RESEARCH ARTICLE

Treatment patterns of glioma in Pakistan: An epidemiological perspective

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Abstract

Objective: To define the landscape of treatment patterns and current epidemiological data regarding gliomas in Pakistan.

Methods: As part of the Pakistan Brain Tumour Epidemiology Study (PBTES), data were collected from 32 neurosurgical centres across the country. Our retrospective study looked at patients who underwent surgical procedures for gliomas in 2019 in neurosurgical centres. The data was collated and analysed using STATA version 15.

Results: A total of 781 patients with gliomas were identified 479(61.8%) in public sector hospitals, 302(39.1%) in the private sector). The most common histopathological subtypes were glioblastoma 262 (33.5%), followed by astrocytoma 147(18.8%) and oligodendroglioma 93(11.9%). Gender distribution was skewed towards men 508(65%). Private institution hospitals performed surgical biopsies as the first surgical procedure 75(23%) more often than public hospitals 38(9%). Chemotherapy was given to 115(29.8%) patients, and there was no data regarding 467(53%) of patients. Similarly, only 202(43.9%) patients received radiation therapy, and there was no data for 469(60%) of patients. For high-grade gliomas specifically, only 95(31.8%) patients with HGG have a record of receiving radiation therapy, and only 57(18.9%) had a record of being started on chemotherapy.

Conclusions: Our study highlighted gaps in glioma management within Pakistan, with only around half of our patients receiving chemotherapy and radiotherapy, despite it being indicated. In our experience, high-grade tumours were diagnosed at a younger age than in high-income countries, but overall, glioblastoma was a smaller constituent of our tumour sample than expected.

Keywords: Glioblastoma. Oligodendroglioma, Glioma, Astrocytoma, Brain Neoplasms, Registries, Epidemiology.

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Introduction

Gliomas constitute a group of tumours arising from glial cells, and while these are not clearly delineated, they generally include astrocytoma, oligodendroglioma, ependymoma and mixed glial tumours such as oligoastrocytoma. These cells are further divided into four grades based on the WHO 2021 classification,[1] dependent on the mitotic index, molecular and genetic characteristics, and the presence of necrosis. Supplemental classification can also be used to classify tumours as low grade, atypical, pilocytic or high grade.

The Central Brain Tumour Registry of the United States (CBTRUS) reports the incidence of gliomas at around six cases per 100,000 in the US,[2] compared to 3.5 per 100,000 previously reported in our region.[3] While the incidence of gliomas is higher than any other primary brain tumour, their biological behaviour is unique due to high rates of tumoral heterogeneity, complex microenvironment, and a tendency to recur despite adequate initial loco-regional control.[4] Advances in management are focussed on developing better diagnostic and treatment modalities, improving surgical outcomes and developing new therapeutic pathways.[5] The standard regimen of maximum safe resection followed by adjuvant chemoradiotherapy has been the most effective recent discovery in improving the lives of patients.[4,5]

Data on treatment patterns for gliomas are sparse within the country, necessitating the development of infrastructure to understand the baseline at which patients are currently being treated. In particular, hospital follow-ups and standardisation of treatment protocols have a large impact on glioma outcomes, as control is predicated on the combination of various therapeutic avenues.[6,7] There have been no reports published from Pakistan to date that have explored the epidemiological distribution of patients diagnosed with glioma and factors for positive or negative outcomes.[6] In addition,

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there is no concrete incidence reporting due to the lack of a central registry and follow-up of patients. The aim of this study was to identify the population characteristics of patients presenting with gliomas to surgical centres and to identify factors affecting their outcomes.

Methods

We conducted a retrospective cross-sectional study titled the Pakistan Brain Tumour Epidemiology Study, involving data collection from 32 neurosurgical centres across the country. Collaborating centres were selected only if they offered dedicated neurosurgical services and performed a minimum of five brain tumour surgeries per year. The study period was from January 1, 2019, to December 31, 2019.

For gliomas, we included patients with a confirmed radiological and histopathological diagnosis. For classification, we used the WHO 2016 Classification of CNS Tumours, as this was applicable at the time of data collection.[8]

Surgeon's notes and radiological reports of preoperative and postoperative neuroimaging (CT or MRI) were used to substantiate tumour location, laterality, and surgical extent of resection, classified either as GTR (gross total resection), STR (subtotal resection), or biopsy only. Outcomes were assessed through preoperative and postoperative KPS scores at the time of last follow-up. Mean time to surgery was calculated through the date of radiological diagnosis and the date of surgery.

Lost to follow-up (LTFU) was defined as patients that had discontinued follow-up at their primary institute of presentation or their primary surgeon within one year of the study (December 2020). The four points of LTFU were before surgery, after surgery, after chemotherapy, or after radiotherapy. Socioeconomic Status (SES) was determined via the occupation of the patients; each occupation was classified into a socioeconomic bracket to estimate the gross monthly income and lifestyle according to the Pakistan Bureau of Statistics guidelines.[9]

Institutes with more than 100 brain tumour surgeries per year were labelled as high-volume centres, while those with a smaller surgical volume were labelled as low-volume centres.

We assessed the normality of the variable using the Shapiro-Wilk test; normally distributed data were reported using means and standard deviation. Non-normally distributed continuous data was reported using median and interquartile range. STATA version 15 was used to analyse and generate visual graphics for data.

Results

Across the 32 centres, we received data of 781 diagnosed glioma cases from a total of 2750 patients with brain tumours. 500(64%) of these patients were male, and 357 (45%) belonged to lower socioeconomic position. The

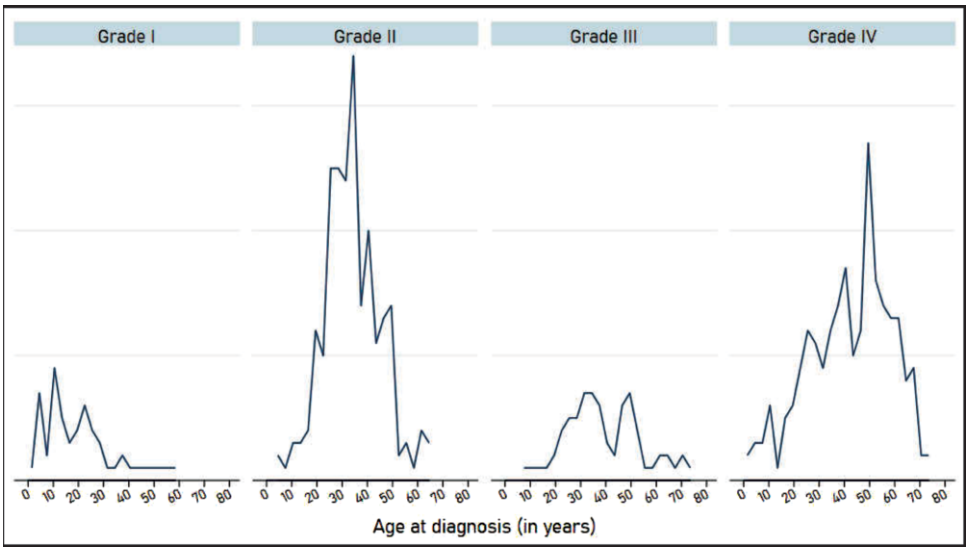

Figure-1: Distribution of age at diagnosis by grade of tumour across the national cohort.

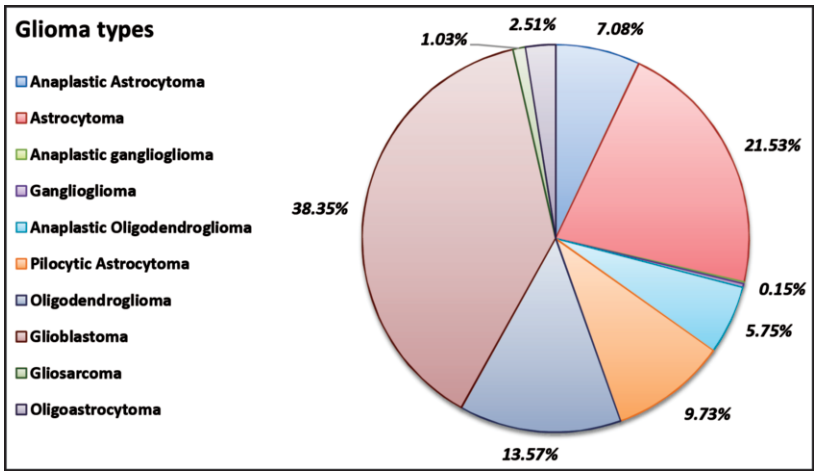

Figure-2: Histological subtypes for glioma reported.

Re-operation	Number
2nd Surgery	60/678 (8.8%)
3rd Surgery	14/678 (2.1%)

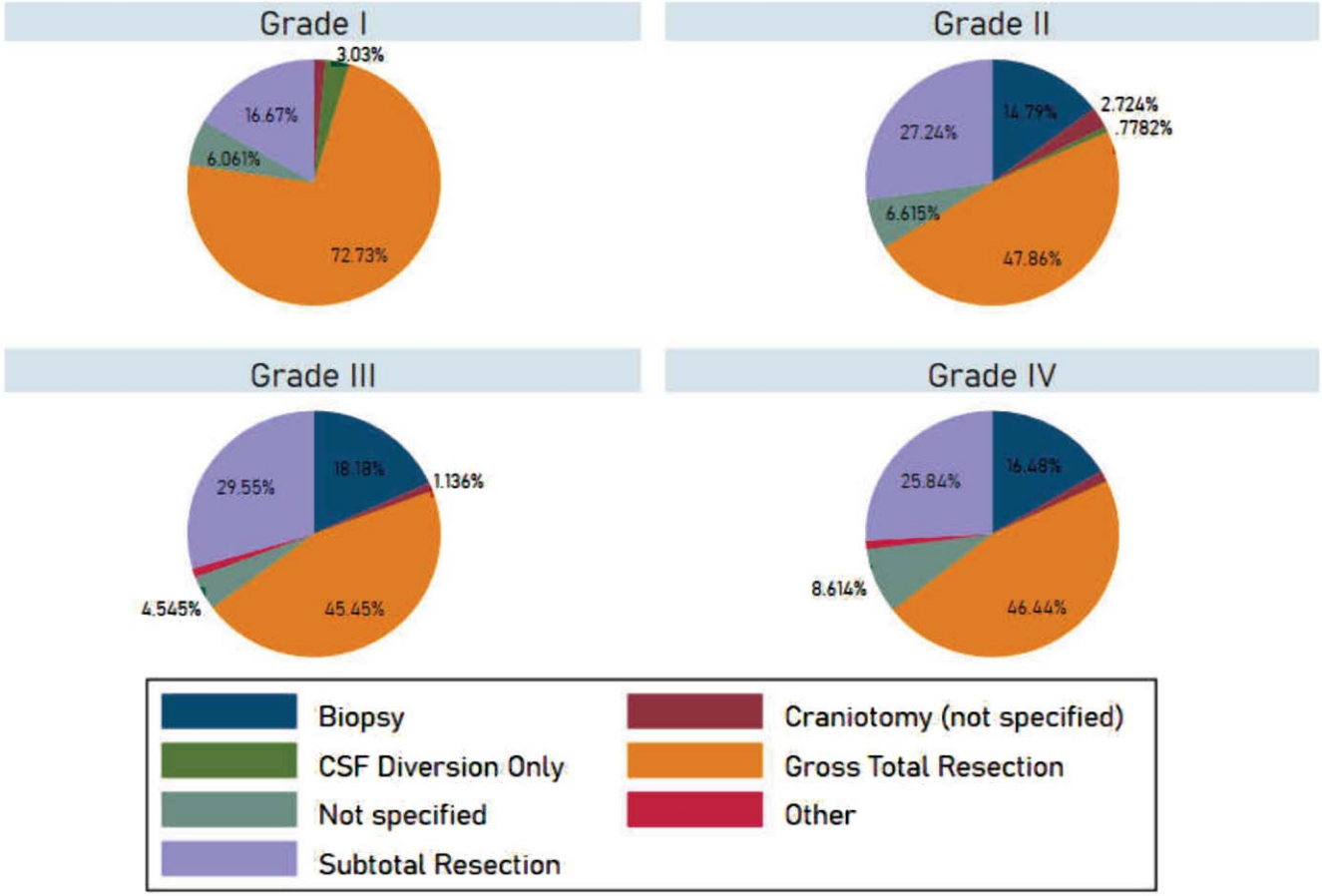

Figure-3: Surgical rates of resection and procedure-wise distribution according to grade of glioma.

greater majority of these were grade IV 267(39.38%) and grade II 257(37.91%). The majority of patients were operated at public sector hospitals 479(61.33%). Mean age at diagnosis progressively increased with higher grades of glioma, with grade 1 tumours having a mean age of 19±13 years and grade IV tumours having a mean age of 42±16 years as shown in Table-1 and Figure-1.

Most of our patients 207(32%) were from Punjab, which is the largest province in the region in terms of both geographical size and population size. Sindh comprised 177(25.6%) patients of all glioma patients. Khyber-Pakhtunkhwa comprised 123(17.7%) patients of our patients, followed by Balochistan with 43(5.8%) patients, and Azad Jammu Kashmir and Gilgit Baltistan at 4(0.5%) patients each.

We had ten subtypes of gliomas in our cohort, with the most common being glioblastoma with 260 (38%) patients. The types of gliomas and their corresponding proportions are reported in Figure-2.

Rates of gross total resection (GTR) were highest for grade I tumours (48, 72.73%) and lowest for grade III 40(45.45%) and grade IV tumours 124(46.44%). Higher rates of subtotal resection (STR) and biopsy were observed in

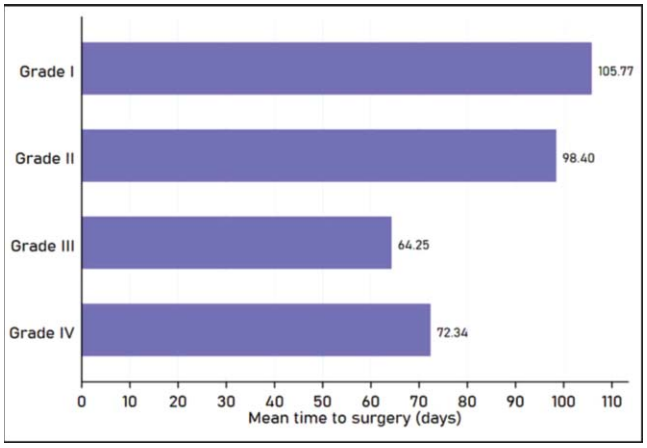

Figure-4: Mean time to surgery according to each tumour grade.

grades II-IV, and approximately 16(9%) of patients required reoperation within the same year, and 4(2.1%) underwent a third surgical procedure, as shown in Figure-3. In terms of surgical outcomes, mean postoperative KPS scores showed significant improvement from mean preoperative KPS scores. On the most recent follow-up, 359(45.97%) patients were alive, with 107(13.70%) being reported as deceased. Mean time to surgery was longest for grade I gliomas (106±137 days), as shown in Figure-4, with extended waiting times for high-grade gliomas as well.

Information regarding rates of radiation therapy after surgical resection is sparse, particularly for grade III and IV tumours 43(36.4%) and 148(30.3%), with the overwhelming majority of patients having no evidence of radiotherapy. Similarly, for chemotherapy, 53(60%) grade III and 163 (61%) grade IV gliomas have no hospital records for a referral or initiating chemotherapy cycles for the patient. Figure-5 shows details about each type of adjuvant therapy according to the grade of tumour.

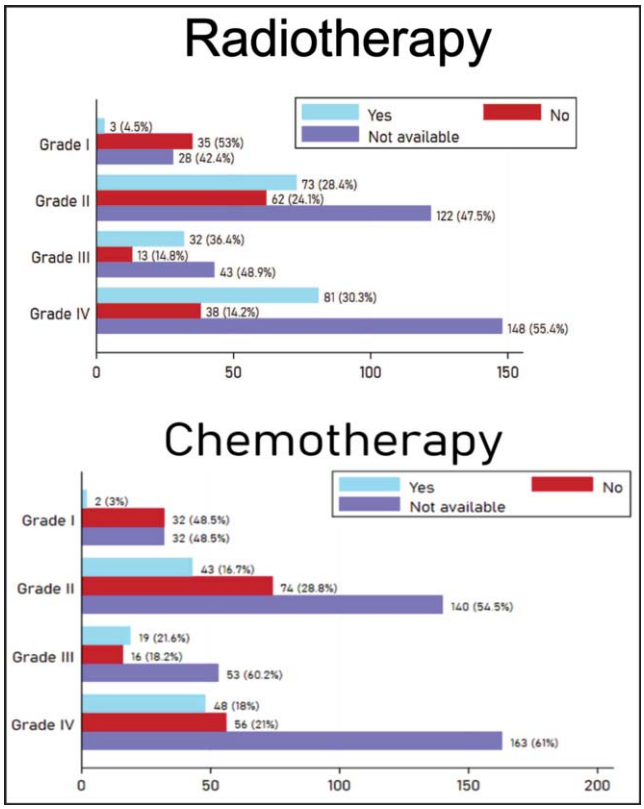

Figure-5: Patterns of post-operative chemotherapy and radiotherapy stratified according to grade of glioma.

Discussion

The overall incidence of gliomas across the world is around 4-5 per 100,000 people, with the highest age-standardised incidence rate (ASIR) for glioblastoma grade IV tumours.[10] Higher grades are often seen with increasing age, usually peaking around 60-80 years of age within the United States and Western Europe, as seen in cancer registries.[2,11] In our cohort, which is to date the largest series of glioma patients reported from Pakistan,

Table-1: Demographic characteristics and treatment-related outcomes of patients diagnosed with gliomas.

		Glioma Grade					
		High Grade		Low Grade		Pilocytic Astrocytoma	
		Count	Percentage	Count	Percentage	Count	Percentage
Age (mean ± SD)		42 ± 16	34 ± 11	19 ± 13			
Gender	Male	236	66.5%	160	62.3%	41	62.1%
	Female	119	33.5%	96	37.4%	25	37.9%
SES	Low	150	42.3%	116	45.1%	27	40.9%
	Middle	125	35.2%	95	37%	25	37.9%
	Upper	22	6.2%	19	7.4%	7	10.6%
KPS before treatment (mean ± SD)		75 ± 15		83 ± 16		72 ± 17	
KPS after treatment (mean ± SD)		84 ± 16		89 ± 13		88 ± 12	
Current Status	Alive	117	33%	153	59.5%	34	51.5%
	Deceased	71	20%	17	6.6%	3	4.5%

patients with high-grade tumours had a mean age of 42±15.5 years, while patients with low-grade tumours had a mean age of 31.5±13.2 years. The lower mean age in our population may be explained by lower diagnostic and presentation rates of elderly patients and a lower overall lifespan.[12]

Our investigation into the current landscape of glioma management revealed disparities, particularly in referrals for chemoradiotherapy. Adjuvant chemoradiotherapy has been shown to have a definite impact on survival for most gliomas. Grade 1 and 2 gliomas are classified as low-grade, while grade 3 and 4 tumours are labelled as high-grade.[8] Generally, lower-grade gliomas are treated with surgical resection (GTR whenever possible) and can be observed without further intervention unless warranted.[13] In the case of STR or grade two tumours with high malignant potential, adjuvant chemotherapy and radiotherapy may be used. In our experience 115(29.8%) patients received chemotherapy, with only 2 of these patients being from those with grade 1 tumours, with 202(43.9%) receiving radiotherapy (from those with adjuvant therapy information available). In contrast, higher-grade tumours are recommended to receive both radiotherapy and chemotherapy post-surgery.[13] In our cohort, only 27(48.2%) of patients received chemotherapy, and 38(68.9%) received radiotherapy (from those with adjuvant therapy information available). This can be interpreted as either a lack of follow-up and reporting of adjuvant therapy, loss to follow-up from treatment, or rapid progression leading to the cessation of treatment. It is likely a combination of all of the above, and the healthcare system in our region is currently not equipped to address the issue holistically due to the lack of a central registry.

The most conclusive factors for survival after glioma diagnosis are currently the extent of tumour resection, KPS score, and adjuvant chemoradiotherapy.[14,15] Recently, the role of molecular markers such as IDH, p53, and MGMT promoter methylation have come to the forefront as important determinants of overall survival.[14] Unfortunately, as is apparent from our study, these markers are not regularly performed after glioma surgery in Pakistan, much like many other LMICs.

Our median age for glioblastoma is also younger than what is seen in other populations and also seen in the CBRTUS Statistical Report 2021.[2] In contrast to this, we saw a bimodal distribution of grade 1 gliomas in our population. It is important to mention here that this data was collected from hospital records of 2019, without molecular analysis details and based on an older WHO classification of CNS tumours. The authors recommend cautious extrapolation from these results.

GBM was the third most common brain tumour subtype in the United States, according to the CBTRUS report, making up nearly half of all malignant brain tumours.[2] These tumours were highest in the age range of 75 to 84 years, and 6.8% of patients diagnosed with glioblastoma survived past the 5-year mark. In our case, GBM made up only 9% of all our brain tumours and about 38% of all gliomas. This contrasts with other studies which demonstrate that GBM makes up 54% of all gliomas and 16% of all primary brain tumours.[5]

What becomes even more complex is the burden of this cancer within low- and middle-income countries (LMICs); Pakistan's current neurosurgical centres are split between government-run public sector hospitals and private-sector hospitals where patients pay out of pocket. Government-run hospitals often have long waiting times for surgical treatment, overburdened resources, and patients presenting at later stages of the disease, while private-sector hospitals are inaccessible to many due to high financial costs for brain tumour surgery and are concentrated in urban regions, far from most of the population of Pakistan.[6]

This is by far the largest series of glioma patients reported from Pakistan, and even though our study sites included 36 major centres from across Pakistan, it is limited by the number of cases contributed by each centre. Wherein some centres may be contributing almost 80% of their cases to the dataset, there are others with less than 10% contribution, making our sample questionable in terms of true representation. We also cannot rule out a natural tendency of selection bias in randomly selected samples with a small sample size. This study is also limited by the poor follow-ups and difficulty obtaining detailed information about each patient. It does highlight the need for a dedicated cancer registry for CNS tumours. Several centres in Pakistan have begun to institute multimodal management for high-grade glioma. However, the importance of multidisciplinary neuro-oncology tumour boards and registries remains to be established as regular practice in most centres.[6] In the future, we hope to expand our study to investigate the molecular epidemiology of gliomas as well.

Conclusion

Our study is the first nationwide assessment of glioma management and patient characteristics in Pakistan. Our experience showed that nearly half of our patients received adjuvant therapy, with patients from even higher-grade glioma having no records of any

chemotherapy or radiotherapy. High grades glioma was diagnosed at a younger mean age in our population, while glioblastoma was overall much lower proportionally than expected from literature. Our low data regarding adjuvant treatment may be influenced by the high rate of loss to follow-up evidenced, which highlights the need for a central CNS registry.

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Conflict of Interest: None to declare.

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