J Cancer Allied Spec 2024;10(1):7

Original Article

Survival Analysis and Correlates with Molecular Epidemiology: 10-Year Retrospective Series of High-Grade Glioma in Pakistan

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Received: 27 July 2023/Accepted: 06 December 2023

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Citation: Shah M, Anis SB, Yousaf I, Bajwa MH. Survival Analysis and Correlates with Molecular Epidemiology: 10-Year Retrospective Series of High-Grade Glioma in Pakistan. J Cancer Allied Spec [Internet]. 2024;10(1):1-7. https://doi.org/10.37029/jcas.v10i1.565

Funding: None.

Competing interest: The author(s) declare(s) that there is no conflict of interest.

Abstract

Introduction: High-grade gliomas are malignant, recurring primary central nervous system (CNS) tumors requiring extensive postoperative chemotherapy and radiation treatment. Isocitrate dehydrogenase (IDH), 1p19q, and ATRX mutations significantly influence survival and response to chemotherapy, as seen in many extensive studies from the Global North. This study aims to report data from the local region regarding progression-free survival and overall survival in light of molecular characteristics. **Materials and Methods:** A 10-year retrospective series was conducted at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, with 285 patients presenting from 2008 to 2018. Prospective follow-up data was collected, and complete molecular profiles were available for patients presenting from 2010 onwards. Survival analysis was conducted through the Kaplan-Meier method, with log-rank reported. **Results:** 70.53% (201) of patients were male, with a mean age at diagnosis of 43.33 ± 15.1 years. 265 patients within the cohort completed postoperative radiotherapy, while 141 patients underwent chemotherapy (procarbazine, lomustine, and vincristine, or temozolomide). Mean survival, in months, within the cohort was as follows: glioblastoma (14.1), anaplastic astrocytoma (27.5), and anaplastic oligodendroglioma (39.8). Survival curves showed a lower survival for IDH wild-type ($P < 0.0001$), ATRX mutated ($P = 0.029$), and 1p19q non-deleted ($P = 0.008$) tumors from Pakistan. **Discussion:** Our findings quantified long-term survival outcomes for high-grade glioma from Pakistan, analyzing the various treatment patterns. Of particular importance, molecular sub-classification significantly predicted survival outcomes for IDH, ATRX, and 1p19 co-deletion mutations. Expanding brain tumor epidemiology will benefit assessing the efficacy of regional oncological centers and establishing standards of care.

Keywords: Glioblastoma, glioma, molecular epidemiology, neuro-oncology, oncology, survival

Introduction

Gliomas are intra-axial primary central nervous system (CNS) tumors with heterogeneous morphology and genetic variance; the 2021 World Health Organization (WHO) Classification of Primary CNS Tumors emphasizes understanding their presentation, outcomes, and response in light of molecular

markers and genetic subtypes.[1] High-grade gliomas (HGG), including anaplastic astrocytomas, anaplastic oligodendroglioma (AO), and glioblastoma, make up 60–75% of all gliomas. HGG has been subtyped based on mutations in isocitrate-dehydrogenase 1 and 2 (IDH1 and IDH2) pathways and chromosomal co-deletions of 1p and 19q. This is based on significantly worse survival in patients with IDH-wild-type gliomas.[2] Regardless of tumor grade, the occurrence of the IDH mutation in gliomas indicates improved progression-free survival (PFS) over IDH-wild-type tumors. Primary glioblastomas typically occurring in older patients without lower-grade precursors are IDH wild-type. In contrast, most secondary glioblastomas that result from low-grade gliomas exhibit mutations in the IDH gene.[3]

Treatment for brain tumors, particularly aggressive HGG, is multidisciplinary and long-term, requiring various specialists working in tandem to achieve the goals of tumor control and surveillance.[4] Surgery for cytoreduction is indicated based on tumor location, proximity to eloquent areas, and other critical structures. While the surgical extent of resection correlates with overall survival (OS), surgeons can be forced to resort to sub-total resection or biopsy procedures to prevent neurological injury. For HGG, studies have shown the presence of glial tumor cells within the brain microenvironment, often beyond the margins of a visualized tumor, making recurrence likely.[5] Therefore, postoperative radiation and chemotherapy are the standards of care, and the extent of resection determines the duration. IDH mutation and 1p19q-codeletion status often determine tumor response to temozolomide (first-line chemotherapy) and radiation.[6]

According to the Central Brain Tumor Registry of the United States (CBTRUS), the most significant ongoing CNS cancer registry, glioblastoma (WHO grade IV) remains the most common subtype in adult glioma. Anaplastic astrocytoma and glioblastoma have higher incidences in older age groups, preferably within 75–84 years. Moreover, the IDH mutation shows improved survival in populations from the global north, as evidenced by large series.[6] Epidemiological data from multiple hospitals in Pakistan have highlighted glioblastoma as the most common presenting glioma subtype, however, with a younger age group than what has been reported in the CBTRUS.[4,7] Despite this, there is a lack of data on the response to chemotherapy and radiotherapy after surgery for HGG in our region, particularly concerning OS and PFS. This study aims to present follow-up data from one of the largest cancer hospitals in our region on HGG with molecular characterization, OS, and PFS and discusses the implications for management.

Materials and Methods

A 10-year retrospective chart review and prospective follow-up data were collected for patients admitted to the Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH), Lahore, Pakistan, a tertiary-care center, from 2008 to 2018. Patients were referred from other hospitals for further specialized management or presented on their own to one of the multiple walk-in clinics established across Pakistan by SKMCH.

The authors obtained ethical approval, and an exemption was granted by the Institutional Review Board (IRB) at the Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan. This study examined demographic, epidemiological, surgical, adjunct therapy, and follow-up data for grade III and IV gliomas confirmed by a histopathological diagnosis. Detailed molecular marker analysis was available for tumors presenting from 2010 onwards. The primary end-points of this study were survival and progress-free survival (as ascertained by follow-up magnetic resonance imaging scans), quantified in months, and sub-stratified according to the histopathological categories, the extent of surgical resection, and specific molecular mutations.

Analysis was performed using IBM SPSS Statistics Version 23 and STATA Version 16. $P < 0.05$ was taken to be statistically significant, with 95% confidence intervals reported. Kaplan-Meier curves stratified according to molecular markers

and surgical procedures show survival time after diagnosis and surgery.

Results

Patient demographics

A total of 285 patients were treated for HGG from 2008 to 2018, of which 201 (70.53%) were male and 84 (29.47%) were female. The mean age at diagnosis for a patient with HGG was 43.44 ± 15.1 years. The HGG identified were glioblastoma (184), anaplastic astrocytoma (35), and AO (32), and the remaining tumors were classified as others (34). Table 1 shows the mean age at diagnosis by tumor subtype.

Surgery, operative specimen histopathology, and adjuvant treatment

For HGG, subtotal resection was more commonly performed (188, 65.96%) compared to gross total resections (29, 10.18%) and biopsies (68, 23.86%). Table 2 shows that a mass effect was seen in 279 (97.89%) HGG tumors, and the frontal lobe was the most common location for tumors to develop (49.82%).

Adjuvant treatment (chemoradiotherapy) was carried out post-surgery. Radiation therapy was provided to 265 patients, and chemotherapy (either temozolomide or procarbazine, lomustine, and vincristine [PCV]) was provided to 141 patients. All those who underwent radiation therapy also underwent chemotherapy. The most common complication was a neurological deficit, occurring in 13 (4.56%) of all patients. Patients with glioblastomas were most likely to have complications. Table 3 elaborates on patterns of adjuvant and surgical treatment by HGG subtype.

Table 1: Age and frequency of high-grade glioma subtypes

Tumor subtype	Frequency	Mean age at diagnosis
Glioblastoma	184	46.98±14.97
Anaplastic astrocytoma	35	37.17±11.41
Anaplastic oligodendroglioma	32	44.03±10.86
Others	34	30.21±13.53

Survival analysis

AOs have the longest mean OS (39.8 months), whereas glioblastomas have the shortest mean OS (14.1 months) [Table 4]. Patients who underwent gross total resections had a mean OS of 40.2 months, and patients who received PCV had a mean OS of 31.1 months. Figure 1 depicts survival trends by molecular markers for the present cohort. Log-rank showed statistically significant differences in survival according to IDH ($P < 0.0001$), ATRX (0.029), 1p19q co-deletion ($P = 0.008$), and histopathology ($P < 0.0001$).

Discussion

We present an overview of management, molecular epidemiology, and survival after surgery and adjuvant therapy in HGG from Pakistan. Our data shows that AOs are the longest-surviving high-grade gliomas (39.8 months), whereas glioblastomas have the shortest mean survival (14.1 months). We also found that, on average, patients with HGG survive twice as long if they have had a gross total resection versus a subtotal resection of the tumor. There was no significant difference in survival between patients who were given temozolomide and patients who were given PCV.

Lassman et al. found that 49% of patients with an AO who received PCV and radiation were alive at 10 years, while only 15% of patients with AO were alive at 10 years if treated with temozolomide and radiation.[8] Ruff *et al.* found that monotherapy with temozolomide was less effective than radiation monotherapy and that radiation therapy with PCV is the most effective treatment regimen for HGG.[9] While a significant difference was not found between survival trends in patients using PCV versus temozolomide, a larger sample size may show results similar to those in the global literature.[10]

Our findings indicate that 13 patients (4.6%) had a neurological deficit post-surgery. A 2019 systematic

Table 2: Patient demographics and tumor-related characteristics stratified according to histopathology

Patient demographics and tumor-related characteristics	Glioblastoma N (%)	Anaplastic Astrocytoma N (%)	Anaplastic Oligodendroglioma N (%)	Others N (%)
Functional Class				
0	30 (16.30)	13 (37.14)	18 (56.25)	3 (8.82)
1	62 (33.70)	12 (34.28)	10 (31.25)	8 (23.53)
2	60 (32.61)	8 (22.86)	3 (9.38)	16 (47.06)
3	25 (13.59)	1 (2.86)	1 (2.13)	8 (23.53)
4	7 (3.80)	1 (2.86)	0 (0.00)	1 (2.94)
Mass Effect				
Yes	182 (98.91)	34 (97.14)	30 (93.75)	33 (97.06)
No	2 (1.09)	1 (2.86)	2 (6.25)	1 (2.94)
Location				
Parietal	26 (14.13)	2 (5.71)	4 (12.5)	5 (14.71)
Frontal	89 (48.37)	21 (60.0)	21 (65.63)	11 (32.35)
Temporal	51 (17.96)	8 (22.86)	6 (18.75)	3 (8.82)
Infratentorial	2 (1.09)	0 (0.00)	0 (0.00)	9 (26.47)
Occipital	12 (6.52)	1 (2.86)	0 (0.00)	2 (5.88)
Basal Ganglia	4 (2.17)	3 (8.57)	0 (0.00)	2 (5.88)
Intraventricular	0 (0.00)	0 (0.00)	1 (3.13)	2 (5.88)

Table 3: Surgical and adjuvant therapy outcomes in HGG cohort with survival rates

Treatment and outcome	Glioblastoma N (%)	Anaplastic Astrocytoma N (%)	Anaplastic Oligodendroglioma N (%)	Others N (%)
Chemotherapy				
PCV	32 (17.39)	18 (51.43)	17 (52.13)	3 (8.82)
Temozolomide	40 (21.74)	5 (14.29)	8 (25.0)	3 (8.82(
Unspecified	6 (3.26)	1 (2.86)	1 (3.13)	7 (20.59)
No	106 (57.61)	11 (31.43)	6 (18.75)	21 (61.76)
Radiation therapy				
Yes	168 (91.30)	35 (100.00)	30 (93.75)	32 (94.12)
No	16 (8.70)	0 (0.00)	2 (6.25)	2 (5.88)
Complications				
Seizures	2 (1.09)	0 (0.00)	0 (0.00)	0 (0.00)
Neurological deficit	10 (5.43)	1 (2.86)	2 (6.25)	0 (0.00)
Hemorrhage	7 (3.80)	0 (0.00)	3 (9.38)	0 (0.00)
Cerebral edema	2 (1.09)	0 (0.00)	2 (6.25)	1 (2.94)
Infection	2 (1.09)	0 (0.00)	0 (0.00)	0 (0.00)
None	162 (88.04)	34 (97.14)	25 (78.13)	33 (97.06)
Survival				
Alive	11 (5.98)	6 (17.14)	12 (37.50)	3 (8.82)
Deceased	173 (94.02)	29 (82.86)	20 (62.50)	31 (91.18)

PCV: Procarbazine, lomustine, and vincristine, HGG: High-grade gliomas

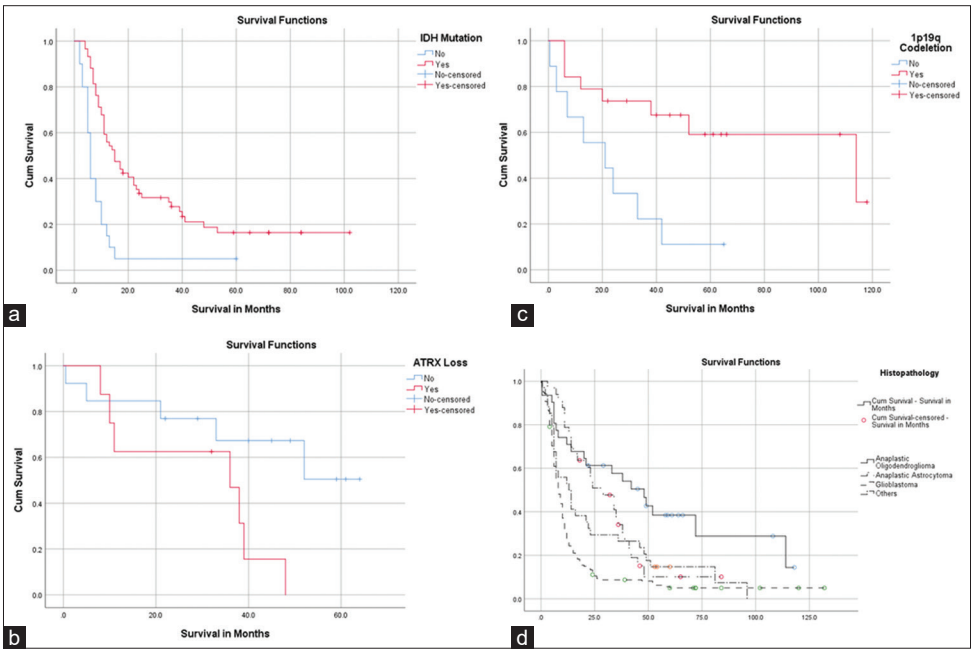

Figure 1: Kaplan Meier estimates for molecular subgroups (a) Isocitrate dehydrogenase (Log-rank < 0.0001), (b) ATRX (log-rank = 0.029), (c) 1p19q (log rank = 0.008), (d) histopathology (log-rank < 0.0001)

Table 4: Median overall survival by HGG subtype and treatment characteristics

HGG subtype and treatment characteristics	Survival in months
	Mean
Histopathology	
Glioblastoma	14.1
Anaplastic astrocytoma	27.5
Anaplastic oligodendroglioma	39.8
Others	23.5
Surgery	
Biopsy	11.8
Subtotal resection	19.6
Gross total resection	40.2
Chemotherapy	
No	10.4
PCV	31.1
Temozolomide	28.4
Unspecified	26.3
Radiotherapy	
Yes	21.2
No	1.8

PCV: Procarbazine, lomustine, and vincristine, HGG: High-grade gliomas

review and meta-analysis found that temporary and permanent motor deficits accounted for 11% (6–17%) and 4% (2–7%) of the pooled patients, respectively, and temporary and permanent language deficits accounted for 11% (6–17%) and 2% (0–4%) of the pooled patients, respectively.[11] While our data does not divide deficits into motor and language, our outcomes fall within the range to appropriately carry out safe glioma surgical resection.

Regarding survival, our findings are broadly in line with the global literature on HGG. Sanai *et al*. found, through a comprehensive review of literature on the extent of resection and high-grade glioma survival, that the extent of resection could be used as a predictor of survival. They found that the mean survival post-surgery increases by 3 months if a gross total resection is carried out versus a subtotal resection.[12] Yamaguchi *et al*. examined the impact of histological subtype on the outcome of adult patients with HGG and found that anaplastic oligodendroglial tumors had more prolonged OS

than anaplastic astrocytic tumors.[13] Data from our study also showed this trend.

Our findings also indicate that HGG with IDH mutations had more prolonged survival than IDH-wild-type tumors. A meta-analysis examining 1669 glioblastoma patients found that the IDH1 mutation was significantly associated with better survival.[14] Zhao *et al*. also found that 1p and 19q co-deletions in gliomas led to better OS, regardless of the grade and subtype of the tumor.[15] Tumors with IDH mutations fared better with radiation therapy than IDH wild-type tumors. IDH mutation status has proven to predict survival equivalent to grading in high-grade astrocytomas. Similarly, 1p19q-codeletion predicts response to chemotherapy. Oligodendroglial tumors with mutations in both have longer survival outcomes than other HGG groups.[6]

This study has a few limitations that need to be addressed. The data revealed that around 106 glioblastoma patients did not receive adjuvant chemotherapy. This is against the standard STUPP protocol, the recommended treatment for glioblastoma. Secondly, patients who could not tolerate chemotherapy and did not complete the entire cycle could not be marked as having completed chemotherapy. Similarly, practices within the region may vary as some patients receive post-operative adjuvant therapy when evidence of recurrence or progression exists, either due to patients not following up with oncologists or lacking referrals. Finally, there may be recall bias due to the retrospective nature of the investigation. This was offset by the prospective follow-up data collected and by an objective assessment of the electronic medical records by a board-certified neurosurgeon with expertise in neuro-oncology.

High-grade glioma from our center shows comparable outcomes with what is reported from other centers worldwide, showing adequate treatment. The usage of molecular classification showed significant differences in OS between subgroups. Defining the molecular epidemiology of brain tumors within our region may benefit assessing outcomes and investing in multidisciplinary interventions in neuro-oncology. Our center's experience with long-term treatment and follow-up of HGG may help define local practices and encourage epidemiological reporting from other centers.

Acknowledgment

None.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval

Prior to the initiation of this study, ethical approval and exemption were granted by the IRB at the Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan.

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Authorship Contributions

Conceived and designed the analysis: MS, SBA, IY, MS, MHB; Collected the data: SBA, IY, MS; Contributed data or analysis tools: MHB, SBA, MS; Performed the analysis: MHB, SBA, MS; Wrote the paper: MHB, SBA, IY, MS.