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Patterns of Care and Treatment outcomes of High-Grade Glioma patients at four Ethiopian teaching Hospitals

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Pattern of care and treatment outcomes of High-Grade glioma patients at four Ethiopian teaching Hospitals, from September 2023 to December 2024, Addis Ababa Ethiopia

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Acronym and abbreviations

AA----------Anaplastic Astrocytoma

EOR---------- Extent of resection

GBM---------- Glioblastoma Multiforme

GOS----------Global Functional Scale

HGG---------- High Grade Glioma

IDH----------Isocitrate Dehydrogenase

KPS---------- Karnofsky Performance Scale

MST---------- Median Survival Time

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Abstract

Background: High-grade gliomas are the most prevalent type of malignant brain tumor in adults. The most prevalent cancers of the primary central nervous system (CNS) in adults are malignant astrocytoma, which includes anaplastic astrocytoma (WHO grade III), Malignant Astrocytoma (IDH mutant) or glioblastoma - IDH wild-type (WHO grade IV), and gliosarcoma (WHO grade IV). They are the second leading cause of cancer-related death in the young adult population and are linked with significant morbidity. Despite extensive study, people with malignant gliomas continue to have a dismal prognosis. The goal of this study is to assess the care and treatment outcomes for people with this condition.

Objectives: To assess the pattern of care, treatment outcome and its associated factors in the treatment of High grade Glioma patients found at Tikur Anbessa Specialized Hospital and affiliate neurosurgical Hospitals in Addis Ababa, Ethiopia, from September 1, 2023-September 1, 2024

Methods: Prospective cohort study collected data on pattern of care, treatment outcome and associated factors High grade Glioma patients found at TikurAnbessa Specialized Hospital and affiliate neurosurgical Hospitals. Data was collected by trained senior neurosurgical residents. Data collected was analyzed using SPSS. Frequency distribution was used to describe the characteristics of the study participants. Data analysis included chi-squared tests and survival analysis tests to assess the treatment outcomes. Variables with $p < 0.05$ were considered as significant.

Result: There were 40 patients with confirmed HGG who participated in this study. The median age at diagnosis was 47 years. Headache is the commonest presenting symptom in this study (97.5%) followed by seizure (52.5%) and weakness (50%). The pre-operative tumor volume among the study participants ranged between 3.9-168 $cm^{3.}$ The mean pre-operative tumor volume was 80.38 cm^3. Out of the 40 patients 22 of them had ≥ 97% extent of resection. In this study 17.5% of the patients diagnosed with HGG died post-surgery from which 71.4% had WHO grade 4 tumor. The median survival time for patients with HGG post-surgery was 11.3 months (95% CI: 6.2-17months). There was significant association in patients with higher KPS (≥ 70) value and their survival outcome. ($\chi 2 = 10.19$ P=0.006). Patients with pre-operative GCS (≤ 14) seem to have significant association on survival outcome compared with patients having GCS of 15. ($\chi 2 = 12.9$ P=0.005). Those patients who received post-operative adjuvant therapy have better survival outcome than those patients with no adjuvant therapy. ($\chi 2 = 6.716$) P=0.035).

Conclusion: High-grade glioma (HGG) represents the most aggressive primary brain tumor, and its incidence continues to rise globally. Higher KPS, pre-operative GCS of 15 and those patients receiving post-OP adjuvant therapy had significant favorable association with survival. It is critical to continue advocating and engaging with the government and stakeholders about the importance of enhancing access to radiotherapy and chemotherapy.

Key Words: High grade glioma, brain tumor, GBM, glioma,

Introduction

1.1 Background

High-grade glioma (HGG), particularly glioblastoma multiforme (GBM), represents the most aggressive primary brain tumor, and its incidence continues to rise globally.(1) While advancements in multimodal treatment, including surgery, radiotherapy, and chemotherapy, have improved prognoses in high-resource settings, disparities in outcomes persist, particularly in low- and middle-income countries (LMICs) such as Ethiopia.

This research proposal investigates the patterns of care and treatment outcomes for HGG patients in a tertiary teaching hospital within the Ethiopian context, aiming to shed light on the unique challenges and opportunities for optimizing care in this resource-constrained settings.

1.2 Statement of the problem

Ethiopia, with a population exceeding 115 million, faces significant healthcare disparities, including limited access to specialized neurosurgical services and advanced oncological interventions like radiation therapy and targeted therapies. These limitations often result in delayed diagnoses, advanced tumor stages at presentation, and limited treatment options, contributing to poorer prognoses for HGG patients compared to counterparts in high-resource settings.(2)

Recent studies in LMICs have highlighted the prevalence of these challenges, emphasizing the need for tailored treatment strategies and resource allocation to improve HGG outcomes. (3)

Despite these difficulties, Ethiopia has witnessed encouraging advancements in neurosurgical infrastructure and expertise in recent years.(4) The establishment of dedicated neurosurgical units within tertiary teaching hospitals, coupled with increased access to basic oncological therapies, offers a foundation for improving HGG care.(2, 5, 6) However, a comprehensive understanding of existing treatment patterns, including the utilization of available resources, treatment adherence, and management of associated complications, is crucial for optimizing patient outcomes within these evolving healthcare landscapes.

Furthermore, understanding the specific challenges faced by Ethiopian HGG patients, such as socioeconomic factors, cultural beliefs, and traditional healthcare practices, is essential for developing culturally sensitive and patient-centered care models. Integrating qualitative research methods alongside quantitative data analysis can provide valuable insights into these experiences and inform the development of effective interventions and support systems.

1.3 Rationale of the Study

This research proposal aims to address critical knowledge gaps in the existing treatment patterns of HGG patients and management of associated complications by comprehensively investigating the patterns of care and treatment outcomes for HGG patients at a tertiary teaching hospital and its affiliate Hospitals in Ethiopia. The findings will provide valuable data to inform evidence-based strategies for optimizing HGG management within the Ethiopian context, ultimately contributing to improved survival rates and quality of life for HGG patients in this underserved region.

2. Literature Review

Gliomas are the most prevalent type of malignant brain tumor in adults. They can form anywhere in the central nervous system, but they are more common in the brain and originate in glial tissue. Gliomas are classified as astrocytic, oligodendrocytic, or a combination of the two cell types, and they are normally graded using the International Classification of Diseases-Oncology, version 3 (ICD-O-3) and World Health Organization WHO). They could fall from WHO grade 1 to IV categories. (7). High grade gliomas (HGG) are a group of tumors that are considered infiltrative and deemed malignant. Traditionally, they have been classified as primary (90%) or secondary (10%).

According to WHO Histologic grading, WHO grades III and IV gliomas are considered malignant or high grade tumors. The most common malignancies of the primary central nervous system (CNS) in adults include anaplastic astrocytoma (WHO grade III), glioblastoma (IDH mutant or IDH wild-type, WHO grade IV), gliosarcoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma. (8-10).

Gliomas make up 25.1% of all primary brain and other central nervous system cancers as well as 80.8% of malignant tumors. Glioblastoma accounted for the majority of gliomas (57.7%). The incidence of these tumors has increased slightly over the past two decades, especially in the elderly, primarily as a result of improved diagnostic imaging. According to Central Brain Tumor Registry of the United States (CBTRUS) report, it is also projected to have increased incidence accounting to the highest number of cases of malignant tumors in 2021. Malignant gliomas cause disproportionately significant morbidity and mortality. Despite excellent treatment, the median survival time for patients with glioblastomas is just 12 to 15 months, and 2 to 5 years for patients with anaplastic gliomas.(8, 11)

Treatment of patients with HGG still remains a challenge. Having better understanding of treatment plan and treatment outcome (survival) of high grade gliomas is important in improving the lives of patients. (12)

Several important genes, such as IDH, TP53, PTEN, CDKN2A, and EGFR, are frequently mutated or otherwise altered in gliomas. These alterations tend to accumulate in a specific order as the tumor progresses to a more aggressive form. A study by Hai Yan et al. conducted a genomic analysis of glioma, revealing that patients with anaplastic astrocytomas or glioblastomas harboring IDH1 or IDH2 mutations were significantly younger, with median ages of 34 years compared to 56 years for anaplastic astrocytomas and 32 years compared to 59 years for glioblastomas. Additionally, 80% of these patients exhibited mutations in the TP53 gene, whereas those with wild-type IDH1 and IDH2 had a lower incidence of TP53 mutations (18%) and more frequent alterations in PTEN, EGFR,

CDKN2A, or CDKN2B. The median overall survival for patients with IDH mutations was 31 months, notably longer than the 15-month survival of patients with wild type IDH. (13)

The role of adjuvant radiation and chemotherapy treatment following debulking surgery for glioblastoma was assessed in a clinical trial by Stupp et.al comparing RT alone with RT plus temozolamide. The combined treatment demonstrated a 37 percent relative reduction in mortality risk, with a median survival increase of 2.5 months (12.1 months for radiotherapy alone). The median progression-free survival was 6.9 months (5.0 months with radiotherapy alone), and the median two-year survival rate was 26.5 percent (10.4 percent with radiotherapy alone). Radiotherapy combined with temozolomide demonstrated a significant enhancement in median overall survival for nearly all patients, except for a minor subgroup who underwent only biopsy and those exhibiting poor performance status. (14)

Kathleen R in San Francisco did a study on predictive markers for survival of patients with Glioblastoma and found that younger age at diagnosis, higher KPS, adjuvant chemotherapy, use of brachytherapy, and greater degree of resection all predicted increased survival. (15) Similarly, a multivariate analysis involving 416 patients with glioblastoma multiforme by Michel L. et al. identified survival predictors for GBM patients. This study highlighted the importance of age, KPS score, the extent of tumor resection, as well as the level of necrosis and enhancement observed in preoperative magnetic resonance imaging (MRI) studies. Furthermore, it demonstrated a significant survival benefit linked to resection of 98% or more of the tumor volume, with a median survival of 13 months (95% confidence interval [CI]: 11.4–14.6 months) compared to 8.8 months (95% CI: 7.4–10.2 months) for those with resections below 98%. (16)

Advanced imaging techniques and surgical navigation tools today play a vital role in enhancing the extent of tumor resection, potentially resulting in prolonged survival and improved quality of life for patients. A randomized controlled trial conducted by Fatih Incekara et al. compared B-mode intraoperative ultrasound for the resection of high-grade gliomas against the conventional 5-aminolevulinic acid (5-ALA) guided surgery. Results showed a median extent of resection of 97% (interquartile range [IQR] 89-100) with intraoperative ultrasound and 95% (IQR 79-98) with standard surgery (p=0.151). The median residual tumor volume was recorded at 0.9 cm^3 (IQR 0.2-3.4) for intraoperative ultrasound and 1.4 cm^3 (IQR 0.7-6.4) for the standard procedure (p=0.205). (17)

A growing body of evidence also suggests that resecting a larger portion of high-grade glioma tumors is linked to improved patient survival. A review article by Kaisorn L. Chaichana et al. indicated that the residual volume (RV) with the most significant reduction in mortality risk was 2 cm^3 (hazard ratio [HR] [95% CI] = 0.472 [0.256 - 0.871], P= 0.01). Patients with less than 2 cm^3 of residual tumor volume had a median survival of 16.3 months, compared to 12.1 months for those with 2 cm^3 or more (P=0.02). Additionally, the extent of resection that most significantly reduced the risk of death was over 95% (HR [95% CI] = 0.528 [0.306 - 0.913], P=0.02), where the median survival for patients with greater than 95% resection was 16.3 months, compared to 11.6 months for those with 95% or less (P= 0.03). (18)

For surgeons, the equilibrium between the extent of resection and functional outcomes in patients with high-grade gliomas (HGG) is essential, as the emergence of new or worsening neurological deficits can adversely affect survival. A retrospective analysis by McGirt revealed that 6% of patients experienced surgically induced motor deficits, while 5% faced surgically introduced language deficits. Median survival reduced significantly for those who developed language deficits (9.6 months, P=0.05) or motor deficits (9.0 months; P=0.05), in comparison to those without surgery-related deficits, who had a median survival of 12.8 months. Moreover, two-year survival rates stood at 8% for patients with surgically acquired motor deficits and at 0% for those with language deficits, contrasted with 23% for individuals without any new deficits. (19)

The surgical and oncological treatments of multiple synchronous gliomas present notable challenges. Older literature differentiates these cases into two categories: multifocal and multicentric, determined by the presence of microscopic connections or its absence respectively. Showalter et al. have characterized multiple gliomas as tumors located at distinct sites with a clear separation between the foci; specifically, lesions that are more than 2 cm apart or situated in opposing lobes. In this retrospective study, only the Karnofsky Performance Status (KPS) (p = 0.022), salvage surgery (p = 0.011), and salvage chemotherapy (p = 0.003) were found to be significant independent predictors of overall survival, which ranged from 0.8 to 43 months (median, 8.1; 95% confidence interval, 5.4–9.9). (20)

Research by Raywat N et al. concerning clinical predictors of survival and treatment outcomes for high-grade glioma (HGG) at the Prasat Neurological Institute in Thailand indicated that the median survival time following surgery was 18 months (95% CI 13.4-22.6). Notably, the median survival time for patients with Grade III gliomas was 26 months (95% CI 19-33), whereas those with Grade IV gliomas had a median survival time of 13 months (95% CI 10.2-15.8). (21)

Li-Nien Chien et al. conducted a study in Taiwan and Ohio, which revealed that patients with glioblastoma (GBM) had a lower survival rate compared to those with anaplastic astrocytoma (AA). The findings demonstrated that the one-year survival rate for glioblastoma was approximately 50%, while for anaplastic astrocytoma, it was around 70%. Furthermore, the research indicated that patients who underwent surgical resection followed by concurrent chemo-radiation experienced the highest one-year survival rates in both regions examined. Additionally, those receiving concurrent chemo-radiation had improved survival rates, with a one-year survival rate of 48.2% in Ohio and 69.0% in Taiwan. In contrast, patients who underwent surgical resection alone or received no treatment exhibited the lowest survival rates at both locations. (12)

The optimal treatment approach for patients with recurrent HGG remains a topic of debate. A review by Hervey-Jumper et al. highlighted the potential benefits of reoperation. Current criteria for considering reoperation include the emergence of new focal neurological deficits, tumor mass effects associated with increased intracranial pressure, heightened seizure frequency, and radiographic indications of tumor progression, regardless of changes in clinical status. A minimum interval of six months between operations and a favorable performance status (KPS score > 70) are associated with better survival outcomes following reoperation. (22)

A study conducted in Nigeria by Chika A et al. assessed the challenges of managing HGG in the country, revealing that only 40% of patients could receive adjuvant treatment during the study period. Among those who did receive adjuvant therapy, the one-year mortality rate was as low as 15%, in stark contrast to an 85% mortality rate observed in the group without access to such treatment. (3)

3. Objective

General

- To assess the pattern of care, treatment outcome and associated factors of High grade Glioma patients found at Tikur Anbessa Specialized Hospital and affiliate neurosurgical Hospitals in Addis Ababa, Ethiopia, from September 1,2023- September 1,2024

Specific

- To assess the pattern of care for patients found at Tikur Anbessa Specialized Hospital and affiliate neurosurgical Hospitals diagnosed with High grade Glioma in Addis Ababa, Ethiopia, from September 1,2023- September 1,2024
- To assess the treatment outcome of patients found at Tikur Anbessa Specialized Hospital and affiliate neurosurgical Hospitals diagnosed with High grade Glioma in Addis Ababa, Ethiopia , from September 1,2023- September 1,2024
- To determine predictors of treatment outcome in patients found at Tikur Anbessa Specialized Hospital and affiliate neurosurgical Hospitals diagnosed with High grade Glioma in Addis Ababa, Ethiopia from September 1,2023- September 1,2024

4. Methods

4.1 Study Area

Tikur Anbessa Specialized Hospital (TASH)

Tikur Anbessa Hospital or Black Lion Hospital in Addis Ababa, Ethiopia, was established in 1964. It serves as the main teaching hospital for both preclinical and clinical training across various disciplines in the School of Medicine at Addis Ababa University.

Myunsung Christian Medical Center (MCM)

Myungsung Christian Medical Center (MCM) is a private Hospital located in the southeastern part of Addis Ababa, Ethiopia. It is neurosurgical affiliated teaching hospital functioning under the Black Lion Hospital and Addis Ababa University.

Zewditu Memorial Hospital (ZMH)

Zewditu Memorial Hospital is a hospital in central Addis Ababa, Ethiopia. The hospital is named after Empress Zewditu. Zewditu Memorial Hospital is a neurosurgical affiliate teaching hospital.

Alert Comprehensive Specialized Hospital

Alert Comprehensive Specialized Hospital is a medical facility located on the outskirts of Addis Ababa, Ethiopia. Originally named the All Africa Leprosy Rehabilitation and Training Center (ALERT) but now provides comprehensive services and training in many specialties including neurosurgery.

4.2 Study Period
September 1, 2023 to September 1, 2024

4.3 Study Design
Prospective cohort Study

4.4 Source and Study Population

Source Population
All patients diagnosed to have WHO grade 3 and 4 high grade (malignant) glioma with MRI and pathology at the study hospitals during the study period.

Study Population
All patients who had been diagnosed with MRI and pathology WHO grade 3 and 4 high grade (malignant) glioma patients at the selected hospitals who fulfill the inclusion criteria

4.5 Eligibility Criteria

Inclusion Criteria
All patients who were newly confirmed High grade glioma patients (WHO grade 3 and 4) diagnosed with MRI and Pathology under treatment for this diagnosis during the study period will be included in this study.

Exclusion Criteria
- Those patients with incomplete medical recording were excluded from the study

- All patients who were unwilling to participate in this study will be excluded.

4.6 Sample size and Sampling technique
Non randomized convenient Sampling technique was employed. All patients who were diagnosed with high grade glioma and fulfilled the inclusion criteria within the study period were enrolled to this study.

4.7 Operational Definition
KPS - Karnofsky Performance Scale (see annex 1)

GOS – Glasgow Outcome score (see annex 2)

Tumor volume calculation

The estimated volume of a tumor = (Height×AP× T)/2 (that is 1/2 the products of the height (measured on coronal section of MRI or CT) times the length in the AP dimension times the thickness T (length and thickness measured in Axial section of MRI or CT). (23)

Extent of resection (EOR) (24)

- Near total resection of enhancing tumor 95% contrast-enhancing tumor + 1cm^3 residual contrast-enhancing tumor
- Complete resection of enhancing tumor: 100% contrast-enhancing tumor.
- Subtotal resection of enhancing tumor: 80% contrast-enhancing tumor +5cm^3 residual contrast-enhancing tumor
- Biopsy of enhancing tumor: No reduction of tumor volume and administered for tissue-based diagnosis
- Partial resection of enhancing tumor: 1-79% contrast-enhancing tumor =/- >5cm residual contrast-enhancing tumor (for mass effect-related symptoms)

Response assessment in Neuroncology criteria **(RANO criteria)** (see annex 3) (25)

Pseudoprogression - an increase in progressive contrast-enhancing areas on MRI that mimic tumor progression, typically seen ≤ 3 months after treatment with XRT + Temozoloamide.(25)

Pseudoresponse - reduction in size of enhancing lesion on MRI with Contrast after treatment with agents that stabilize the BBB (agents targeting VEGF and VEGF receptors such as bevacizumab).(25)

Multiple glioma - multiple tumor sites with clear separation between foci; lesions with >2 cm of separation or in contralateral lobes

Wounded Glioma – bleeding or cerebral edema in the tumor bed of high grade glioma patients shortly after the surgery with accompanying neurological decline.(26)

4.7 Study Variables

Dependent variable

- Treatment Outcome: Overall survival and Progression free survival
- Functional-Outcome(GOS)

Independent Variable

- Age
- KPS
- Histopathology
- Extent of resection
- Extent of residual tumor

- Post-op adjuvant treatment

4.8 Data collection tool and procedure

The data was collected by trained senior neurosurgical residents who worked at the specific institution and were involved in the active care of these patients. The data was collected using structured questioner; which has 5 components including demographic, preoperative, perioperative, post-op and follow up sections. The data was collected from the patients, the previous medical records and follow up visit which started from 2 weeks post-op period and continued for 1 year. Each patient's medical chart was coded with specific designation to avoid repetition in recording.

4.9 Data Quality Assurance

Data was collected using structured questionnaire after training was provided to the data collectors on the details of the questionnaire. Two data collectors participated in the data collection process. The data collectors were given one day training on the objectives of the study and different sections of the questionnaire, and interviewing techniques by the researcher. Questionnaires filled were checked for its completeness and consistency daily by the primary investigator. The investigator was responsible for monitoring the overall data collection process and providing supportive supervision on the spot. The data collected was carefully entered and cleaned before analysis.

4.10 Data processing and Analysis

Data was entered after it was checked for its completeness into SPSS and analyzed. Descriptive analysis was done using frequency, mean, median and standard deviation analysis for all the important variables. Chi-square test was done to assess association between categorical variables. Variables with $p<0.05$ were considered as significant. Survival and treatment success probabilities were estimated using Kaplan-Meir method.

4.11 Ethical Consideration

Before data collection to conduct this study, ethical clearance was obtained from the institutional review board (IRB) at Black Lion Specialized Hospital and submitted to MCM (Myung Sung Christian Medical Center), Zewditu Memorial hospital, Alert Specialized Hospital research affairs. The aim of the study was clearly explained to the study participants and their right to refuse was maintained. Information was collected after obtaining informed

verbal consent from each participant's care givers. The personal information of study participants was kept entirely anonymous, and confidentiality was assured throughout the study period. The name and address of the patient was omitted from the questioner.

4.12 Dissemination of results

After being completed, the research paper was submitted to Black Lion Specialized Hospital Neurosurgery department. The findings of this study was distributed to Black Lion Specialized Hospital, Zewditu Memorial Hospital, MCM (Myung Sung Christian Medical Center), and Alert Specialized Hospital research affairs. If possible, the findings will be presented in different seminars, meetings and workshops and will be published in scientific journals.

5. Result

Socio-demographic Characteristics

There were 40 patients with confirmed HGG who participated in this study. The minimum follow up time was 23 days and the maximum amount of time patients were followed in this study 362 days. Among the study participants the minimum age was 10 years old and maximum age 75 years old with the median age at diagnosis being 47 years. Most of the participants (35%) in this study are 50 years old and above. Male to female ratio was 1.85:1. More than half (52.5%) of the patients who participated in this study are from Addis Ababa the remaining participants are from other regions of the country. (Table 1) 50% of study participants were operated at MCM Hospital and 40% at BLH. Majority of the patients (92%) were right handed.

Table 1: Socio-demographic characteristics of patients

Socio-demographic Characters		**Frequency(N=40)**	**Percent**
Age	<30 yrs	5	12.5 %
	30-40	8	20%
	41-50	13	32.5%
	≥50	14	35%
Sex	Male	26	65%
	Female	14	35%
Hospital operated			
Black Lion		16	40%
MCM		20	50%
Zewditu		3	7.5%
Alert		1	2.5%

Pre-Operative Presentation

The median duration of symptom prior to presentation to hospital is 3 months (IQR of 2- 7.5 months). There was no significant association between WHO grade and duration of symptom prior to presentation (χ^2= 6.77, p = 0.486).

Majority of the patients (82.5%) had pre -operative GCS of 15. Headache is the commonest presenting symptom in this study (97.5%) followed by seizure (52.5%) and weakness (50%). (Table 2)

Commonest comorbidity identified was hypertension (5%) followed by Diabetes (2.5%). Only one patient had ionizing radiation treatment for breast cancer following surgery identified as a risk factor for developing HGG.

Most of the cases (70%) presented with KPS of 70-80% followed by KPS ≥ 90 in 20% of the patients.

Table 2: Frequency Distribution of Pre-operative Presentation of patients

Symptoms	**Frequency(N=40)**	**Percent**
Headache	39	97.5%
Seizure	21	52.5%
Weakness	20	50%
Behavioral Change	9	22.5%
Decreased mentation	3	7.5%
Vomiting	2	5%
Speech difficulty	7	17.5%
Visual complaint	4	10%
Cranial nerve Deficit	1	2.5%
Pre-operative GCS	**Frequency**	**Percent**
9	1	2.5%
10	1	2.5%
14	5	12.5%
15	33	82.5%
KPS		
10-60	4	10%
70-80	28	70%
≥ 90	8	20%

Tumor Location

Most of the patients (47.5%) in this study had the tumor located in the frontal area followed by temporal area. There was no significant association between WHO grade and tumor location in this study (**χ^2=1.847, p =0.7**). There is equal distribution of tumor across the two hemispheres. Only 2(5%) of the patients had midline involvement.

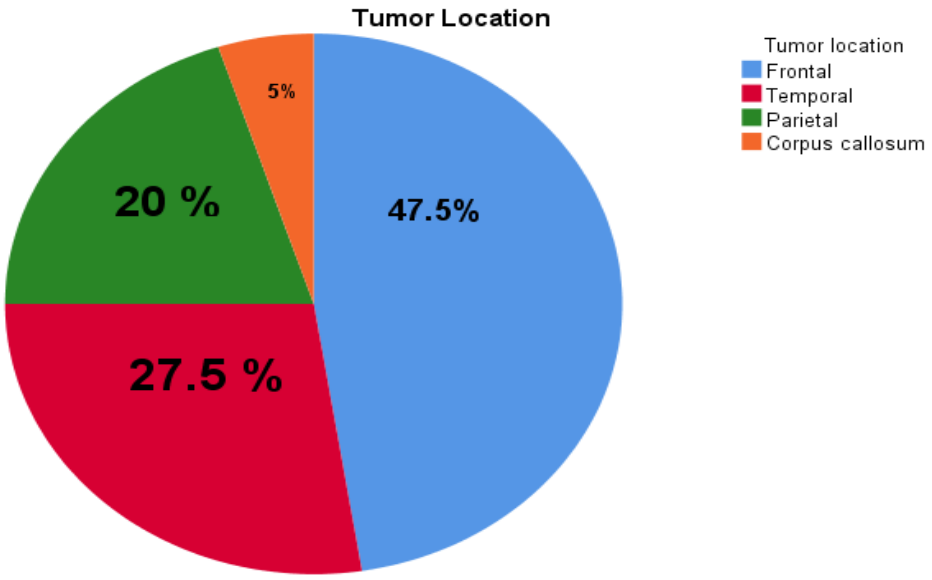


Figure 1: Tumor Location

Pre-operative tumor volume and number of sites involved

The pre-operative tumor volume among the study participants ranged between 3.9-168 $cm^{3.}$ The mean pre-operative tumor volume was 80.38 cm^3± SD 42.9 cm^3. Most of the patients (87.5%) in this study, had single focus lesion whereas the rest (12.5%) had multiple focus.

Pre-Operative Medications*

All patients were given corticosteroids before surgery. Among the 40 patients who participated in the study, 45% have received prophylactic anti-seizure medications. Remaining 55% of the patients who had seizure preoperatively had received therapeutic anti-seizure medication. Unfractionated heparin or other prophylactic anti-coagulants were given for 14 (35%) patients.

Type of Intervention

Among the patients 90% of them had primary surgery whereas 10% of them had re-operation for recurrent GBM. The mean time of operation after initial diagnosis is 16 weeks.

Histopathology

The commonest tumor histology (85%) seen in this study is astrocytoma followed by oligodedroglioma (12.5%). Only one patient had pleomorphic xanthoastrocytoma. 72.5% of the patients had tumor with WHO grade 4 and the remaining 27.5% are

WHO grade 3. Only 1 (2.5%) of the study participant had IDH mutant status determination while the remaining is unknown.

Extent of Resection (EOR)

9 patients had extent of resection between 70-96% and 22 of the patients had ≥ 97% extent of resection. 20% of the cases had biopsy. Intraoperative Ultrasound was used to maximize EOR in only 7 of the patients (17.5%). Surgeon's estimate of extent of tumor resection is significantly associated with the objective EOR. (χ^2=32.759, P=0.0000)

Post -Operative residual tumor volume and complications

After surgery 23 of the patients (57.5%) had post-op residual tumor volume of <5cm^3 with median tumor volume of 1.96 cm^3 (IQR 0-21 cm^3).The commonest (27.5%) post-operative complication was worsening and/or new neurological deficit. 5% of the patients developed thromboembolic (PE and/or DVT) complications. One patient (2.5%) had tumor bed hematoma (wounded glioma).

Post-Operative Adjuvant therapy

57.5% of the patients received post-operative adjuvant treatment as radiation (RT) with or without temozolamide (TMZ) as per Stupp protocol. The remaining 17 patients didn't receive any adjuvant treatment. (Table 3)

Table 3: Frequency Distribution Post-adjuvant therapy

Post-op Adjuvant therapy	Frequency(N=40)	Percent
RT	13	32.5%
RT+TMZ	10	20%
No RT+TMZ or RT	17	42.5%

Survival

In this study 17.5% of the patients diagnosed with HGG died post-surgery from which 71.4% had WHO grade 4 tumor. The median overall survival time for patients with HGG post-surgery was 11.3 months (95% CI: 6.2-17months).

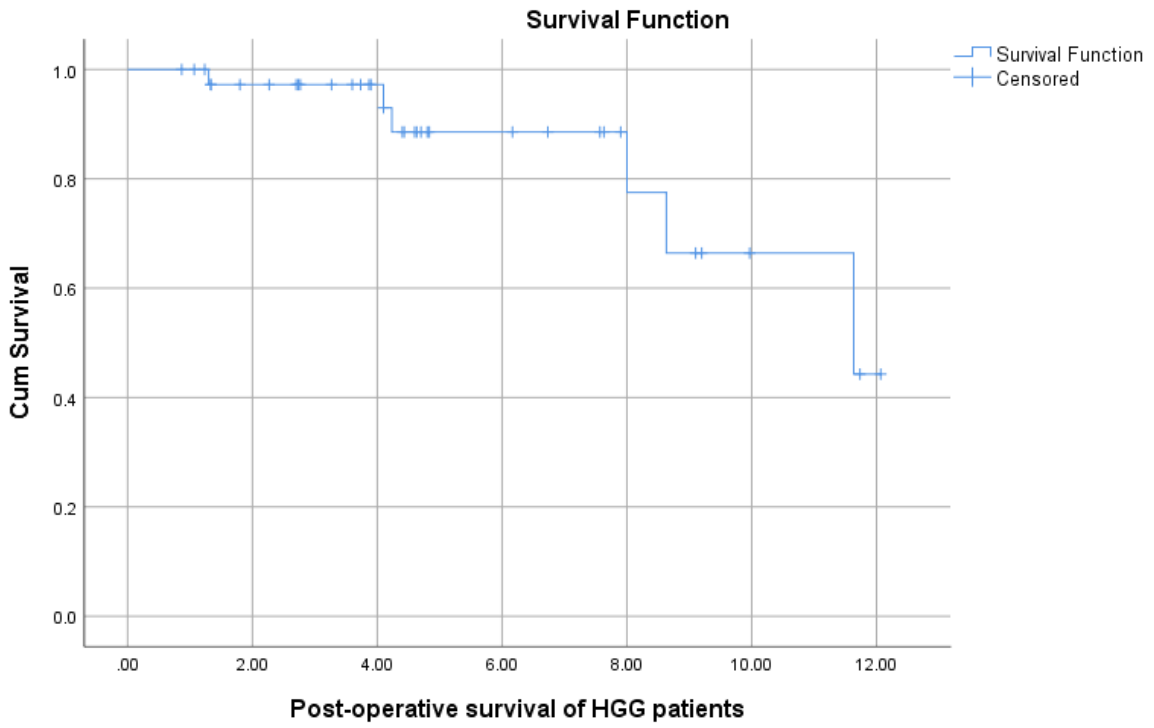


Figure 2: Kaplan-Meir Overall Survival Plot for patients with HGG post-Surgery

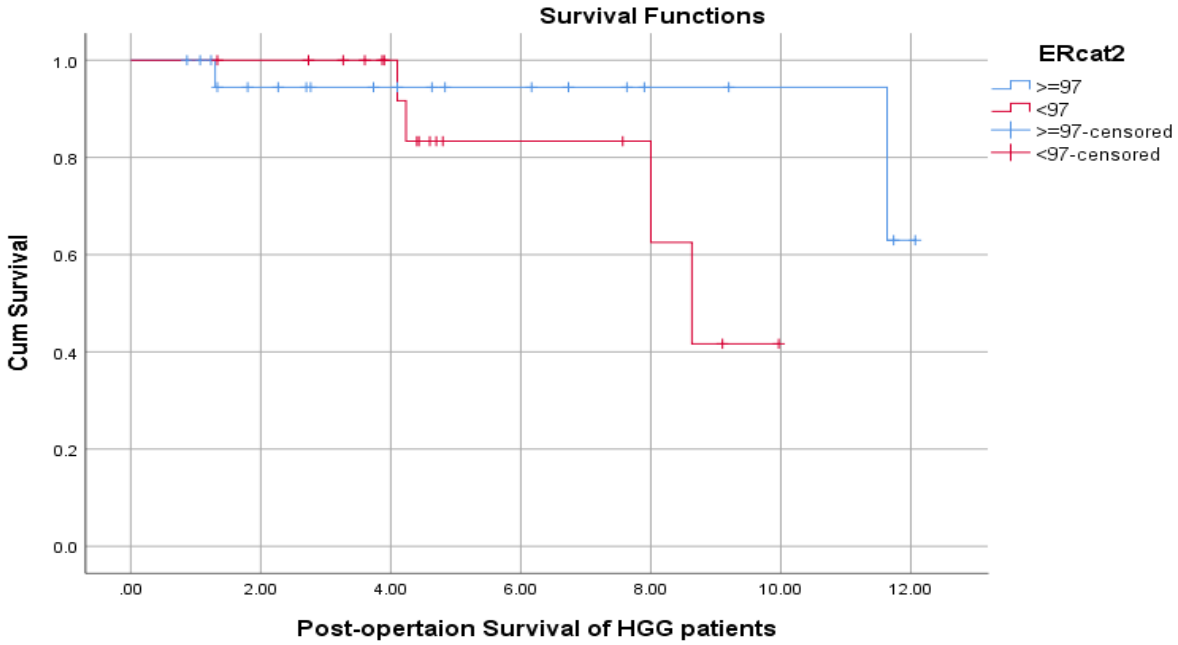
There was significant association in patients with higher KPS (≥ 70) value and their survival outcome. ($\chi 2$= 10.19 P=0.006). Patients with pre-operative GCS (≤ 14) seem to have significant association on survival outcome compared with patients having GCS of 15. ($\chi 2$= 12.9 P=0.005). Those patients who received post-operative adjuvant therapy have better survival outcome than those patients with no adjuvant therapy. ($\chi 2$= 6.716) P=0.035). There was no association between survival and WHO grade. (Table 4)

Table 4: Chi-square test for KPS, Pre-operative GCS, and Post-adjuvant therapy compared with Survival

	Survival		**χ^2**	**p-value**
	Alive(n=33)	Dead(n=7)		
Age				
<30 years	3	2	3.458	0.284
30-40	8	0		
41-50	11	2		
≥50	11	3		
KPS				

10-60	1	3	10.19	0.006
70-80	25	3		
≥90	7	1		
GCS				
9	0	1	12.79	0.005
10	0	1		
14	3	2		
15	30	3		
WHO Grade				
3	9	2	0.005	0.944
4	24	5		
Post-op Adjuvant				
RT	12	1	6.71	0.035
RT+ TMZ	10	0		
No RT+ TMZ or RT	11	6		

The median survival time for those patients with extent of resection <97% is 8.3 months (CI: 7.3-9.9 months, p=0.171). The median survival of patients who didn't receive adjuvant treatment is 8 months with log rank off (P=0.005, CI: 1.95-11.82 months).



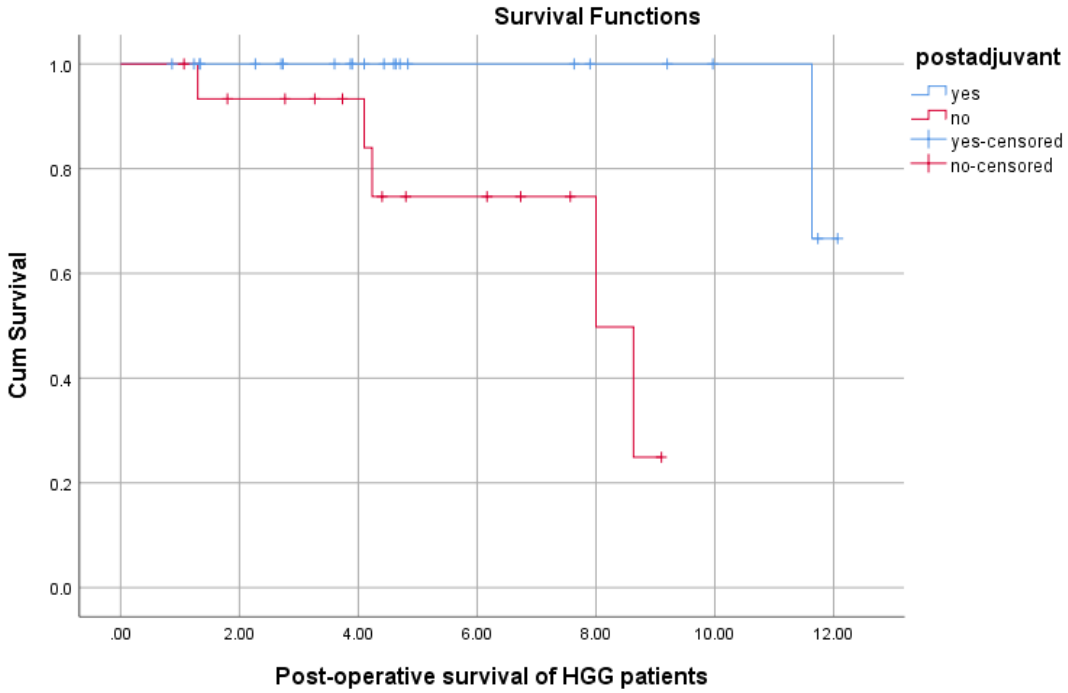


Figure 3 : Kaplan Meir analysis. A. Survival Outcome for extent of resection. B. Survival Outcome for adjuvant treatment.

There was no significant association seen between functional status (GOS) of patients and extent of resection in this study. Similarly, no association was found between functional status (GOS) and having post adjuvant treatment. (Table 5)

Table 5 Chi-square test comparing functional status with EOR and Post-adjuvant therapy

	Functional Status(GOS)				χ^2	p-value
Extent of resection	GOS 1	GOS 3	GOS 4	GOS 5		
<97	2	3	6	7	13.112	0.088
≥97	1	3	2	16		
Post-Adjuvant therapy						
Yes	0	2	6	15	6.429	0.080
No	3	4	2	8		
WHO Grade						
3	0	2	2	7	1.130	0.892
4	3	4	6	16		

6. DISCUSSION

In this study the findings showed clinical characteristics of operated HGG patient's preoperatively and post-operatively. This research also estimated the survival outcome of these patients after treatment.

The treatment outcomes for 40 patients diagnosed with high-grade gliomas (HGG) were evaluated over a one-year period, commencing September 1, 2023, and concluding September 1, 2024. The median survival duration following surgery was recorded at 11.3 months, with 7 patients (17.5%) having succumbed by the end of the observation period. Notably, the median survival in this analysis was lower compared to findings in other studies (14, 27, 28).

This investigation indicated that the most affected age group for HGG was individuals aged 50 years and above, a finding consistent with research conducted in the U.S. concerning prognostic indicators of survival in glioblastoma patients. Various studies suggest that a younger age correlates significantly with enhanced survival outcomes (1, 22). However, this study did not find a significant link between age and survival rates. A higher male-to-female ratio was observed, aligning with results from previous research (27, 29).

The predominant initial symptoms reported were headaches and seizures, corroborating findings from a U.S. study on care patterns for adults newly diagnosed

with malignant glioma (30). This research revealed that solitary lesions were more prevalent than multifocal ones, representing 87.5% of cases. This observation aligns with that of Dr. Akinmoladun and colleagues, who examined MRI patterns of glioblastoma in a tertiary care setting (31).

A majority of the patients (70%) had a Karnofsky Performance Status (KPS) score between 70 and 80, while 20% achieved scores of 90 or higher, and 10% fell between scores of 10 and 60. The Glasgow Coma Scale (GCS) recorded a score of 15 in most cases (82.5%). These results are consistent with a Nigerian study investigating the challenges related to the management of high-grade gliomas. A notable difference in patient outcomes was found between those with KPS scores lower than 60 compared to those with scores greater than 90, a finding that aligns with previous research conducted in Nigeria (3).

In contrast to other studies, this investigation did not establish a significant relationship between the World Health Organization (WHO) grade and survival outcomes (28, 32). The frontal lobe (47.5%) was identified as the most common tumor location, followed by the temporal (27.5%) and parietal (20%) lobes. These results are in agreement with a Bulgarian study that focused on the clinical aspects and prognostic factors of HGG surgery (29).

The mean preoperative tumor volume was calculated at 80.38 cm^3 (range 3.9-168 cm^3), with 52.5% of cases achieving an extent of resection (EOR) of 97% or higher. This is comparable to a U.S. study examining the prognosis, extent of resection, and survival in glioblastoma patients, albeit with a higher mean preoperative tumor volume (33). Although an EOR of 97% is frequently associated with improved survival outcomes in numerous studies, this investigation did not find a statistically significant survival difference between patients with EOR $\geq$ 97% and those with EOR $<$ 97% ($p=0.171$) (15, 29, 33).

Postoperative adjuvant therapy, either radiation (RT) or temozolomide (TMZ), was administered to 57.5% of the patients. This figure is notably lower than that reported by Joanna et al., who found that 68% of patients received postoperative adjuvant therapy following radiation treatment for HGG (28). The reduced percentage in the present study may be attributed to the expense associated with TMZ and the lengthy waiting periods for radiation therapy. A significant difference was noted in survival outcomes between patients who received adjuvant therapy following surgery and those who did not. Similar results were observed in a Nigerian study addressing the challenges in managing high-grade gliomas (3).

A clinical review by Antonio on glioblastoma and other malignant gliomas indicated that venous thromboembolic events occur in 20%-30% of patients, contrasting with this study, where only 5% of patients experienced such events (10).

7. Strength and Limitation

Strength

This research assessed the treatment outcome, pattern of care of HGG patients during the study period along in detailed manner. I believe this research provides valuable information on patient's characteristics and outcome after surgery.

Limitation

In this study IDH status of almost all patients couldn't be assessed. This is an important tool in assessing the prognosis of these patients. The reason we identified were its being very costly and unavailability at the hospitals patients were treated. The psychosocial and functional (Quality of life) outcome of the patients were also not assessed.

8. Conclusion

High-grade glioma (HGG) represents the most aggressive primary brain tumor, and its incidence continues to rise globally. In this study we had 40 patients who were diagnosed with HGG with histopathologic confirmation. The median survival time for patients with HGG post-surgery was 11.3 months (95% CI: 6.2-17months). There was significant association between survival outcome and Preoperative KPS, Pre-operative GCS and getting post- operative adjuvant therapy.

Recommendation

- Continuing advocacy and engagement with the government and stakeholders on the need for improving access to radiotherapy and chemotherapy will be important.
- Increasing use of available (ultrasound) and new intraoperative adjuncts that can maximize the extent of resection during surgery is also crucial.
- Increasing awareness about the disease among the general population, and medical community (non-neurosurgical) to minimize late presentations which can negatively impact post-operative outcome.
- Genetic testing for IDH status is crucial tool in prognosis, starting this service and steps to increase diagnostic capacity of pathology service will be important.

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Annex

Questioner Tool

The purpose of this data collection tool is to capture data regarding pattern of care, treatment outcome and associated factors of High grade Glioma patients found at TikurAnbessa Specialized Hospital and affiliate neurosurgical Hospitals in Addis Ababa, Ethiopia. . This structured data collection tool will use medical data record collected routinely from Tikur Anbessa Specialized Hospital, Zewditu memorial hospital, MCM and Alert Specialized Hospital and data entered on patient chart and direct interview with the attendant of the children for the treatment outcome. It will take 15 to 20 minutes and be collected by the data collectors. This questioner has five sections assessing demographic, preoperative, perioperative, post-op and follow up conditions of the study participants, Treatment outcome of each participant of this study will be collected during each follow up visit. It is very important to ensure quality of data collected since it will be used to plan appropriate measures that could be taken.

Name of Health facility- _____

Unique ID- _____

Date of data collection-_____

Name of data collector _____

Name of supervisor-_____

Data collection completeness: Not completed ☐ Completed ☐ Partially completed ☐

Questioner

Part 1: Demographics

1. Name:
2. Age:
3. Handedness
   - ☐ Right Handed
   - ☐ Left Handed
   - ☐ Ambidextrous
4. Sex
   - ☐ Male
   - ☐ Female
5. Phone Number:
6. Alternative Phone Number 1:
7. Alternative Phone Number 2:
8. Occupation:

9. Region

☐ Tigray ☐ Addis Ababa ☐ SNNRP

☐ Afar ☐ Harari ☐ Somali

☐ Amahara ☐ Diredawa ☐ Gambela

☐ Oromia ☐ Sidama

10. MRN:

11. Hospital

☐ MCM ☐ BLH ☐ ZMH ☐ Alert

Part 2: Preoperative Clinical data

12. Preoperative clinical presentation

☐ Headache ☐ Seizure ☐ Vomiting ☐ Weakness ☐ CN deficit
☐ Decreased mentation ☐ Speech difficulty ☐ Behavioral change
☐ Endocrine disturbance ☐ visual complaint
☐ Others:

13. Duration of symptoms & Signs:

14. Risk factors identified

☐ Family history
☐ Prior ionizing Radiation therapy
☐ History of Asthma, Hay fever, Eczema, and Food allergies
☐ Occupational Risks - use of pesticides
☐ Others:

15. Preoperative GCS:

16. Tumor localization

☐ Frontal ☐ Temporal ☐ Parietal ☐ Occipital ☐ Brainstem

☐ Multiple ☐ OPHG ☐ Basal ganglia/Thalamic ☐ Insular

17. Tumor location

☐ Right ☐ Left ☐ Midline ☐ Bilateral

18. Preoperative Tumor size in CM:

19. Preoperative Tumor Volume in CM3:

20. Number of sites involved

☐ Single ☐ Multiple

21. Comorbidity

☐ DM ☐ HTN ☐ CKD
☐ Cardiovascular disorders ☐ Cerebrovascular disorders
☐ Others:

22. Seeding

☐ CSF ☐ White matter tract ☐ Distant ☐ None

23. Associated Hydrocephalus

☐ Yes ☐ No

24 If the answer to the above Q is yes what kind of CSF diversion was used

☐ Permanent: Shunt or ETV

☐ Temporary: EVD

25. KPS level

☐ 10 ☐ 40 ☐ 70 ☐ 100
☐ 20 ☐ 50 ☐ 80
☐ 30 ☐ 60 ☐ 90

26. Preoperative Medications.

☐ Mannitol
☐ Corticosteroids
☐ Anti-seizure medication - Prophylactic
☐ Anti-seizure Medication –Therapeutic
☐ Unfractionated heparin or other

☐ Prophylactic anticoagulation
☐ Antipsychotics

Part 3: Perioperative data

27. Type of Intervention

☐ Primary Surgery
☐ Re-Operation
☐ Observation
☐ Palliative care
☐ Chemo-radiation

28. Timing of the surgery from initial Diagnosis:

29. Histopathologic Diagnosis

☐ Astrocytoma
☐ Oligodendroglioma
☐ Oligosarcoma
☐ Gliosarcoma
☐ Ependymosarcoma
☐ Oligoastrocytoma

30. Use of Intraoperative US to maximize Extent of resection
☐ Yes
☐ NO

31. Extent of Resection Gross Estimation by the surgeon

☐ Biopsy
☐ MSR
☐ GTR
☐ STR
☐ Supramarginal

32. Extent of Resection in %:

33. IDH Status

- ☐ Mutant
- ☐ Wild type
- ☐ Unknown

34. WHO Grade

- ☐ Grade 3
- ☐ Grade 4

Part 4: Post-Operative data

35. Post OP Control Image in the 1st 72hours
    ☐ CT ☐ MRI
36. Post-Operative residual tumor Volume in cm3:
37. Post OP Complications

- ☐ New onset or worsening weakness
- ☐ New Onset language deficit
- ☐ Confusion or memory loss
- ☐ Cerebral edema
- ☐ CSF Leak
- ☐ Vascular injury or Spasm
- ☐ Surgical site infection
- ☐ Health Care Associated Meningitis/Ventriculitis
- ☐ Hospital Acquired Pneumonia
- ☐ Urinary tract infection
- ☐ Tension Pneumocephalus
- ☐ Tumor Bed Hematoma
- ☐ Wounded glioma Syndrome
- ☐ DVT/PE
- ☐ DI
- ☐ Seizure
- ☐ Bed sore
- ☐ SIADH/Cerebral salt wasting
- ☐ Other

38. Post OP duration of stay in the Hospital:
39. Post OP Adjuvant Rx
    ☐ Chemotherapy ☐ RT ☐ Chemotherapy + RT ☐ None

40. Day of Adjuvant Therapy from initial Surgery if received:

Part 5: Follow-up

41. Subsequent Follow-up image
    - ☐ Pseudoprogression
    - ☐ Radiation necrosis
    - ☐ Recurrence
    - ☐ No Recurrence
    - ☐ Pseudoresponse
42. Response Assessment in Neuro-Oncology (RANO) criteria for high-grade gliomas at 3 months

    - ☐ Complete Response
    - ☐ Partial Response
    - ☐ Stable Disease
    - ☐ Progression
43. Response Assessment in Neuro-Oncology (RANO) criteria for high-grade gliomas at 6 months

    - ☐ Complete Response
    - ☐ Partial
    - ☐ Response Stable
    - ☐ Progression
44. Response Assessment in Neuro-Oncology (RANO) criteria for high-grade gliomas at 9 months

    - ☐ Complete Response
    - ☐ Partial
    - ☐ Response Stable
    - ☐ Progression
45. Response Assessment in Neuro-Oncology (RANO) criteria for high-grade gliomas at 12 months

    - ☐ Complete Response
    - ☐ Partial
    - ☐ Response Stable
    - ☐ Progression
46. Functional Status at 1 month

☐ GOS 1
☐ GOS 2
☐ GOS 3
☐ GOS 4
☐ GOS 5

47. Functional Status at 3 months

☐ GOS 1
☐ GOS 2
☐ GOS 3
☐ GOS 4
☐ GOS 5

48. Functional Status at 6 months

☐ GOS 1
☐ GOS 2
☐ GOS 3
☐ GOS 4
☐ GOS 5

50. Functional Status at 12 months

☐ GOS 1
☐ GOS 2
☐ GOS 3
☐ GOS 4
☐ GOS 5

Annex 2

1. Karnofsky performance scale

Table 98.1 Karnofsky performance status scale (modified[1,2])

Score	Criteria	General category
100	normal: no complaints, no evidence of disease	Able to carry on normal activity and work. No special care is needed
90	able to carry on normal activity: minor signs or symptoms	
80	normal activity with effort: some signs or symptoms	
70	cares for self: unable to carry on normal activity or to do active work	Unable to work. Able to live at home, care for most personal needs. Variable assistance is required
60	requires occasional assistance: cares for most of needs	
50	requires considerable assistance and frequent care	
40	disabled: requires special care and assistance	Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be rapidly progressing
30	severely disabled: hospitalized; death not imminent	
20	very sick: hospitalized; active supportive care needed	
10	moribund: fatal processes are progressing rapidly	
0	dead	

2. Glascow Outcome Scale

Score	Glasgow Outcome Scale (original)[4]
1	death—most deaths ascribable to primary head injury occur within 48 hrs
2	persistent vegetative state—unresponsive & speechless. After 2–3 weeks, may open eyes & have sleep/wake cycles
3	severe disability (conscious but disabled)—dependent for daily support (may be institutionalized, but this is not a criterion)
4	moderate disability (disabled but independent)—travel by public transportation, can work in sheltered setting (exceeds mere ability to perform "activities of daily living")
5	good recovery—resumption of normal life despite minor deficits ("return to work" not reliable)

3. Response assessment in Neurooncology Criteria for High grade glioma

Table 37.6 Response Assessment in Neuro-Oncology (RANO) criteria for high-grade gliomas[a]

Complete response
Requires all of the following: 1. complete disappearance of all disease (measurable and nonmeasurable) for ≥ 4 weeks 2. no new lesions 3. stable or improved nonenhancing lesions (on T2/FLAIR) 4. patient off corticosteroids (except for physiologic replacement) 5. clinically stable or improved Patients with only nonmeasurable disease cannot have complete response (stable disease is best possible response)
Partial response
Requires all of the following: 1. (compared to baseline) ≥ 50% decrease of the sum of products of perpendicular diameters of all measurable enhancing lesions for ≥ 4 weeks 2. no progression of nonmeasurable disease 3. no new lesions 4. stable or improved nonenhancing lesions (on T2/FLAIR) on same or lower doses of corticosteroids compared to doses at baseline scan 5. corticosteroid dose at the time of the scan is no greater than dose at time of baseline scan 6. clinically stable or improved Patients with only nonmeasurable disease cannot have partial response (stable disease is best possible response)
Stable disease
Requires all of the following: 1. does not qualify for complete response, partial response or progression 2. stable nonenhancing lesions (T2/FLAIR) on same or lower doses of corticosteroids compared to doses at baseline scan 3. if steroid dose was increased for new symptoms and signs without confirming progression on imaging, and subsequent imaging shows that the need for increased steroids was due to disease progression, the last scan considered to show stable disease will be the one obtained when the steroid dose was the same as at the baseline scan
Progression
Defined by any of the following: 1. ≥ 25% increase in sum of products of perpendicular diameters enhancing lesions compared with the smallest lesion measurement at either baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids 2. significant increase in nonenhancing lesions (on T2/FLAIR) on equal or increased doses of steroids compared to dose at baseline or best response after initiation of therapy not caused by comorbid events (e.g., XRT, demyelination, ischemic injury, infection, seizures, post-op changes, or other treatment effects...) 3. any new lesion 4. clear clinical deterioration not attributable to causes other than tumor (e.g., seizures, adverse effects of medication, stroke, infection...) or changes in steroid dose 5. failure to return for evaluation due to death or deterioration 6. or clear progression of nonmeasurable disease
[a]see reference[104] for definitions (e.g., measurable and nonmeasurable disease...) and for measurement technique. All lesions (measurable and nonmeasurable) must be assessed using the same technique as baseline imaging.