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A HOSPITAL-BASED OBSERVATIONAL STUDY ON THE SURVIVAL OUTCOMES OF PATIENTS WITH HIGH-GRADE GLIOMA ABOUT DIVERSE PROGNOSTIC FACTORS.

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ABSTRACT

Background:
Despite the treatment available for tumors in the brain, the prognosis of these tumors has a significant effect on the emotional and cognitive abilities of the patients. Early diagnosis and suitable treatment can prevent the worsening of the tumor. The effect of the tumor on the brain leads to a negative impact on an individual's social life. This necessitates the requirement for a treatment that is reliable and prevents the worsening of tumors. This study aimed to study the various clinical presentations, various imaging features, Immunohistochemical expression of various tumor markers, and the outcome after surgery and adjuvant chemotherapy and radiotherapy and to analyze various prognostic factors of high-grade glioma.

Material & Methods:
This includes 103 cases of High-grade gliomas admitted to the Department of Neurosurgery, SCB Medical College & Hospital, Cuttack between January 20202 to March 2023. Before the resection of the tumor, neurological and radiological examinations were carried out. The extent of removal was determined by running a CT scan after the surgery.

Results:
In the present study of 103 cases, males constituted 62.1% as compared to females who constituted 37.9%. 48.5% of all tumors were found in the frontal lobe, followed by the temporal lobe (32%) of cases. Enhancement was seen in 89% of cases, mostly it was seen in Glioblastomas. Hemorrhage was seen in 40.8% of cases mostly seen in grade 4 gliomas. Lipid lactate peak was seen in 71.8% of cases.

Conclusion:
KPS score, surgical resection, Adjuvant chemotherapy, and radiotherapy showed statistically significant association with the outcome and survival rate.

Recommendation:
Further studies with a larger number of patients, using multiple immunohistochemical markers, and a longer follow-up are needed, which will provide significant data to conclude on the outcome and survival analysis.

Keywords: *Glioblastoma, Anaplastic Astrocytoma, Anaplastic Oligodendroglioma, Gliosarcoma, Prognostic factors of High-Grade Glioma*
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INTRODUCTION.

Gliomas negatively impact an individual's life. The cognitive abilities and emotional and social life of the patient are severely affected [1]. Even after treating gliomas, their progression cannot be arrested. There are numerous patients with glioma with disrupted social and mental well-being. Considering the ill effects of gliomas on the quality of life of the patient, a new treatment modality is necessary [2, 3].

WHO classifies gliomas into 4 stages. The first stage of the gliomas is the least malignant and can be easily differentiated from others. However, stage IV gliomas cannot be differentiated easily and they are generally anaplastic.

Gliomas have been classified based on vascularization, necrosis, and mitotic activity but in recent times histological and molecular studies have combined to classify gliomas.

Various research studies have been carried out to identify the key factors indicating the progress of gliomas [2-4].

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Although various factors are identified throughout the years none of them are clear and none of them can be stated as the only factor that determines the progress of the disease.

Although novel therapies have been shown to improve survival over the past decade, glioblastoma continues to have a dismal prognosis [5]. After giving the optimum treatment available patients with glioblastoma survive only up to 2 years while patients with anaplastic glioma survive up to 2-5 years.

Over the last decade, significant progress has been made in identifying crucial molecular characteristics that have enhanced our understanding of the behavior of these tumors [5-8]. However, it is important to note that the range of available treatment choices for these tumors is still limited. Furthermore, the final factors leading to mortality in individuals with gliomas exhibit variability and are characterized by an unpredictable nature [9]. Due to the intricate nature of these determinants, the prediction of outcomes for gliomas remains quite challenging.

The objective of this research is to examine the topic of prognostication in high-grade gliomas, including the heterogeneity in treatment approaches for these tumors, the clinical characteristics associated with poor prognosis, and the disparities in prognostic comprehension across patients, carers, and healthcare practitioners.

AIMS AND OBJECTIVE.

- To study the various clinical presentations, and various imaging features. Immunohistochemical expression of various tumor markers and the outcome after surgery and adjuvant chemotherapy and radiotherapy in case of High-Grade Gliomas
- To analyze various prognostic factors of high-grade glioma

MATERIALS AND METHODS.

Study Location and Duration.

The present study is a hospital-based observational study that has been conducted on 103 cases of High-Grade glioma who were admitted and treated in the Department of Neurosurgery of Srirama Chandra Bhanja Medical College and Hospital, Cuttack, Odisha, India during the period from January 2021 to March 2023.

Study Design.

Hospital-based observational study, Srirama Chandra Bhanja Medical College and Hospital, Cuttack, Odisha, India.

Study Period.

Two years and Two Months (January 2021 to March 2023)

Study Population.

Patients presenting to the Department of Neurosurgery, SCBMCH, India who were diagnosed and treated for high-grade glioma.

Inclusion Criteria.

All patients presenting to the Department of Neurosurgery, SCB Medical College and Hospital with High-Grade Glioma, as confirmed by histology.

Exclusion Criteria.

1. Patients who underwent any form of surgical intervention at some other institution.
2. Patients who died before commencing any form of intervention.

Evaluation.

The demographic profile, clinical presentation, KPS score, course of illness, radiological evaluation, treatment, histological and molecular grouping, complications, and outcome of the patients were studied in detail.

Radiological Investigations.

All patients were evaluated preoperatively with CT and MRI scans of the brain. Post-operative radiological evaluation in the form of CECT brain was done in all patients within 48 hours of surgery, to determine the extent of resection and residual lesion. If an enhanced CT scan showed no enhancing tumor, then the tumor was considered resected. Areas on CT of contrast enhancement were considered residual tumors.

Surgery.

The goal of surgical management was to achieve maximal safe, ideally gross total or near-total resection.

Histology and immunohistochemistry.

A presumptive diagnosis of High-grade glioma was confirmed by histopathological examination after resection surgery. Using hematoxylin and eosin the histological studies were performed and cytological features of the cells were identified.

Immunohistochemistry staining IHC was done with antibodies against IDH1, GFAP, p53, and Ki-67. Required reagents were used for staining. A manual examination of the cytological features was done under a microscope.

Adjuvant therapy.

The patients were referred for adjuvant therapy in a tertiary-level oncology center, where they were evaluated

by an oncologist and underwent therapy in the form of chemotherapy and/or radiotherapy. The patients were given radiotherapy of 60 units in 30 sessions. They simultaneously received 75 mg of temozolide for chemotherapy. After the completion of the radiotherapy, they were given chemotherapy of 150 mg for 5 days a week over the next 28 days.

Complications.

All the patients undergoing treatment were assessed and observed for complications and managed. Operative mortality was operationally defined as any mortality event that transpired 30 days after the surgical procedure, regardless of whether it occurred inside or outside the hospital setting. Additionally, deaths that transpired beyond the initial 30-day period but within the same hospitalization after the operation were also considered operative mortality.

Follow-Up.

All patients were called to the outpatient department for follow-up at regular intervals (1,3,6,12 months and half-yearly thereafter), and a detailed neurological examination was done.

Outcome.

The outcomes of the patients in terms of recurrence, completed treatment, and death were analyzed concerning different risk factors and histological and molecular subtypes. Disease remission was defined as patients who completed treatment and were disease-free since then in subsequent follow-ups.

Lost to follow-up included patients who completed treatment, achieved disease remission, and subsequently failed to review in follow-ups and were not contactable.

Relapse was operationally defined as the presence of fresh tumor development or the advancement of the remaining tumor, as seen by radiographic proof during following therapy follow-up imaging.

Progression-free survival (PFS) was operationally defined as the period starting from the date of diagnosis (specifically, the date of surgery) and ending at the occurrence of confirmed clinic radiological progression or death. The calculation of overall survival (OS) included the period from the first diagnosis to the occurrence of mortality resulting from any cause.

Bias.

There was a chance that bias would arise when the study first started, but we avoided it by giving all participants identical information and hiding the group allocation from the nurses who collected the data.

Ethical Consideration.

Written informed consent was obtained from all the patients or their relatives before their enrolment in the study. The study protocol was approved by the local ethical committee of this hospital. A definite scheme of taking up the cases for the study was planned and followed in each case.

Statistical Analysis.

The acquired data was copied into Microsoft Excel sheets for further analysis. The data analysis was conducted with SPSS version 16.0. The study examined the relationships between several clinical aspects (namely, sex, age at diagnosis, and clinical risk group), radiological findings, histological characteristics, molecular factors, and the ultimate result. To analyze these associations, the Chi-square test for multivariate analysis with discrete parameters was used. The Kaplan-Meier curve was used to examine the survival result of many parameters.

RESULTS.

At the initial stage, several 300 patients were examined for eligibility, however, 197 patients were excluded from this study due to not being eligible. In the present study of 103 cases, males constituted 62.1% as compared to females who constituted 37.9%. The male: female ratio was 1.6:1

Table 1: LOCATION OF THE TUMOR.

Location:	Frequency	Percent
FRONTAL	50	48.5
FRONTAL, PARIETAL	2	1.9
INTRAVENTRICULAR	2	1.9
PARIETAL	16	15.5
TEMPORAL	33	32.0
TOTAL	103	100.0

In the present study, 48.5% of all tumors were found in the frontal lobe, followed by the temporal lobe (32%) of cases.

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Table 2: RADIOLOGICAL CHARACTERISTICS.

Features	Frequency	Percentage
Necrosis	78	75.7
Heterogenicity	83	80.6
Irregular margin	87	84.5
Mass Effect	87	84.5
Enhancement	89	86.4
Hemorrhage	42	40.8
Edema	77	74.8
DWI	16	15.5
Lipid Lactate peak	74	71.8
Calcification	11	10.7

In this study, Margin irregularity, signal heterogenicity, mass effect, edema, and necrosis are prominent features in grade 4 tumors and anaplastic gliomas. Calcification was only seen in anaplastic oligodendrogliomas. Enhancement was seen in 89% of cases, mostly it was seen in Glioblastomas. Hemorrhage was seen in 40.8% of cases mostly seen in grade 4 gliomas. Lipid lactate peak was seen in 71.8% of cases.

Table 3: HISTOPATHOLOGICAL DIAGNOSIS.

Characteristics	Frequency	Percent
ANAPLASTIC ASTROCYTOMA	20	19.4
ANAPLASTIC OLIGODENDROGLIOMA	10	9.7
B/L ANAPLASTIC OLIGODENDROGLIOMA	2	1.9
GBM GRADE IV NOS	58	56.3
GBM GRADE IV NOS secondary	10	9.7
GLIOSARCOMA	3	2.9

In the present study, 58 (56.3%) of the tumors were GBM, which was the commonest diagnosis, followed by anaplastic astrocytoma in 20 cases (19.4%), which is higher as compared to the rest of the studies. GBM secondary was seen in10 cases (9.7%), anaplastic oligodendroglioma was the diagnosis of 10 cases (9.7%), Gliosarcoma was the diagnosis of 3 cases (2.9%) and B/L Oligodendroglioma was seen in 2 cases (1.9%).

IMMUNOHISTOCHEMISTRY MARKERS.

In the present study:

- *Primary glioblastoma:* IDH1 was found positive in 12 cases (20.6%) of cases. GFAP was found positive in all 58 cases (100%). Ki67 was found positive in all 58 cases (100%) and P53 was found positive in 18 cases (31%).
- *Secondary glioblastoma:* IDH1 was found positive in 9 cases (90%) of cases. GFAP was found positive in all 10 cases (100%). Ki67 was found positive in all 10 cases (100%) and P53 was found positive in 8 cases (80%).
- *Anaplastic Astrocytoma:* IDH1 was found positive in 13 cases (65%) of cases. GFAP was found positive in 5 cases (25%). Ki67 was found positive in 15 cases (75%) and P53 was found positive in 13 cases (65%).
- *Anaplastic oligodendroglioma:* IDH1 was found positive in 10 cases (83.3%) of cases. GFAP was found positive in 6 cases (50%). Ki67 was found positive in all 12 cases (100%) and P53 was found positive in 12 cases (100%).
- *Gliosarcoma:* IDH1 was not found positive in any of the cases. GFAP was found positive in all 3 cases (100%). Ki67 was found positive in only 1 case out of 3 cases (33.33%) and P53 was found positive in all 3 cases (100%).

50% of the patients with IDH1 positive status had their treatment completed and were alive after two years of follow-up. 30.5% of patients who died within 1 year and had IDH negative mutation were all diagnosed to have Glioblastoma. The difference in outcome was not found to be statistically significant ($p > 0.05$). IDH1 was found positive in 12 cases (20.6%) of primary glioblastoma cases, 9 cases (90%) of secondary glioblastoma, and 13 cases (65%) of Anaplastic Astrocytoma. 10 cases (83.3%) of cases. IDH1 was found negative in all cases of gliosarcoma. Recurrence was seen in 6.8% of IDH-negative cases.

37.3% of the patients with GFAP-positive status had their treatment completed and were alive after two years of follow-up. 20% of patients who died after 2 years had GFAP positive and negative status. The difference in outcome was not found to be statistically significant ($p > 0.05$). GFAP was found positive in all 58 cases (100%) of glioblastoma, 10 cases (100%) of secondary glioblastoma, 5 cases (25%) of anaplastic astrocytoma and 6 cases (50%) of anaplastic oligodendroglioma and 3 cases (100%) of gliosarcoma. Recurrence was seen in 4.8% of GFAP-positive cases.

48.1 %of the patients with p53 positive status had their treatment completed and were alive after two years of follow-up. 24.1% of patients who died after 2 years had p53 positive and 8% had negative status. The difference

in outcome was not found to be statistically significant (p > 0.05). p53 was found positive in 18 cases (31%) of glioblastoma, 8 cases (80%) of secondary glioblastoma, 13 cases (65%) of anaplastic astrocytoma, and 12 cases (100%) of anaplastic oligodendroglioma and 3 (100%) cases of gliosarcoma. Recurrence was seen in 8.2% of cases with p53 negative status.

43.8 %of the patients with KI-67 positive status had their treatment completed and were alive after two years of follow-up. 19.8% of patients who died after 2 years had KI-67 positive and 28.6% had negative status. The difference in outcome was not found to be statistically significant (p > 0.05). KI67 was found positive in 58 cases (100%) of primary glioblastoma, 10 cases (100%) of secondary glioblastoma, 15 cases (75%) of anaplastic astrocytoma and 12 cases (100%) of anaplastic oligodendroglioma and 1 (33.33%) case of gliosarcoma. KPS score was found statistically significant in the outcome of the patient (p< 0.05). 80% of patients were alive at the end of 2 years with a KPS score more than or equal to 70. The difference in outcome in residual volume was not found to be statistically significant (p > 0.05). 54.2% of cases were alive at the end of 2 years and had no residual volume.

Table 4: SURVIVAL AFTER SURGERY.

Case Processing Summary				
SURGERY	**Total N**	**N of Events**	**Censored**	
			N	**Percent**
GTR	**48**	**19**	**29**	**60.4%**
STR	**55**	**37**	**18**	**32.7%**
Overall	**103**	**56**	**47**	**45.6%**

Cases with GTR had better survival rate and was statistically significant (p<0.05).

Table 5: SURVIVAL AFTER RADIOTHERAPY

RADIOTHERAPY	Total N	N of Events	Censored	
			N	Percent
YES	70	25	45	64.3%
No	33	31	2	6.1%
Overall	103	56	47	45.6%

Means and Medians for Survival Time

RADIOTHERAPY	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
YES	19.478	.834	17.844	21.113	.	.	.	.
No	6.000	1.055	3.932	8.068	6.000	.947	4.144	7.856
Overall	15.136	.907	13.358	16.914	12.000	.	.	.

According to Kaplan Meir curve analysis patients who had received radiotherapy had better survival rates (p< 0.05).

Table 6: Survival after chemotherapy.

CHEMOTHERAPY	Total N	N of Events	Censored	
			N	Percent
YES	68	23	45	66.2%
No	35	33	2	5.7%
Overall	103	56	47	45.6%

Means and Medians for Survival Time

Chemotherapy	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
YES	19.791	.829	18.166	21.416	.	.	.	.
No	6.171	1.002	4.208	8.135	6.000	1.069	3.905	8.095
Overall	15.136	.907	13.358	16.914	12.000	.	.	.

According to Kaplan Meir curve analysis patients who had received Chemotherapy had better survival rates ($p< 0.05$)

Table 7: Survival outcome with IDH1 marker.

IDH1	Total N	N of Events	Censored	
			N	Percent
YES	44	23	21	47.7%
No	59	33	26	44.1%
Overall	103	56	47	45.6%

Means and Medians for Survival Time

IDH1	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
YES	15.091	1.453	12.244	17.938	12.000	.	.	.
No	15.166	1.176	12.861	17.470	12.000	4.502	3.175	20.825
Overall	15.136	.907	13.358	16.914	12.000	.	.	.

According to Kaplan Meir curve analysis, patients who had IDH1 positive had better survival rates but was not statistically significant ($p<0.05$).

Table 8: GFAP

Case Processing Summary				
GFAP	Total N	N of Events	Censored	
			N	Percent
YES	83	48	35	42.2%
No	20	8	12	60.0%
Overall	103	56	47	45.6%

Table 9: Survival outcome with GFAP

Means and Medians for Survival Time								
GFAP	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
YES	14.149	1.039	12.112	16.186	12.000	1.794	8.483	15.517
No	19.200	1.594	16.076	22.324	.	.	.	.
Overall	15.136	.907	13.358	16.914	12.000	.	.	.

Table 10: P53

P53	**Total N**	**N of Events**	**Censored**	
			N	**Percent**
YES	54	30	24	44.4%
No	49	26	23	46.9%
Overall	103	56	47	45.6%

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Table 11: Survival outcome with P53

P53	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
YES	15.667	1.193	13.328	18.006	12.000	3.672	4.803	19.197
No	14.539	1.404	11.787	17.292	12.000	.	.	.
Overall	15.136	.907	13.358	16.914	12.000	.	.	.

Table 12: KI67.

KI67	Total N	N of Events	Censored	
			N	Percent
YES	96	52	44	45.8%
No	7	4	3	42.9%
Overall	103	56	47	45.6%

Table 13: Survival Outcome with KI67.

Means and Medians for Survival Time								
KI67	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
YES	15.116	.950	13.254	16.978	12.000	.	.	.
No	15.429	2.934	9.679	21.179	12.000	3.928	4.301	19.699
Overall	15.136	.907	13.358	16.914	12.000	.	.	.

According to Kaplan Meir survival curve analysis, IHC markers were not statistically significant ($p<0.05$)

Table 14: RESIDUAL VOLUME.

RESIDUAL_VOLUME (CM^3)	Total N	N of Events	Censored	
			N	Percent
<5	39	28	11	28.2%
>5	16	9	7	43.8%
N	48	19	29	60.4%
Overall	103	56	47	45.6%

Table 15: Survival outcome with Residual volume.

Means and Medians for Survival Time								
RESIDUAL _VOLUME (CM^3)	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
<5	11.974	1.445	9.142	14.807	12.000	1.729	8.610	15.390
>5	14.661	2.150	10.447	18.875	12.000	2.270	7.551	16.449
N	17.833	1.282	15.322	20.345	.	.	.	.
Overall	15.136	.907	13.358	16.914	12.000	.	.	.

According to Kaplan-Meir curve analysis, patients who had no residual volume had better survival rates and residual volume was statistically significant ($p< 0.05$)

Table 16: KPS SCORE:

Case Processing Summary				
KPS	Total N	N of Events	Censored	
			N	Percent
Less than 70	68	50	18	26.5%
More than or equal to 70	35	6	29	82.9%
Overall	103	56	47	45.6%

Table 17: Survival outcome with KPS

Means and Medians for Survival Time								
KPS	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Less than 70	11.317	1.056	9.247	13.386	12.000	1.066	9.911	14.089
More than 70	22.457	.801	20.888	24.027	.	.	.	.
Overall	15.136	.907	13.358	16.914	12.000	.	.	.

According to Kaplan Meir curve analysis patients whose KPS scores were more than or equal to 70 had better survival rates and residual volume was statistically significant ($p< 0.05$)

DISCUSSION.

A hospital-based observational study was conducted in 103 cases of high-grade glioma in the Department of Neurosurgery, SCBMCH, Cuttack, Odisha for a period of two years two months from January 2021 to March 2023. The age and sex incidence, clinical presentation, KPS scoring, radiological findings, histological findings, immunohistochemistry markers, surgical management, adjuvant therapy, and outcome, were all studied and compared with standard published literature.

In the present study, just like many other studies [9-13], 48.5% of all tumors were found in the frontal lobe, followed by the temporal lobe (32%) of cases. 57.3% of cases had a single lobe involved and 42.7% of cases had multiple lobes involved. Margin irregularity, signal heterogenicity, mass effect, edema, and necrosis are prominent features in grade 4 tumors and anaplastic gliomas. Calcification was only seen in anaplastic oligodendrogliomas. Enhancement was seen in 89% of cases, mostly it was seen in Glioblastomas. Hemorrhage was seen in 40.8% of cases mostly seen in grade 4 gliomas. Lipid lactate peak was seen in 71.8% of cases.
Glioblastoma is more common in men, with a male-to-female ratio of 1.5:1 [4]. In a study of 335 patients with High-grade glioma by Liang et al. aged 0-19 years, the frequency in males (56.72%) was higher than in females (43.28%) [5]. In the present study, the mean age was 40 years. In an analysis of 100 patients by Valiyaveettil, et al, the most common location of the tumor was the frontal lobe followed by the temporal lobe [8]. In a study of 335 patients with High-grade glioma by Liang et al., 26% of gliomas were found in the frontal lobe [5]. In a study of High-grade glioma in the elderly by Gupta et al., the most common site of the location of the tumor was temporoparietal i.e. in 37% of cases [7]. In an analysis of 157 recurrent glioblastoma, in 77% of cases single lobe was involved [14].

Edema in the tumoral area is the cause of morbidity in patients with malignant glioma [15]. A study reported a substantial decrease in the overall survival rate in patients with malignant gliomas [6]. Glioma cells are present in the infiltrate surrounding the tumor [16, 17], they also cause relapses [18-20]. From this data, it can be concluded that gliomas with PTE have worsened prognosis and decreased survival rate. However, a recent systematic review [21] suggested that the association between pre-operative PTE and survival in patients with glioma remains a controversial topic; one explanation may be that considerable heterogeneity exists in terms of patient clinical characteristics and the MRI technology used in these studies.

The death of cells represents a prominent pathogenic feature seen in cases of cancerous glioma. Prior research has shown a correlation between the amount of tumor necrosis and an unfavorable prognosis for survival in cases of malignant glioma [9, 10]. The current investigation further discovered that the presence of tumor necrosis, as indicated by radiological studies, was identified as an independent adverse prognostic risk. The observed phenomenon might perhaps be linked to the malignant biological behaviors shown by glioma cells inside necrotic regions. The increased proliferation of the cells of malignant glioma results in a decreased oxygen supply in that region causing cell death. Necrotic regions are often encircled by pseudopalisading cells, which is specific to malignant gliomas and results in unfavorable prognosis [22]. which not only is suspected to contribute to glioma development and progress, but also would promote tumor relapse, and improve the invasion ability and resistance to radiochemotherapy [23]. It was previously believed that enhancement on pre-operative MRI was an independent predictor of survival in

malignant glioma [24]. However, in the present study, the enhancement extent was associated with the overall survival rate of the patients with malignant glioma on univariate analysis, while it failed to retain its significance on multivariate analysis. Increased Choline/creatine ratio occurred because the malignant cells destroyed the neurons which released the choline and increased its quantity compared to the metabolic creatinine [25, 26].

In the present study, Margin irregularity, signal heterogenicity, mass effect, edema, and necrosis are prominent features in grade 4 tumors and anaplastic gliomas. Calcification was only seen in anaplastic oligodendrogliomas. Enhancement was seen in 89% of cases, mostly it was seen in Glioblastomas. Hemorrhage was seen in 40.8% of cases mostly seen in grade 4 gliomas. Lipid lactate peak was seen in 71.8% of cases. The choline/creatine ratio was increased in 77.7% of cases.

In a study conducted by Dahuja et al. [13], a total of 115 patients diagnosed with glioma were analyzed. Among the 45 instances of glioblastoma, only 14 cases (31.11%) had positive results for IDH1. The expression of P53 was observed in 35 instances, whereas all cases of glioblastoma had a Ki-67 antibody level of over 5%. The prevalence of IDH1 mutation in anaplastic oligodendrogliomas (ODG) was found to be 58.33%. Among the cohort of 45 patients in Grade 4, a total of 35 individuals tested positive for p53, representing a prevalence rate of 77.77%. Additionally, 21 patients, accounting for 80.76% of the Grade 4 group, exhibited positive results for Grade 3. In 10 instances of Anaplastic Astrocytoma (71.42%), a positive presence of the Ki-67 antibody at a level of more than 5% was seen. Additionally, the Ki-67 antibody was reported to be positive in all cases of anaplastic oligodendroglioma.

In an analysis by Oliver et al [27], the immunohistochemical staining of tumors using GFAP showed 25–50% immunostaining in 50% of the cases with 28% showing <25% staining. Despite notable advancements in therapy in recent times, the relapse of tumors in patients with GBM continues to be an unavoidable occurrence. Furthermore, there is a lack of consensus regarding the advantages of a second operation and its potential role when combined with other therapeutic alternatives, such as chemotherapy, targeted therapy, or repeat radiation therapy. Relapse of conditions often originates from the peritumoral zone, even in instances where the original resection was deemed complete [28, 29]. The presence of tumor clones and stromal cells with tumorigenic and angiogenic capabilities in the peritumoral zone around the resection cavity has been seen in patients diagnosed with GBM. This finding has prompted inquiries on the optimal approach to resection [30]. Furthermore, it has been shown that the molecular characteristics of cells in recurring tumors undergo changes and exhibit variations compared to the gene expression profiles of the original tumor cells. [31].
In an analysis of 100 patients by Valiyaveettil et al [8], twenty-three patients had documented recurrence with an average time to recurrence being 37 months. In the present study, 4 cases had recurrence, one case had a histopathological diagnosis of Anaplastic Astrocytoma, and rest 3 cases were Primary Glioblastoma Grade 4. All cases were IDH negative, p53 negative, Ki-67, and GFAP positive status, 3 cases of primary glioblastoma had no residual volume, and one case of anaplastic astrocytoma with residual volume >5cm3.
I
n an analysis of 115 patients of glioma by Dahuja et al [13], in Grade 3 patients out of 26, 4 patients expired. In 45 Grade 4 patients, 17 expired for 1 year. In a study of 335 patients with High-grade glioma by Liang et al., the survival and mortality rates were 51.8 and 20%, respectively [5]. In the present study, 34 patients died within 1 year of surgery and 21 patients died within 2 years of surgery. 50 patients had a KPS score of less than 70. Out of 55 patients who died 33 patients, subtotal resection was done, 30 patients did not receive radiotherapy and 34 patients did not receive chemotherapy. Maximum mortality was seen in patients diagnosed with Gliosarcoma (100%), 35 patients with primary glioblastoma died, 7 patients with secondary glioblastoma, 8 cases with anaplastic astrocytoma and 2 cases with anaplastic oligodendroglioma died.

In a research conducted by Liang et al. [5], a total of 335 patients diagnosed with High-grade glioma were examined. The majority of these patients (83.3%) had surgical treatment. Among the surgical cases, 24% underwent subtotal resection while 73.5% underwent gross complete resection. The surgical methods used did not exhibit any significant correlation with the survival results of the patients [5]. Valiyaveettil et al. conducted a study including a cohort of 100 patients [8]. The survival of patients was shown to be reduced in cases when the postoperative residual tumor was detected on imaging. In a recent study of 157 cases of glioblastoma conducted in 2021, it was shown that those who had gross total resection (GTR) saw a notably higher median survival rate compared to those who underwent subtotal resection (STR) (risk ratio [RR] = 0.50 [95% CI 0.25–0.99], P = 0.028). On the other hand, it was shown that among patients with multi-lobar tumors, those who had gross total resection (GTR) had a comparatively worse median survival rate than those who underwent subtotal resection (STR) [14].

According to research [32], there was an observed enhancement in median survival rates, with a notable increase from 8 months for subtotal resection to 13 months for gross total resection (GTR). This finding was further corroborated by Pichlmeier et al [33], whose investigation using the Recursive Partitioning investigation (RPA) demonstrated that the survival advantage was most pronounced in patients with higher RPA scores, indicating a more severe baseline illness as determined by factors such as age, performance status, neurology, and mental state. According to the study [33], the median survival rates for patients who had gross total resection (GTR) compared to those who had partial resection were found to be 17.7 months and 12.9 months respectively for patients classified under RPA IV. Similarly, for patients classified under RPA V, the median

survival rates were observed to be 13.7 months for those who underwent GTR and 10.4 months for those who had incomplete resection [33]. The challenge associated with GTR persists in the need to strike a balance between achieving maximum resection and minimizing the risk of probable neurological deficits.

In the present study, GTR of the tumors resulted in better outcomes; and recurrence and death were more commonly seen in patients who had STR resection and more than 5cm3 residual volume. In a study of 335 patients with High-grade glioma by Liang et al. [5], Patients with KPS < 85 also presented less favorable survival outcomes compared to those with KPS ≥ 85 (P = 0.001) [5]. In an analysis of 100 patients by Valiyaveettil, et al [8], patients with pre-radiotherapy Karnofsky Performance Score (KPS) ≤70 had a 5-year OS of 33.3% and those with KPS >70 had a 5-year OS of 65.1%. In the present study too, patients whose KPS score was more than or equal to 70 had a better survival rate.

The prognostic significance of IDH mutation status in glioblastoma is substantial. Patients with IDH-mutant glioblastoma, albeit representing a lower proportion of the total cases, exhibit significantly longer median survival compared to those with IDH-wildtype glioblastoma. A study revealed that a mutation in the IDH-1 gene was detected in 12% of patients diagnosed with glioblastoma multiforme (GBM). This mutation seems to be associated with a significantly improved median survival rate, with patients experiencing a median survival of 3.7 years compared to 1.1 years for those without the mutation. Weller et al [34] reaffirmed this observation via the German Glioma Network investigation, whereby IDH-1 mutations were identified in 16 out of 286 individuals (5.6%). An enhancement was seen in both progression-free survival (16.2 months vs. 6.5 months) and overall survival (30.2 months vs. 11.2 months) as reported by the authors [34]. The study conducted by Weller et al. [34] examined a cohort of 301 patients diagnosed with glioblastoma multiforme (GBM). The findings of this investigation revealed that the presence of IDH1 mutation in GBM patients was associated with improved progression-free survival and overall survival outcomes. In a study conducted by Dahuja et al. [13], an examination was performed on a cohort of 115 individuals diagnosed with glioma. Out of a cohort of 45 patients diagnosed with glioblastoma multiforme (GBM), a total of 17 individuals had mortality during 12 months of follow-up. Among the cohort of 17 patients, it was observed that 13 individuals had a negative status for the isocitrate dehydrogenase (IDH) gene. These findings imply a potential association between IDH positivity and improved survival outcomes.

The incidence of p53 immunopositivity is elevated among individuals diagnosed with high-grade glioma. The expression of Ki-67 serves as an indicator of the rate of proliferation in cancer cells, with an elevated level of expression being linked to a less favorable prognosis. High-grade gliomas are characterized by elevated levels of Ki-67 antibodies. There was a significant correlation between Ki-67 expression and mortality during the first year of post-treatment follow-up (P < 0.001). Furthermore, it was shown that individuals exhibiting increased levels of Ki-67 (≥ 20) had a reduced duration of life compared to those with lower levels of Ki-67 (< 20) during a 40-month post-treatment timeframe [35].

In this study, IDH1 IDH1-positive patients had better survival rates and lower recurrence rates. However overall estimation of survival rate with IHC markers were not statistically significant. In a multicenter experiment conducted by Stupp et al. [35], it was shown that patients survived for about 15 months after 28 months of follow-up when concurrent chemotherapy was given but they survived for about 13 months only when radiotherapy was given alone. According to this study [35], the two-year survival rate in the TMZ group was found to be 26.5% compared to 10.4% in the radiation group. Additionally, the five-year evaluation of the same population showed a 9.8% survival rate in the TMZ group, while the radiotherapy group had a survival rate of 1.9%. This finding signifies a notable progression in survival statistics for high-grade glioma when compared to earlier studies. In a retrospective analysis conducted on a cohort of 165 patients with anaplastic astrocytoma (AA) [36], the researchers investigated the impact of contemporaneous temozolomide (TMZ) administration with adjuvant radiotherapy (RT). The study revealed a statistically significant association between concurrent TMZ and better 5-year overall survival (OS) rates, as compared to patients who received RT alone.

Valiyaveettil et al. [8] conducted a study including 100 patients to examine the outcomes of different histological types. The research revealed that patients with AO histology had a 5-year overall survival (OS) rate of 65.7%, while those with AA histology had a rate of 51.9%. The statistical analysis using the log-rank test yielded a p-value of 0.27 [8]. The use of concurrent chemotherapy in combination with TMZ demonstrated a greater 5-year overall survival rate when compared to radiation treatment alone. The use of adjuvant chemotherapy in conjunction with TMZ demonstrated a significantly higher 5-year overall survival rate of 67.7% in comparison to the 36% seen in patients who did not get adjuvant chemotherapy. Patients who received both contemporaneous and adjuvant TMZ had a significantly greater 5-year overall survival rate compared to those who did not receive this treatment combination. The current research observed a reduced death rate among individuals who had both chemotherapy and radiation. The statistical significance of the survival result was seen.

CONCLUSION.

It was observed in the study that the male-to-female ratio was 1.6:1, and the median age was 40 years. Headache followed by nausea, vomiting, and seizures were the commonest clinical presentations, and the maximum patients were under a KPS score of less than 70. Margin irregularity, signal heterogenicity, mass effect, edema, enhancement, necrosis, and increase in lipid lactate peak are prominent features in grade 4 tumors and anaplastic gliomas. 53% of patients underwent subtotal resection and Glioblastoma grade 4 was the commonest histological

diagnosis. IDH1-positive status patients were less commonly seen in Glioblastoma grade 4.
Recurrence was seen in maximum in patients with GBM with IDH negative status, p53 negative, Ki-67, and GFAP positive status. Maximum mortality was seen in patients with a KPS score less than 70. Maximum mortality was seen in gliosarcoma patients followed by glioblastoma with IDH negative status. Mortality was seen in patients who underwent STR and were not able to receive adjuvant chemotherapy and radiotherapy. KPS score, surgical resection, Adjuvant chemotherapy, and radiotherapy showed statistically significant association with the outcome and survival rate.

LIMITATION.

IHC markers and radiological findings did not show a statistically significant association with the outcome and survival rate, probably because of a few shortcomings of the study:
- The sample size was small
The follow-up period was very short

RECOMMENDATION.

Further studies with a larger number of patients, using multiple immunohistochemical markers, and a longer follow-up are needed, which will provide significant data to conclude on the outcome and survival analysis.

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LIST OF ABBREVIATIONS

IHC- Immunohistochemistry staining
PFS- Progression-free survival
KPS-Karnofsky Performance Scale
PTE -Pulmonary tumor embolism
MRI - Magnetic resonance imaging
GBM- Glioblastoma multiforme
TMZ- Temozolomide
STR- Subtotal resection
GTR- Gross total resection
RT-Radiotherapy

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No conflict of interest declared.

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