutation. Additional molecular alterations present are *TERT* promoter mutations, *EGFR* gene alterations, or alterations in chromosome 7 (gain) or chromosome 10 (loss) [2]. Glioblastoma is an aggressive form of cancer that affects the brain or spinal cord, with a higher incidence observed in older adults, although it can manifest at any age. The prognosis for glioblastoma relies on numerous factors, with recurrence and survival being pivotal prognostic indicators following primary tumor resection and chemoradiotherapy. Recurrence is characterized by tumor regrowth, despite treatment. Standard treatment for glioblastoma involves surgical resection, if feasible, followed by radiotherapy and chemotherapy using temozolomide. Radiotherapy is administered at a dose of 60 Gray (Gy) in 2 Gy fractions, with temozolomide given concurrently and continued for 6 months thereafter. Hypofractionated radiotherapy may be considered for patients unable to tolerate standard radiotherapy [3]. Proton beam therapy (PBT) emerges as a viable alternative, as evidenced by a multicenter prospective registry study conducted in Japan, which suggests that PBT demonstrates comparable efficacy to conventional radiotherapy in the management of glioblastomas [4]. At the time of relapse, nitrosourea-based chemotherapy is commonly administered, although no therapies at this stage have shown significant survival benefits in clinical trials. The median overall survival (OS) for glioblastoma patients receiving standard treatment is approximately 13 months, with survival rates of 82% at 6 months, 55% at 12 months, and 19% at 24 months [5]. In the GLORIA trial, which examined the combination of olaptesed pegol with radiation and other treatments, the median OS was reported to be 19.9 months for patients with newly diagnosed, inoperable, or partially resected glioblastoma with unmethylated *MGMT* status [6]. Additionally, a study reported a mean OS of 29 months for glioblastoma patients, although only 5.02% of patients survived beyond this period. Factors such as age and gender significantly impacted survival, with younger patients and males generally having better outcomes [7]. This study aimed to analyze various biological, radiological, and molecular alterations associated with glioblastoma recurrence and to estimate survival outcomes for both recurrent and non-recurrent glioblastoma cases in order to assess the impact of different treatment modalities.

2. Materials and Methods

2.1. Patients Characteristics

A review of the laboratory information system (LIS) identified all patients with primary glioblastoma that were histologically diagnosed at Northwell health system/Lenox Hill Hospital from January 2017 to September 2022 using the 2016 WHO Classification of Tumors of the CNS and comprehensive molecular workup equivalent to glioblastoma *IDH*-wild type/grade 4 according to the 2021 WHO classification. Patients were excluded if they had a previously identified primary brain tumor, either histologically or radiologically. Patient demographics, treatment received, relapse history if present, and date of death or last contact were collated from the Electronic Patient Record (EPR). A total of 93.2% of patients had expired at the time of analysis, suggesting an adequate capture of patient death records. The tumor molecular characteristics were collated via the center's LIS. The molecular workup included tissue testing with OnkoSight Advanced CNS NGS (Next Generation Sequencing) panel (GenPath) targeting 29 genes per NCCN/WHO guidelines

(except *CDKN2B*) and reporting the immunotherapy genomic biomarkers tumor mutation burden and microsatellite instability. In addition, *MGMT* (O6 -methylguanine DNA-methyltransferase) promoter methylation was performed using bisulfite pyrosequencing. The assessment of resection extent and recurrence status was conducted as follows: After surgery, all patients received a postoperative MRI with and without contrast within 48–72 h. We determined the extent of resection by comparing pre- and postoperative MRIs. A patient was classified as having achieved complete resection if the postoperative MRI showed minimal or no residual tumor. Glioblastoma tumor recurrence was defined by a combination of clinical symptoms, radiological findings, and histopathological examination, specifically identifying worsening neurological symptoms and an increase in tumor size on periodic MRIs. All 36 patients diagnosed with recurrent glioblastoma underwent either a biopsy or frozen section diagnosis to confirm their recurrence. Survival was defined as the time from the date of diagnosis to death or last known contact.

2.2. Statistical Analysis

Two main sets of analyses were performed. First, a prognostic model for glioblastoma tumor recurrence: data were independently extracted in the form of variables from the included cases. The following variables were collected from each case; biological factors (age, gender, and BMI); radiological factors (size, location, and focality); and molecular markers (*MGMT* promoter methylation status and *EGFR*, among others). Data were coded and entered into a database constructed through the SPSS version 21. Bivariate analysis was conducted, followed by multivariate analysis to develop a prognostic model for glioblastoma tumor recurrence. For estimating the survival rate of the patients, the following variables were collected from each case; treatment received, surgery (biopsy, partial, or complete resection); chemoradiotherapy (standard, non-standard, or no treatment); and postoperative follow up (development of recurrence and survival duration). Data analysis was performed using Jamovi (Version 2.3). Data were analyzed by using the Kruskal–Wallis test for continuous variables after testing for normality using the Shapiro–Wilk test, whereas the chi-square test or Fisher's exact test were used for categorical variables. Bivariate analysis was conducted to determine the association between variables. Survival analysis using Kaplan–Meier estimate graphs was done to compare survival probabilities between groups.

3. Results

3.1. Baseline Characteristics of the Study Population

A total of 104 glioblastoma patients were enrolled in this study. The baseline characteristics and radiological features of all the patients are summarized in Table 1. Continuous variables like age and BMI tumor size were found to be normally distributed with Skewness and Kurtosis (0.09, −0.74), (0.95, 1.17), and (0.197, −0.06), respectively, that highlight the accurate representation of the sample to the general population. Our study included 68 male and 36 female patients with a mean age of 63 ± (15.5) years. Among the cases, 68 (65.4%) patients had no recurrence, and 36 (34.6%) patients developed a recurrence during follow-up. The mean BMI of the included patients was calculated as 26.6 ± (5.3). No differences were observed in gender and BMI. However, the patient's age was statistically associated with tumor recurrence, as shown in Table 1.

3.2. Radiological Findings

The mean size of the tumor was found to be 4 cm ± (1.5). Necrosis was reported in half of the included cases (52 cases) and the tumors were found to be equally distributed among different brain sites, like parietal, frontal, or temporal lobes as 26%, 31.7%, and 29.8%, respectively. A total of 86% tumors were unifocal and 9.6% were bifocal. No statistical differences were observed in tumor sizes, presence of necrosis, tumor locations, or tumor focalities (Table 1).

Table 1. Demographic and radiological features of the included cases (n = 104).

	Frequency	%	Glioblastoma Tumor Recurrence		p Value
			Yes n (%)	No n (%)	
Age					
Mean age ± (SD)	63.3 ± (15.5)	-	-	-	0.02 [a,*]
Less than 60	45	43.3	21 (46.7)	24 (53.3)	
More than 60	59	56.7	15 (25.4)	44 (74.6)	
Gender					
Male	68	65.4	27 (39.7)	41 (60.3)	0.13 [a]
Female	36	34.6	9 (25.0)	27 (75.0)	
BMI					
Mean BMI ± (SD)	26.6 ± (5.3)	-	-	-	
Normal	45	43.3	18 (40.0)	27 (60.0)	0.14 [a]
Overweight	36	34.6	14 (38.9)	22 (61.1)	
Obese	23	22.1	4 (17.4)	19 (82.6)	
Tumor Size (Radiology)					
Mean size ± (SD)	4	-	-	-	0.5 [a]
Less than 4 cm	68	65.4	22 (32.4)	46 (67.6)	
More than 4 cm	36	34.6	14 (38.9)	22 (61.1)	
Necrosis (Radiology)					
No	52	50.0	14 (26.9)	30 (73.1)	0.09 [a]
Yes	52	50.0	22 (42.3)	38 (57.7)	
Radiological Site					
Parietal	27	26.0	5 (18.5)	22 (81.5)	
Frontal	33	31.7	13 (39.4)	20 (61.6)	0.07 [a]
Temporal	31	29.8	15 (48.4)	16 (51.6)	
Others	13	12.5	3 (23.1)	10 (76.9)	
Focality (Radiology)					
1 focus	90	86.5	33 (36.7)	57 (63.3)	0.6 [b]
2 foci	10	9.6	2 (20.0)	8 (80.0)	
3 foci	4	3.8	1 (25.0)	3 (75.0)	

BMI: Body Mass Index, SD: standard deviation. a: Chi-square test, b: Fisher exact test. * $p \leq 0.05$.

3.3. Predictors of Glioblastoma Tumor Recurrence

Among the studied 104 patients, 36 had tumor recurrence, the median (IQR) of recurrence duration was 10 (8) months (range: 2 months–51 months). Table 2 expresses the adjusted and unadjusted analysis between the glioblastoma tumor recurrence and the main independent variables. In the multivariate analysis, female gender, obesity (BMI $\geq$ 30), old age >60 years, bifocal tumors were statistically associated with decreased glioblastoma recurrence. On the contrary, factors like tumor site, especially temporal and frontal tumors, were statistically associated with a significant increase in glioblastoma recurrence. Factors like tumor size, presence of necrosis, *MGMT* promotor methylation status, and *EGFR* alteration were forced in the final model in light of their association with the dependent variable in the previous literature, but these factors failed to show any statistical significance for glioblastoma tumor recurrence.

Table 2. Simple and multivariate analysis of factors associated with glioblastoma tumor recurrence among the study population.

Explanatory Variables	Univariate Analysis			Multivariate Analysis		
	Crude OR	95% CI	*p* Value	AOR †	95% CI	*p* Value
Age Less than 60 More than 60	0.40	(0.17–0.89)	0.02 *	0.23	(0.08–0.66)	0.007 *
Gender Male Female	0.50	(0.21–1.20)	0.13	0.11	(0.04–0.59)	0.007 *
BMI Normal Overweight Obese	1.00 0.95 0.32	Reference (0.39–2.34) (0.92–1.08)	0.92 0.07	1.00 0.43 0.11	Reference (0.12–1.57) (0.19–0.54)	0.199 0.008 *
Tumor Size Less than 4 More than 4	0.75	(0.32–1.74)	0.50	0.38	(0.12–1.32)	0.128
Necrosis (Radiology) No Yes	2.00	(0.87–4.53)	0.10	2.75	(0.84–8.94)	0.093
Radiological Site Parietal Frontal Temporal Others	1.00 2.86 4.13 1.32	Reference (0.86–9.45) (1.24–13.7) (0.26–6.64)	0.08 0.02 * 0.73	1.00 6.36 7.09 1.51	Reference (1.28–31.7) (1.59–31.6) (0.21–11.3)	0.024 * 0.010 * 0.684
Focality 1 focus 2 foci 3 foci	1.00 0.43 0.58	Reference (0.09–2.16) (0.06–5.76)	0.31 0.64	1.00 0.09 0.29	Reference (0.01–1.78) (0.01–5.89)	0.05 * 0.425
MGMT promotor methylation status No Yes	1.33	(0.61–2.95)	0.47	0.55	(0.18–1.67)	0.294
EGFR Positive Negative	0.97	(0.424–2.24)	0.95	1.21	(0.42–3.47)	0.735

AOR: Adjusted Odds Ratio, BMI: Body Mass Index, CI: confidence interval, EGFR: Epidermal growth factor receptor, OR: Odds Ratio, † AOR: Adjusted for (Age, Gender, BMI, Necrosis, Size, Site, Focality, Methylation, and EGFR) factors. * $p \leq 0.05$. Nagelkerke R Square of the model: 0.39.

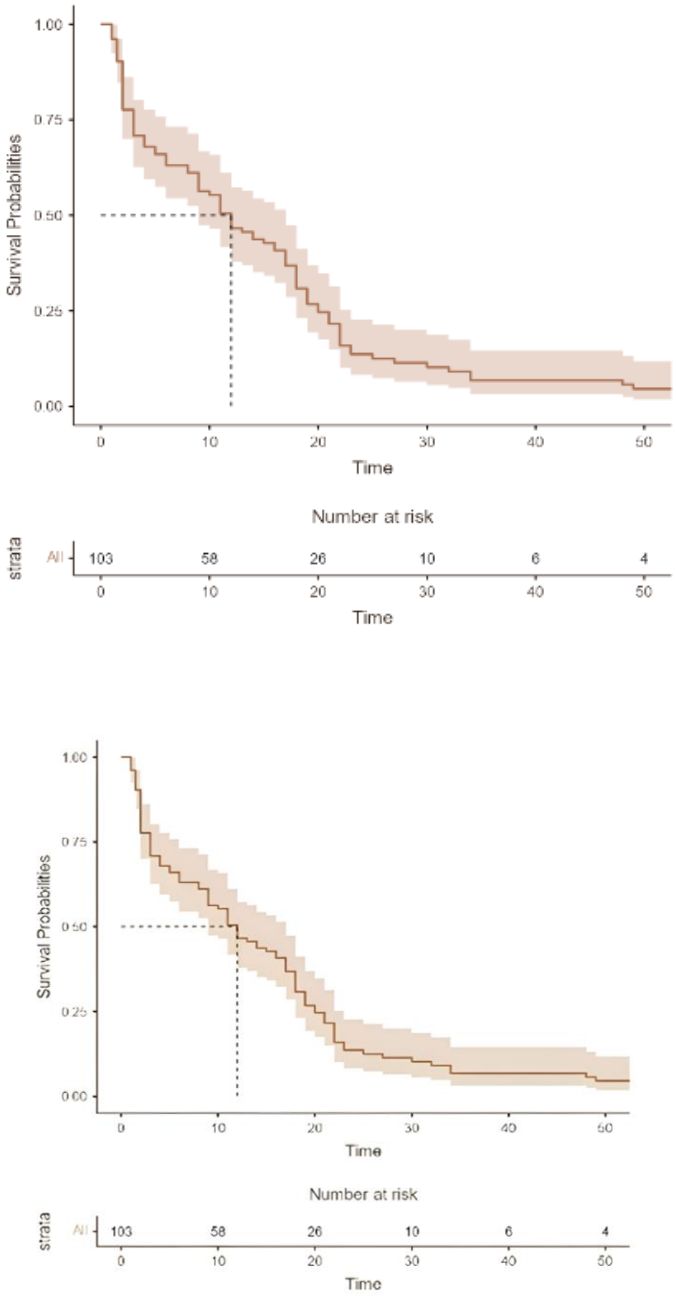
Table 3 expresses the association between tumor recurrence among patients and the type of treatment they received. There was a significant difference between patients with tumor recurrence and those without as regards the types of treatment each received; as (86.1%) of patients with tumor recurrence were on non-standard treatment, while (39.7% of patients without tumor recurrence were on no treatment ($p < 0.001$).

Table 3. Association between tumor recurrences among studied patients and types of treatment.

	Recurrence		*p*-Value
	Yes (*n* = 36)	No (*n* = 68)	
No treatment	2 (5.6%)	27 (39.7%)	<0.001
Standard treatment	3 (8.3%)	5 (7.35%)	
Non-standard treatment	31 (86.1%)	35 (51.4%)	

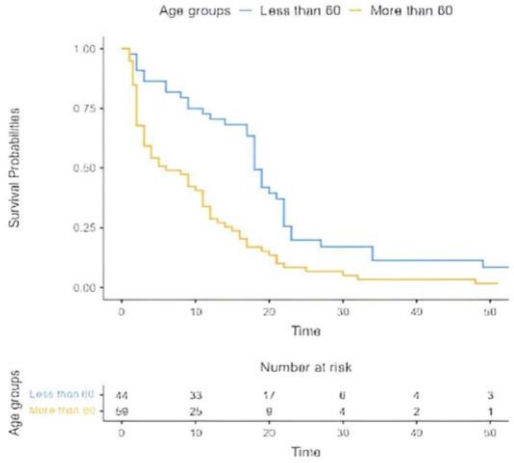
3.4. Survival Analysis

Of the 104 total of patients, only 7 (6.7%) were still alive by the end of the study, while the other 96 patients (93.2%) either died or were missed in the follow up, and the overall median survival was 12 months (IQR: 16.5 months) [Figure 1A].

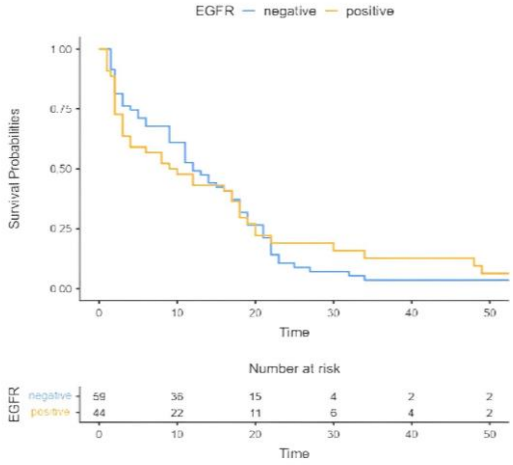


(**A**)

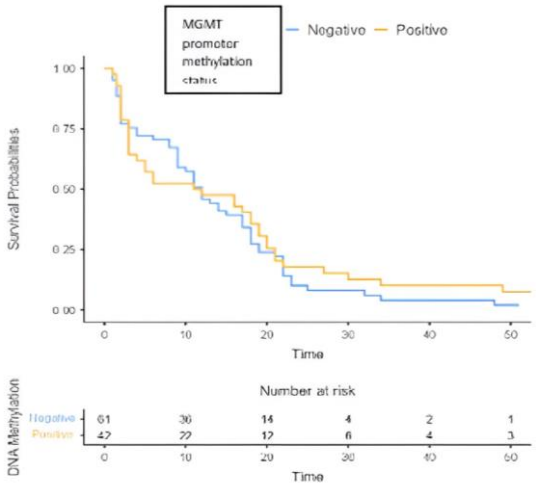
Figure 1. *Cont.*



(**B**)

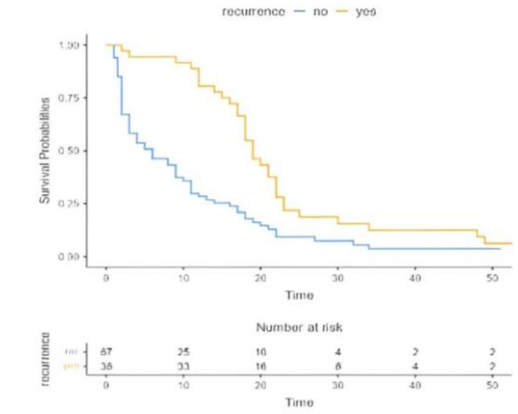


(**C**)

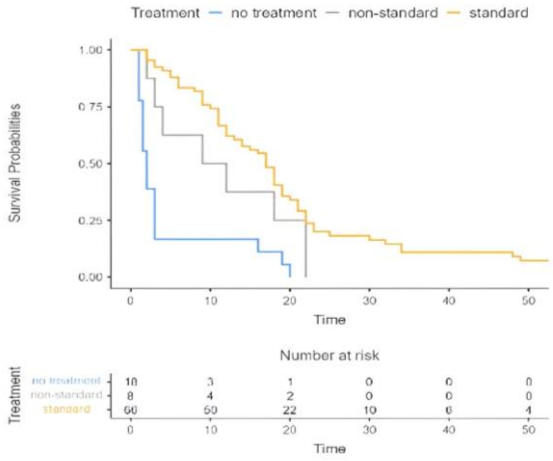


(**D**)

Figure 1. *Cont*.



(**E**)



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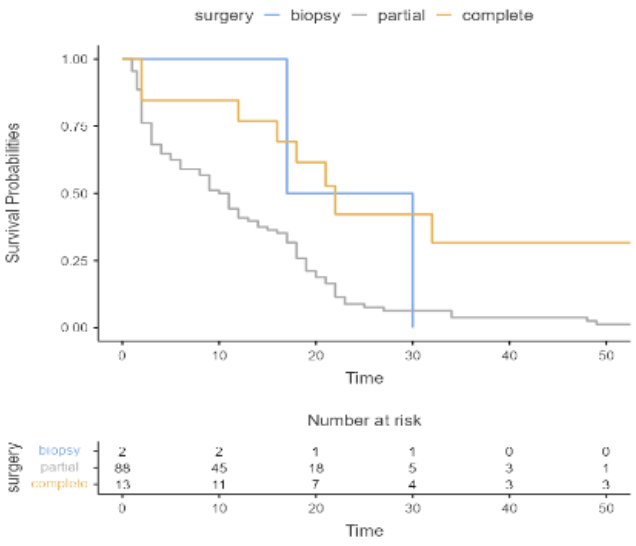

(**G**)

Figure 1. Kaplan–Meier survival estimates: (**A**) Overall survival, (**B**) Age groups, (**C**) *EGFR alterations*, (**D**) *MGMT* promoter methylation status, (**E**) Recurrence, (**F**) chemoradiotherapy treatment, (**G**) Surgery.

On comparing patients' characteristics to survival, older age was significantly associated with shorter survival ($p < 0.001$) [Figure 1B], while there was no significant difference in survival based on gender ($p = 0.78$). According to tumor characteristics, patients who had tumors larger than 4 cm in size had shorter survival rates in comparison to those with tumors smaller than 4 cm (9 months versus 14 months), although this difference was not statistically significant ($p = 0.336$).

Other tumor characteristics such as *EGFR* alteration and *MGMT* promotor methylation status were not significantly associated with survival [Figure 1C,D]. A total of 36 patients experienced tumor recurrence, with a median recurrence duration of 10 months (standard deviation: 8 months), ranging from 2 to 51 months. The median survival time for those with recurrence was 19 months (interquartile range: 18–22 months). In contrast, patients without recurrence had a significantly shorter median survival of 6 months (interquartile range: 3–10 months). Participants who did not experience recurrence had a significantly shorter survival rate compared to those with recurrence ($p < 0.001$) [Figure 1E]. Patients who received standard and non-standard treatments had significantly longer median survival rates (17 months and 10.5 months, respectively) in comparison to patients who received no treatment (2 months) ($p < 0.001$) [Figure 1F]. Patients who went for complete tumor resection had significant longer survival rates when compared with patients that went for partial tumor resection (22 and 10.5 months, respectively ($p < 0.003$)) [Figure 1G]. In multivariate analyses, only age, chemoradiotherapy treatments, and surgery remained significant predictors of survival (Table 4).

Table 4. Survival according to different patient and tumor characteristics.

Variable	N.	Median Survival 95% CI	*p*-Value	Hazard Ratio Univariate	Hazard Ratio Multivariate
Age					
Less than 60 years	45	19 (18–22)	0.001	2.47 (1.61–3.77)	2.30 (1.36–3.88)
More than 60 years	59	5 (3–11)			
Sex					
Male	68	10 (3–18)	0.78	0.75 (0.50–1.14)	-
female	36	12 (9–18)			
Recurrence					
No	68	6 (3–10)	<0.001	0.43 (0.28–0.67)	1.94 (1.17–3.24)
Yes	36	19 (18–22)			
Tumor size					
Less than 4 cm	45	14 (12–19)	0.336	0.82 (0.54–1.24)	-
More than 4 cm	51	9 (4–17)			
Radiological Site					
Parietal	27	8.5 (4–19)	0.231	-	-
Frontal	33	11.5 (4–19)		1.04 (0.60–1.79)	
Temporal	31	17 (11–21)		0.86 (0.50–1.47)	
Others	13	4.5 (2–21)		1.74 (0.86–3.53)	
EGFR alteration					
Negative	59	12 (9–18)	0.953	0.99 (0.66–1.49)	0.92 (0.55–1.54)
Positive	45	9.50 (4–18)			
MGMT promoter Methylation Status					
Negative	62	12 (9–17)	0.501	0.87 (0.57–1.31)	0.79 (0.46–1.36)
Positive	42	11.5 (4–19)			
Treatment					
No treatment	18	2 (1.5–3)	<0.001	-	-
Non-standard	8	10.5 (4–20)		0.36 (0.15–.083)	0.38 (0.14–1.03)
Standard	66	17 (13–19)		0.20 (0.12–0.36)	0.22 (0.11–0.44)
Surgery					
Biopsy	2	23.5 (17–30)	0.003	-	-
Partial resection	88	10.5 (6–14)		1.94 (0.47–7.92)	1.32 (0.29–6.04)
Complete resection	14	22 (16–29)		0.60 (0.13–2.84)	0.31 (0.05–1.78)

4. Discussion

The neurosurgical literature has long debated the efficacy of total resections of malignant gliomas [7,8]. Surgery is preferred for patients displaying radiological signs of glioblastoma tumor progression post-chemoradiotherapy, aiding in both diagnosis and tumor debulking [9,10]. Molinaro AM et al. confirmed that maximal resection of contrast-enhancing tumors is associated with a longer overall survival in glioblastoma patients across all subgroups. Furthermore, a maximal resection of non-contrast-enhancing tumors was linked to longer overall survival in younger patients [11]. Sanai N et al. found that the median overall survival for 500 glioblastoma patients was 12.2 months, with a significant survival advantage seen with as little as a 78% extent of resection (EOR) of the tumor. They observed further improvements in survival in the 95–100% EOR range. In our cohort, patients who underwent complete tumor resection had a significantly longer survival rate compared to those who had a partial tumor resection, with median survival times of 22 and 10.5 months, respectively ($p < 0.003$) [12].

After considering various clinical factors, histopathological results from repeat surgeries are often used to assess prior treatment efficacy, anticipate diagnosis, and formulate subsequent management plans. However, clarity is lacking in the literature regarding which histopathological variables, if any, are associated with prognosis following repeat surgeries. Additionally, post-radiation and temozolomide treatment, most glioblastoma specimens exhibit a mix of therapy-related changes and viable tumor, complicating clinical interpretations of the histopathology results [13,14]. Hence, our study was conducted involving 104 glioblastoma patients to evaluate various factors significantly affecting tumor recurrence and patient survival.

Our findings indicated that an age of >60 years, the female gender, or obesity significantly decrease glioblastoma recurrence. These results align with Stark et al.'s study [12], which reported a higher proportion of females having better prognosis and longer survival rates with glioblastoma tumors. Our study result corresponds with other studies showing a male predominance, with a male-to-female ratio ranging from 1.2:1 to 2.1:1 [15–19].

The literature suggests that age significantly associates with glioblastoma patient survival and low recurrence rates. Patients aged 45–65 years are often categorized based on favorable and unfavorable prognosis [17,18]. A study found individuals aged 60 years or younger had significantly favorable prognoses and lower recurrence rates [18]. However, in our study, most patients with glioblastoma tumor recurrence were under 60 years old, with a median survival time of 19 months. In contrast, those without recurrence had a significantly shorter median survival of just 6 months. This notably lower survival rate in the non-recurrent group may be linked to their older age (>60 years) and the fact that about 40% of them did not receive standard chemoradiotherapy after surgery. Additionally, the lack of recurrence in these patients may be attributed to the fact that they did not live long enough to experience it.

Histological records by Batzdorf and Malamud suggest that multifocal tumors arise due to dissemination or growth through established brain routes, while multicentric studies show widely spread lesions across different brain hemispheres and lobes without following such pathways [20,21]. The incidence of multiple independent tumors ranges from 2.4% to 7.5% [22]. Stark et al. [23] reported a significant association between better prognosis and fewer recurrence with single lesions. Although our study indicated few recurrences in unifocal tumors, the association was insignificant. Li et al. demonstrated improved survival rates and fewer recurrences in patients with single frontal lobe tumors compared to multiple or other single lobe locations [24]. Filippini reported prognostic impacts based on tumor extensions (single vs. multiple lobes affected) among patients who underwent resection or biopsy only [17]. Our study found no significant relation between radiological sites and recurrence.

Patients with *MGMT* promoter methylation in glioblastoma usually experience better outcomes with temozolomide treatment, as methylation silences the *MGMT* gene, increasing tumor susceptibility to chemotherapy. Szylberg reported that *MGMT* promoter

methylation is associated with a favorable prognostic factor, showing the longest survival rates in younger patients at the time of diagnosis ($\leq$50 years) and in those with smaller tumors ($\leq$32 cm^3) [25]. Conversely, Egaña reported no association between methylation of the *MGMT* promoter and molecular markers such as *ATRX*, *IDH*, p53, and Ki67. These findings suggest that *MGMT* methylation did not influence glioblastoma patient survival in their cohort [26]. In a meta-analysis involving 1458 patients, *EGFR* overexpression was found to be an indicator of poor prognosis in overall survival in glioma patients [27]. Additionally, Song reported that *EGFR* overexpression had a significantly deleterious effect on the survival of glioblastoma patients [28]. In our study, we did not find any significant association between *MGMT* promoter methylation status or *EGFR* alteration and glioblastoma tumor recurrence or patient survival. The lack of significance for *MGMT* promoter methylation status could be due to the fact that nearly two-thirds of the cases had unmethylated *MGMT* promoters.

Our study also demonstrated that age, chemoradiotherapy, and surgery significantly affect glioblastoma patient survival. Patients younger than 60 years and those receiving standard treatment had significantly longer survival times. Furthermore, patients with longer survival times tended to experience more tumor recurrence incidents. These results provide further understanding of the factors influencing glioblastoma outcomes and may guide treatment decisions in clinical practice.

This study's limitations include its single-center design, which restricted the scope of data collection and variable analysis, potentially limiting the generalizability of the results. Additionally, the retrospective nature of the study and the relatively small sample size may have affected the robustness of the findings, as opposed to a controlled or randomized trial. Approximately two-thirds of the participants had unmethylated *MGMT* promoters, which might have led to an underestimation of the role of *MGMT* promoter methylation as a significant prognostic factor. Moreover, our NGS panel did not include other critical mutations, such as *TERT*, which are known to significantly impact patient survival

5. Conclusions

To the best of our knowledge, this is the first study addressing variables associated with glioblastoma tumor recurrence. Our data highlight the importance of using biological and radiological factors like age, gender, BMI, and tumor location in the clinical implications and decision-making for glioblastoma cases. A further larger multicentric investigation is required to validate our single-centered study.

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