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Original Article

Oncology Section

Survival Analysis and Factors Affecting Treatment Outcome in Glioblastoma Multiforme: A Cohort Study

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ABSTRACT

Introduction: High-grade gliomas, especially Glioblastoma Multiforme (GBM), are the most prevalent primary brain tumours in adults. Treating GBM is challenging due to resistant tumour cells, resulting in a dismal prognosis. While GBM often develops spontaneously, familial gliomas have also been identified in 1% of cases. Primary and secondary glioblastoma are the subtypes that affect patients of varying ages and develop via different paths.

Aim: To estimate the two year survival and to assess factors affecting survival in patients diagnosed with GBM and to evaluate the "ability for self-care" following treatment.

Materials and Methods: The cohort study investigated treatment outcomes in GBM using a sample of 65 patients from the Department of Radiation Oncology at Government Medical College Thrissur, a tertiary care centre in Kerala, India. The patients were diagnosed between January 2018 and December 2019. Survival and the factors determining survival were explored through case records and telephonic interviews with primary caregivers. Median survival and two year survival rates were calculated. The study examined possible associations of survival with patient-related, tumour-related, and treatment-related factors. Patient-related factors assessed were age, gender, and Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis. Tumour-related factors assessed included tumour location, laterality, and volume based on pretreatment Magnetic Resonance Imaging (MRI). Treatment-related factors such as extent of surgery, postoperative radiotherapy, and chemotherapy were also assessed. Data analysis was performed using the Statistical Package for Social Sciences (SPSS version 21.0). Qualitative variables were expressed in percentage and compared using the Chi-square test or Fisher's-exact test. Quantitative variables were expressed as mean and standard deviation and compared using unpaired t-tests. Telephonic interviews with primary caregivers were conducted to assess the "ability for self-care" following treatment.

Results: The study included a total of 65 cases, with a mean patient age of 54 years. Out of the patients, 45 (68%) patients were male, while 20 (32%) patients were female. The median survival for GBM was found to be eight months. The one year and two year survival rates were 18.46% (12 patients) and 10.8% (7 patients), respectively. The survivors had a mean age of 48 years. There were no statistically significant differences in survival based on sex (p-value=0.527), tumour location (p-value=0.765), and laterality (p-value=0.596). Survival was found to be related to ECOG performance status at diagnosis (p-value=0.001) and tumour volume (p-value=0.002). Among the patients, 37 (58%) patients were able to perform self-care after treatment, while 28 (42%) patients were unable to do so.

Conclusion: The survival of patients with GBM is related to ECOG performance status at diagnosis and the pretreatment volume of the tumour. The evidence was insufficient to establish a relationship between survival and the administration of postoperative radiotherapy and chemotherapy. Despite multimodality treatment protocols, the survival of patients with GBM remains dismal. A tailored treatment protocol that weighing morbidity of treatment and cost effectiveness on one side and survival on the other side is the need of the hour.

Keywords: Brain tumours, Familial gliomas, Temozolomide

INTRODUCTION

Primary brain tumours account for about 2% of all malignant diseases. In the United States (US), there are over 17,000 diagnosed cases annually, resulting in approximately 13,000 deaths at a rate of 5 per 100,000 people [1]. Among these, high-grade gliomas, particularly Glioblastoma Multiforme (GBM) or Grade-IV glioma, are the most common primary brain tumours in adults. GBM includes primary and secondary subtypes, affecting patients of different ages and developing through various pathways [1]. The Central Brain Tumour Registry of the United States (CBTRUS) reported average annual age-adjusted incidence rates of 2.53 and 3.98 per 100,000 person-years for females and males, respectively. The male-to-female incidence ratio was 1.58. The frontal lobe and temporal lobe had the highest rates of brain cancers overall (25.6% and 19.6% respectively) [2].

The GBM often occurs spontaneously, although familial gliomas have been identified in 1% of cases [1]. The clinical manifestations of GBM depend on the size, location, and architectural configuration of the areas affected by the tumour. As many as 30% to 50% of patients with high grade glioma present with seizures [3]. Due to resistant tumour cells and the limited ability of most chemotherapy drugs to cross the blood brain barrier, treating GBM is difficult. Since, the landmark study by Stupp R et al., in 2005, the new standard of care has been postoperative concurrent chemoradiotherapy followed by adjuvant chemotherapy with Temozolomide (TMZ) [4]. Although this comprehensive strategy has been used, the prognosis for GBM patients with GBM is still dismal [5]. The GBM has a 4.7% five year survival rate. Rarely, does the median survival period after diagnosis surpass 12 months; occasionally, it may even be less. Long-term survivors are patients who live for more than 36 months [5].

In 2021, there were 31 reported cases of GBM in the Radiation Oncology Outpatient Department (OPD) at Government Medical College Thrissur, a tertiary care centre in Kerala, India. With this context, the objective of present study conducted in 2022 was to retrospectively evaluate the treatment outcome and two year survival of patients diagnosed with GBM in 2018 and 2019 at present Medical College. Hence the present study aimed to evaluate two year survival of patients diagnosed with GBM and to examine the relationship between survival and various patients-related factors, tumour-related factors, and treatment-related factors. Assessment

of quality of life of patients after treatment by conducting telephonic interviews with the primary caregivers was also done.

MATERIALS AND METHODS

The present cohort study was conducted after obtaining approval and clearance from the Institutional Ethics Committee (IEC/GMCTSR/2022/120). Permission was also obtained from the Superintendent to collect case records of patients with GBM from study institute.

The present cohort study was conducted in 2022, and case records of patients diagnosed with GBM between January 2018 and December 2019 in the Outpatient Department of Radiation Oncology at Government Medical College Thrissur, Kerala, India were reviewed.

Inclusion criteria: The inclusion criteria consisted of patients histopathologically proven to have GBM according to the World Health Organisation (WHO) Grade-IV classification [4], patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-4 [6], and patients who received surgery and adjuvant treatment (either radiotherapy, chemotherapy, or both). All patients who reported with GBM in Outpatient Department in 2018 and 2019 and met the eligibility criteria were included in the study. The number of patients reported January 2018 was 36, and the number of patients reported December 2019 was 29, resulting in a total of 65 patients included in the study.

Exclusion criteria: Patients with active infections and pregnant patients were excluded.

Study Procedure

Data regarding patient-related factors, tumour-related factors, and treatment given were collected from the case records. Patient-related factors assessed included age, gender, and ECOG performance status at diagnosis. Tumour-related factors studied were tumour location, laterality, and volume based-on pre-treatment MRI. Treatment-related factors such as the extent of surgery, postoperative radiotherapy, and chemotherapy were also assessed. The treatment outcome measure was survival. Primary caregivers of each patient were contacted using the phone numbers provided in the case records. The relationship of the caregiver to the patient was verified, and a telephonic interview was conducted using a questionnaire. Verbal consent for the study and consent for recording the telephonic conversation were obtained from the caregiver. Details regarding the date of death or, if alive, the present condition of the patient or the condition after treatment completion till death were collected. The "ability to do self-care" data were also collected using a questionnaire. The questions asked were whether the patient was able to independently have food, dress themselves, and go to the toilet after completing treatment. If, the patient was able to perform all three components, it was considered as "able to do self-care." If, any of the components were not possible, it was considered as "not able to do self-care." All details of the telephonic interview were recorded while maintaining confidentiality. The details of each patient were entered in a structured proforma.

STATISTICAL ANALYSIS

Qualitative variables are expressed as percentages, while quantitative variables are expressed as mean and standard deviation. Unpaired t-tests were used to compare quantitative variables, while Chi-square tests or Fisher's-exact tests were used to compare qualitative variables. A p-value <0.05 was considered statistically significant. The data was entered into an MS Excel spreadsheet and analysed using SPSS version 21.

RESULTS

The majority of the patients belonged to Thrissur and Palakkad districts of Kerala. The mean age of the patients was 54 years, with a minimum age of 19 years and a maximum age of 79 years. Among the patients, 44 (68%) patients were male and 20 (32%) patients were female. [Table/Fig-1] shows the ECOG performance status of the patients at diagnosis, with 53 (81.53%) patients having an ECOG performance status of either 2 or 3.

ECOG performance status	Frequency (n)	Percentage (%)
1	3	4.6
2	29	44.6
3	24	36.9
4	9	13.8
Total	65	100.0

[Table/Fig-1]: ECOG performance status at diagnosis (N=65).

Tumour-related factors: [Table/Fig-2] shows the distribution of tumour location. The most observed location was frontal tumour 26 (40%) patients, followed by two lobes combined 14 (21.51%) patients. Occipital 3 (4.61%) patients and three lobes combined 3 (4.61%) patients were the least observed locations. Temporal tumours accounted for 10 (15.40%) patients and parietal tumours accounted for 9 (13.80%) patients. Right-sided tumours were observed in 36 (55.41%) patients, left-sided tumours in 22 (33.81%) patients, and 7 (10.82%) patients had bilateral tumours. The severity of the tumour correlated with its volume. [Table/Fig-3] shows the distribution of tumour volume, with 43 (66.24%) patients having a volume >5 cm and 22 (33.81%) patients having a tumour size <5 cm.

Tumour location	Frequency (n)	Percentage (%)
Frontal	26	40.0
Temporal	10	15.4
Parietal	9	13.8
Occipital	3	4.6
Two lobes combined	14	21.5
Three lobes combined	3	4.6
Total	65	100.0

[Table/Fig-2]: Tumour location (N=65).

Volume	Frequency (n)	Percentage (%)
<5 cm	22	33.8
>5 cm	43	66.2
Total	65	100.0

[Table/Fig-3]: Volume of tumour (N=65).

Treatment-related factors: [Table/Fig-4] shows the extent of surgery undergone by the patients, with 7 (10.82%) patients undergoing total resection, 49 (75.41%) patients undergoing subtotal resection, and 9 (13.81%) patients having only a biopsy. A total of 63 (97%) patients received postoperative radiotherapy, while the rest were unable to do so. The majority of the patients received both postoperative radiotherapy and chemotherapy. [Table/Fig-5] shows the type of postoperative radiotherapy undergone by the patients, with curative radiotherapy being the dominant approach 61 (93.81%) patients. The curative radiation dose given was 60 Gy in 30 fractions, 2 Gy per fraction, treated five days per week over six weeks. Tele-Cobalt radiotherapy machines were used for treatment based on pretreatment MRI brain and postoperative Computed Tomography (CT) brain reports. A small percentage 2 (3.1%) patients received only palliative radiotherapy (8 Gy given as a single fraction) due to poor general condition and poor patient compliance. Total 92 % (60) patients received postoperative chemotherapy. [Table/Fig-6] shows the type of chemotherapy undergone by the patients, with 38 (58.5%) patients receiving concurrent TMZ (150 mg/m^2) and adjuvant TMZ (75 mg/m^2 for 5 days q28 days). Other patients received various combinations of concurrent and adjuvant TMZ, as well as adjuvant chemotherapy with other drugs. Adjuvant TMZ was administered for

an average of six months, with a maximum duration of 16 months. Five cases didn't receive chemotherapy due to poor patient tolerance and compliance.

Extent of surgery	Frequency (n)	Percentage (%)
Total resection	7	10.8
Subtotal resection	49	75.4
Biopsy	9	13.8
Total	65	100.0

[Table/Fig-4]: Extent of surgery (N=65).

Radiotherapy	Frequency (n)	Percentage (%)
Palliative	2	3.1
Curative	61	93.8
Total	63	96.9
NA	2	3.1
Total	65	100.0

[Table/Fig-5]: Type of postoperative radiotheray (N=65).
NA: Not applicable

Chemotherapy	Frequency (n)	Percentage (%)
Concurrent TMZ +adjuvant TMZ	38	58.5
Concurrent TMZ only	13	20.0
Adjuvant TMZ only	3	4.6
Other Chemotherapy: Drugs	6	9.2
Total	60	92.3
Not received chemotherapy	5	7.7
Total	65	100.0

[Table/Fig-6]: Type of chemotherapy considering patient's.

Quality of living after treatment: The ability of patients to do self-care after treatment was assessed through telephonic interviews with primary caregivers using a questionnaire. Out of the patients, 37 (58%) patients were able to do self-care, while 28 (42%) patients were not able to do the same.

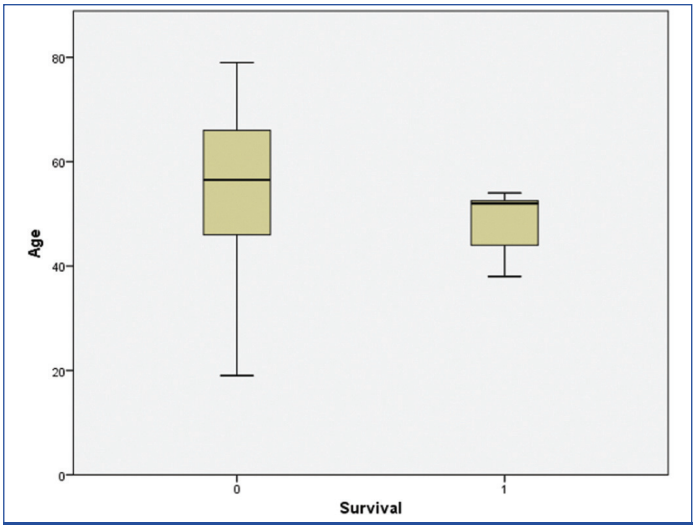
Survival analysis: The median survival in GBM was found to be eight months, with a minimum survival of six months and a maximum survival of 28 months. The one year and two year survival rates were 18.46% and 10.8%, respectively, among the 65 patients. Among the deaths, 4.6% were due to other causes, while 84.6% were tumour-related. [Table/Fig-7] shows the distribution of the causes of death.

Variables	Frequency (n)	Percentage (%)
Tumour-related	55	84.6
Other causes (myocardial infarction, uremic encephalopathy)	3	4.6
Total	58	89.2
Alive patients	7	10.8
Total	65	100.0

[Table/Fig-7]: Causes of death.

Determinants of survival: In this section, authors examined the possible relationship between patient-related, tumour-related, and treatment-related factors on the likelihood of survival in GBM patients.

Survival and patient-related factors: The patients who survived had a mean age of 48 years, while those who died had a mean age of 55 years. [Table/Fig-8] shows a Box and Whisker plot depicting survival across different age groups. [Table/Fig-9] shows survival across patient-related factors. There was no statistically significant difference in survival based on gender (p=0.527). However, survival was related to ECOG performance status at diagnosis, with all the survivors belonging to ECOG performance status 1 and 2. There was a statistically significant difference in ECOG performance score between the survivors and non survivors (χ^2=29.116, p<0.01).



[Table/Fig-8]: Survival across age: Box and Whisker plot.

Patient factors	Died	Survived	Total	p-value
Gender				
a) Female	18	3	21	0.527
b) Male	40	4	44	
ECOG performance status				
a) 1	0	3	3	0.000
b) 2	25	4	29	
c) 3	24	0	24	
d) 4	9	0	9	

[Table/Fig-9]: Survival across patient related factors.

Survival and tumour-related factors: The relationship between tumour location and survival was not statistically significant (p=0.765). Similarly, the relation between survival and laterality (right-sided, left-sided, or bilateral) was not statistically significant (p=0.595). However, patients with volume of tumour <5 cm were more likely to survive. There was a statistically significant difference in tumour volume between the survivors and non survivors (χ^2 (1)=9.426, p=0.002). [Table/Fig-10] shows the relationship between survival across tumour related factors.

Tumour-related factors	Died	Survived	Total	p-value
Tumour location				
a) Frontal	22	4	26	0.765
b) Temporal	9	1	10	
c) Parietal	9	0	9	
d) Occipital	3	0	3	
e) Two lobes combined	12	2	14	
f) Three lobes combined	3	0	3	
Laterality				
a) Right	32	4	36	0.595
b) Left	3	3	22	
c) Bilateral	0	0	7	
Volume of tumour				
a) <5 cm	16	6	22	0.002
b) >5 cm	42	1	43	

[Table/Fig-10]: Survival across tumour-related factors.

Survival and treatment-related factors: [Table/Fig-11] shows the relationship between survival and treatment-related factors. The extent of surgery was not statistically related to survival (p=0.182). The administration of radiotherapy and the type of radiotherapy given (curative or palliative) did not show a statistically significant relationship with survival, with p-value of 0.618 and 0.075,

respectively. Similarly, the administration of chemotherapy and the type of chemotherapy given did not show a statistically significant relationship with survival, with p-values of 0.419 and 0.569, respectively. The evidence was not sufficient to substantiate the relationship between survival and the administration of radiotherapy and chemotherapy.

Treatment-related factors	Died	Survived	Total	p-value
Extent of surgery				
a) Total resection	5	2	7	0.182
b) Subtotal resection	44	5	49	
c) Biopsy	9	0	9	
Postoperative radiotherapy				
a) Given	56	7	63	0.618
b) Not given	2	0	2	
Type of radiotherapy				
a) Curative	55	6	61	0.075
b) Palliative	1	1	2	
Chemotherapy				
a) Given	53	7	60	0.419
b) Not given	5	0	5	
Type of chemotherapy				
a) Concurrent TMZ+adjuvant TMZ	32	6	38	0.569
b) Concurrent TMZ only	12	1	13	
c) Adjuvant TMZ only	3	0	3	
d) Other chemotherapy drugs	6	0	6	

[Table/Fig-11]: Survival across treatment related factors.

DISCUSSION

In the present study, the treatment outcomes in GBM were investigated in a sample of 65 patients at the study Institute, diagnosed in 2018 and 2019. The survival and factors determining survival were explored, including patient-related, tumour-related, and treatment-related factors. The median survival in GBM was found to be 8 months in present study. The one year and two year survival rates were 18.46% and 10.8%, respectively, among the 65 patients. [Table/Fig-12] [1,7-9] shows the survival rates from present study compared to various other existing studies. Ghosh M et al., conducted a retrospective study called "Survival and prognostic factors for GBM" [1]. GBM was found to be diagnosed in the sixth decade of life. Men outnumber women by a ratio of 2.6:1. The right frontal lobe is the most common location. The overall one year and two year survival rates for their cohort were 19.15% and 3.27%, respectively, with a median survival of eight months.

Author's name and year of the study	Median survival	1 year survival	2 year survival
Present study (Kerala, 2022) 65 cases	8 months	18.46%	10.8%
Ghosh M et al., [1] (Bihar, India, 2017) 61 cases	7.2 months	19.15%	3.27%
Witthayanuwat S et al., [8] (Thailand, 2018) 77 cases	12 months	43.75%	21.3%
Martin San E et al., [9] (Chile, 2021) 67 cases	11.4 months	48%	15%
Brown NF et al., [7] (Basel, 2022) 490 cases	9.2 months	40.7%	13.3%

[Table/Fig-12]: Survival according to various studies [1,7-9].

The historic phase-III multi-institutional trial by Stupp R et al., found that patients who received concurrent chemoradiotherapy had a median survival of 14.6 months, compared to 12.1 months for those who received radiation alone (p=0.001). In 2009, Stupp R et al., reported long-term findings and a five-year survival rate of 9.8% with combined therapy, compared to 1.9% without it [4].

In present study, determinants of survival were examined. Survival was found to be related to ECOG performance status at diagnosis, with all survivors belonging to ECOG performance status 1 and 2. There was a statistically significant difference in ECOG performance score between the survivors and non survivors (p<0.01). Patients with a tumour volume less than 5 cm were more likely to survive, and there was a statistically significant difference in tumour volume between the survivors and non-survivors (p=0.002). Ghosh M et al., also found that age and Karnofsky Performance Status (KPS) scale were significantly related to survival [1].

The evidence in present study was not adequate to substantiate the relationship between survival and the extent of surgery, administration of postoperative radiotherapy, and chemotherapy. However, other studies have shown that the degree of surgical resection, concurrent chemotherapy, and adjuvant chemotherapy have a significant impact on survival [1,10]. The median survival period for all GBM patients, according to Witthayanuwat S et al., survival study was 12 months [8]. At 2 and 5 years, the overall survival rates were found to be 21 .3% and 13.8%, respectively. The patient groups receiving postoperative RT and postoperative Concurrent chemoradiation (CCRT) with or without adjuvant TMZ had median survival periods of 11 and 23 months, respectively (p=0.03).

The 12 and 24 month survival rates were 40.7% and 13.3%, respectively, according to the survival analysis by Brown NF et al., with a median survival of 9.2 months [7]. Martin ES et al., examined overall survival in patients who received adjuvant radiotherapy with and without TMZ in their retrospective study conducted on patients with resected glioblastoma [9]. With a median OS of 11.4 months, the 1,2 and 5 year Overall Survival (OS) were 48%, 1 5%, and 3%, respectively. Recently, there has also been a change in surgical management for glioblastoma, with a shift from limited surgery or a biopsy towards maximal safe resection [11]. Trials showing that maximal safe resection is associated with better survival are not level 1 evidence because majority of them are retrospective. The studies according to Allahdini F et al., and McGirt MJ et al., suggest that maximal safe resection is associated with improved overall survival [12,13]. Despite advancements in treatment, 55 cases in present study died due to tumour-related factors. The prognosis for GBM patients remains poor, indicating the aggressive nature of the disease. It may be challenging to identify a reliable final common pathway for therapeutic targeting due to molecular heterogeneity and tumour evolution.

Based on present study, a good ECOG performance score at diagnosis and a tumour volume <5 cm are associated with improved survival in GBM patients. These factors can help in prognosticating treatment outcomes at the time of diagnosis. The standard treatment approach involves maximum safe resection followed by concurrent chemoradiation and sequential chemotherapy with TMZ. However, in patients with a poor ECOG performance score and a tumour volume >5 cm aggressive surgical procedures may contribute to significant morbidity and affect quality of life. Tailored treatment strategies should be developed, considering patients' quality of life and survival, and further studies are needed.

Limitation(s)

Limitations of present study include a small sample size and being a single institutional study.

CONCLUSION(S)

Survival in GBM patients is related to ECOG performance status at diagnosis and pretreatment volume of tumour. The evidence is

not sufficient to establish a relationship between survival and the administration of postoperative radiotherapy and chemotherapy. Despite multimodality treatment protocols, the survival in GBM patients remains poor. Further studies are needed to develop tailored treatment protocols that consider both patient's survival and quality of life. A treatment approach that balances treatment-related morbidity, cost-effectiveness, and survival is necessary.

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