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Research Article

A CLINICAL INSIGHT ON PATTERNS OF CARE AND PROGNOSTIC FACTORS IN ADULT HIGH GRADE GLIOMA: EXPERIENCE FROM A TERTIARY CANCER HOSPITAL FROM EASTERN INDIA

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ABSTRACT

Objective: The Central Nervous System Tumors account for 2.4% of all malignancies in India, but are associated with high mortality in high-grade tumors which result in poor death-adjusted life years. This study focuses on patterns of care and prognostic factors of adult high-grade glioma to explore the unaddressed nuances in treating such patients.

Methods: It was a retrospective single institutional study from June 2018 to July 2021 with an age group between 16 to 70 years. All histopathologically or clinicoradiologically proven cases of high-grade (World Health Organization Grades III and IV) gliomas were assessed. Defaulters and recurrent glioma at presentation were excluded from the analysis. Baseline characteristics were analyzed by Chi-square and unpaired t-test, and the Kaplan–Meir test was used for survival analysis. $p<0.05$ was considered significant.

Results: 41 patients were accrued for final analysis with a median follow-up period of 18 months. The most common histology was Astrocytoma, followed by Glioblastoma with a female preponderance. The Frontal and Temporal lobe was the predominant site in the study population. A majority (82%) of the patients underwent maximal safe resection followed by chemoradiation therapy (63.4%). Median progression free survival was 24 months and 8 months for Grades III and IV gliomas, respectively. The median overall survival for Grade IV gliomas was 7 months.

Conclusion: Resection status, Grade IV, IDH and 1p19q codeletion status were significant prognostic factors, while intensity modulated radiotherapy showed better dosimetry. More prospective randomized studies with larger sample sizes and longer follow-ups are required for validation and drafting an outcome nomogram.

Keywords: Glioma, Brain tumor, Radiotherapy, Indian data, Prognosis, Glioblastoma.

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INTRODUCTION

Gliomas represent the majority of malignant central nervous system tumors, with the most aggressive subtype, glioblastoma, accounting for almost 57% of this entity. Although Gliomas are graded as per the World Health Organization (WHO) Classification depending on various histopathological features, their clinical behavior depends on several molecular factors too [1]. High-grade gliomas are the aggressive ones, with less differentiation and more complex molecular pattern.

The most recent WHO classification of gliomas was updated in 2021, which was a modification of the previous landmark classification in 2016 and included some important updates around molecular integration which has allowed for increased clarity and objectivity in many cases [2]. The incidence of central nervous system (CNS) tumors in India according to GLOBOCAN 2020 data is around 31,000 with 2.4% of all cancers and a mortality rate is 3.1% [3]. The prognosis can vary depending on histology, age, site, and various tumor-specific factors. Although, rare its increasing trend in developing countries like India and poor outcomes in High-Grade gliomas compels the researchers to analyze the patterns of care and factors associated with it. Keeping this in mind Indian data are scarce especially in high-grade adult gliomas treated with conformal radiotherapy and optimum chemotherapy. Unfortunately, even after treatment with chemoradiation therapy, the outcome of glioblastoma remains very dismal, with 2 year survival and 5 year survival rate is around 17.2% and 5.4% respectively [4,5]. This study gauges the clinical and dosimetric characteristics, along with the correlation of prognostic factors with survival in Indian patients.

Aim and objectives

Primary endpoint: Identification of prognostic factors and correlation with progression-free survival.

Secondary endpoint: To assess hematological toxicity and overall survival (OS).

METHODS

It was a retrospective observational study from a prospectively maintained database. All patients attending outpatient department from June 2018 to July 2021 were initially assessed. Based on the following inclusion and exclusion criteria 41 patients were finally accrued for analysis.

Inclusion criteria

The following criteria were included in the study:

i. Age group 18–70 years
ii. Histopathologically and/or Clinicoradiologically proven cases of Grade III and IV Glioma
iii. Informed Consent
iv. Completed treatment as per protocol in individual cases.

Exclusion criteria

The following criteria were excluded from the study:

1. Recurrent glioma at presentation
2. History of other malignancies in the past
3. Treatment defaulters and lost to follow-up patients
4. Malignant transformation of previously treated low-grade glioma.

All patient-specific and tumor-specific data were extracted from a well-maintained file archive. Informed consent was taken in all cases before

initiation of treatment. In our institution, we treated high-grade glioma as per standard international guidelines, which comprise maximal safe surgical resection followed by chemoradiation. The radiation treatment plan began with computer tomography (CT) simulation at our departmental CT simulator followed by contouring as per international guidelines [6,7] and each plan was evaluated by the radiation oncologist and physicist's team. All acute treatment-related toxicities were graded using the Common Terminology Criteria for Adverse Events, version 3.0 [8]. All the relevant data were put in an excel sheet and assessed using SPSS v23 software. Patterns of failure were compared between the treatment groups using the Chi-squared test and unpaired t-test. Survival analysis was done using the Kaplan–Meir survival test with a log-rank test for intergroup comparison. $p<0.05$ was considered significant.

The follow-up period was defined as the time from clinical (histopathologic and/or radiological) diagnosis to the date of last follow-up or death. Patients' data were meticulously stored in file archives during their visits to the department. Those who were unable to follow-up due to poor performance status were contacted over the telephone or their caregivers were asked for clinical feedback.

RESULTS

We analyzed 41 patients with median follow-up period of 18 months (range 6–30 months). In all cases, response assessment was done by 3 monthly clinical examination and biannual MRI. The median age of the study population was 48 years (range 21–66 years) with slight female predominance (M: F = 1:1.4). The most common histology was astrocytoma (53.7%) followed by (Glioblastoma multiforme [GBM] 19.5%). The most common site was Fronto- temporal while 12.2% patients experienced brainstem glioma (Fig. 2). The incidence of Grades III and IV glioma was 68.3% and 31.7%, respectively. On further evaluation, we noted that around 50% of the cases were having MGMT methylation and 1p19q codeletion as unique molecular signature (Table 1).

Regarding the treatment part almost 88% of the cases were diagnosed histopathologically barring few exceptions where the tumor was located in an eloquent area. In any cases of diagnostic ambiguity, it was discussed in multidisciplinary tumor board comprising of radiation oncologists, medical oncologist, surgical oncologist, pathologist, and radiologist. Analyzing the history sheet, we came to know that the most common symptom was headache and altered sensorium while three patients reported dimness of vision while eight patients complained of convulsions. A majority of the patients (82.9%) underwent MSR (maximal safe resection) as their primary treatment. Adjuvant radiotherapy is mainstay in high-grade glioma, our observation was no different.

All most every patients received temozolamide during any period of their therapy while 53.7% received further six cycles of adjuvant chemotherapy (Table 2). Conformal radiation therapy was offered in each case as our institutional protocol while 39% patients were treated with advanced technologies such as intensity modulated radiotherapy and volumetric modulated arc therapy (Fig. 1). Dosimetric analysis revealed that mean volume of the gross tumor was 93 cc while the planning target volume mean was 342 cc.

Two distinct and recognized contouring guidelines was used, in RTOG guideline it was a two phase treatment planning while in EORTC guideline a single phase treatment was delivered. Mean value of whole brain max dose was 58.51 Gy and volume receiving 60 Gy (V60) was 20.50% in our study population which was even better than standard limits. Median value of whole brain mean dose was 30.47 Gy. It was noteworthy that around 83% of the study population had a history of taking anticonvulsant during some part of their treatment. The Chi-square test and unpaired t-test revealed that patients with subtotal resection (STR), Grade IV, non oligo histology had a worse 1 year OS. Among the molecular characteristics IDH mutant and 1p19q codeleted cases had a favorable outcome.

Apart from ECOG PS; age group, treatment modality or other tumor related factors were not statistically significant in view of OS and progression free survival (PFS) (Table 3).

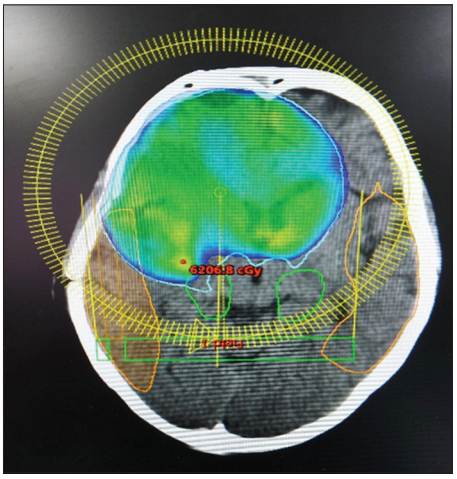

Fig. 1: Dose color wash of a Grade IV Glioma case treated with VMAT/Rapid arc Radiotherapy. Volumes – Cyan = PTV, Orange = Temporal lobes, Green = Hippocampus

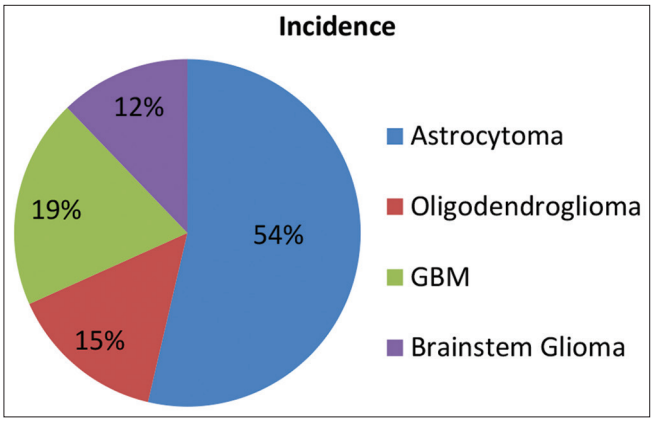

Fig. 2: Pie chart showing histologic distribution of cases

Table 1: Baseline characteristics of the study population

Tumor characteristics	Frequencies (%)
Grade	
III	28 (68.3)
IV	13 (31.7)
HPE	
Astrocytoma	22 (53.7)
Oligodendroglioma	06 (14.6)
GBM	08 (19.5)
Brainstem glioma	05 (12.2)
Sites	
Temporal	16 (39)
Parietal	02 (4.9)
Frontal	18 (43.9)
Brainstem	05 (12.2)
Molecular markers	
IDH mutant	20 (48.8)
MGMT methylated	26 (63.4)
ATRX loss	22 (53.7)
1p19q codeleted	22 (53.7)
Resectibilty	
MSR	34 (82.9)
STR	07 (17.9)

Table 2: Dosimetric analysis

Characteristics	Frequencies (%)
Mode of treatment	
EBRT+Adj TMZ	19 (46.3)
CTRT+Adj TMZ	22 (53.7)
Radiation techniques	
3DCRT	25 (61)
IMRT	14 (34.1)
VMAT	02 (4.9)
Anticonvulsants	34 (82.9)
Contouring details	
RTOG (2 phase)	14 (34.1)
EORTC (1 phase)	27 (65.9)
Dosimetric analysis	
GTV mean	93.2cc
PTV mean	342cc
V95%	95.32cc
Whole brain max dose (mean)	58.51Gy
Whole brain V60	20.50%
Brainstem Dmax (mean)	30.62Gy

VMAT: Volumetric modulated arc therapy, IMRT: Intensity modulated radiotherapy, GTV: Gross tumor, GBM: Glioblastoma multiforme

Table 3: Prognostic factors and their correlation with survival

Characteristics (n=41)	1 year OS (%)	p-value (<0.05 is significant)
Age group		0.70
<40 years	34.39	
>40 years	43.90	
ECOG PS		0.02
≤2	74.55%	
≥3	25.45%	
Resection status		0.03
MSR	63.40	
STR	04.87	
Grade		0.01
Grade 3	58.53	
Grade 4	09.70	
HPE		0.01
Astrocytoma	43.90	
Oligodendroglioma	14.63	
GBM	09.75	
Brainstem glioma	00.00	
Midline crossing		0.04
Yes	34.55	
No	65.45	
Treatment received		
EBRT+Adj TMZ	34.14	0.24
CTRT+Adj TMZ	39.02	0.31
Molecular markers		
IDH mutant	43.90	0.01
1p19q codeletion	53.65	0.01
MGMT methylation	39.02	0.31

STR: Subtotal resection, OS: Overall survival, GBM: Glioblastoma multiforme

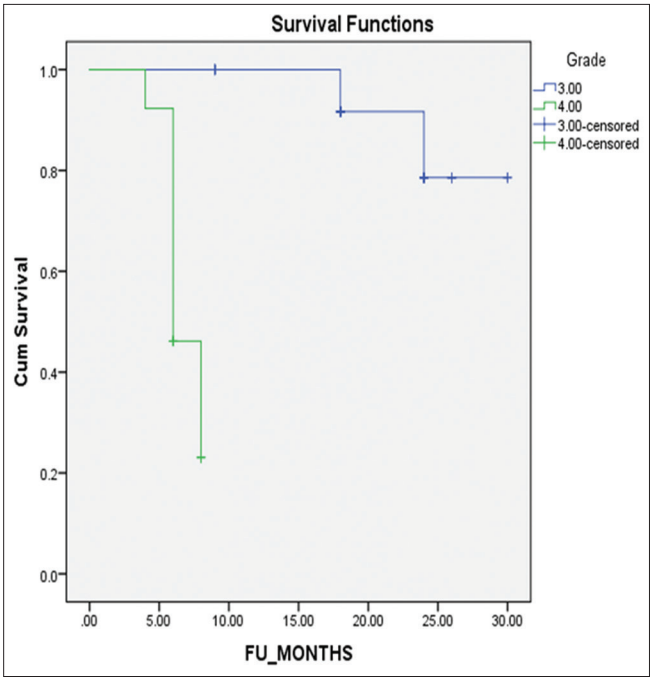

Fig. 3: Kaplan–Meir survival curve of overall survival among Grades III and IV Glioma

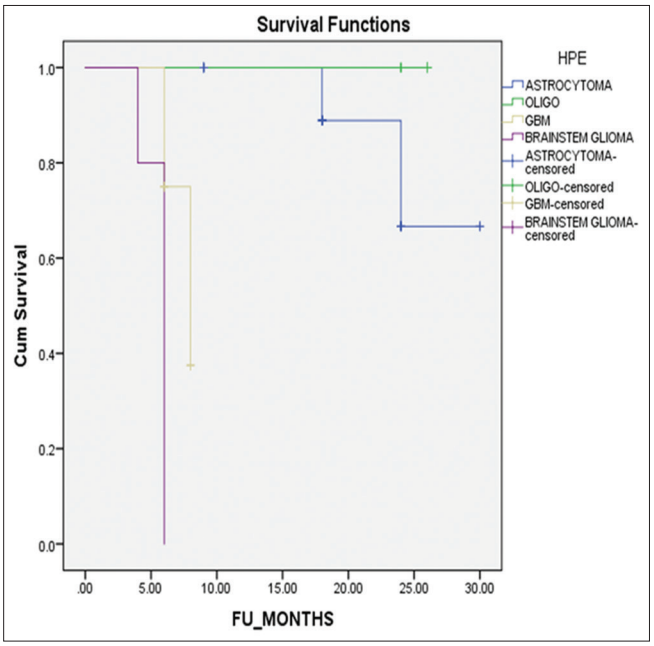

Fig. 4: Kaplan–Meir survival curve of progression free survival as per histologic subtype

Median PFS was 24 months and 8 months for Grades III and IV gliomas, respectively. The median OS for Grade IV gliomas was 7 months, while it was not reached in grade III cases (Figs. 3 and 4). Grades I and II hematological toxicity was reported in 25% and 15% of patients, respectively. No Grades III and IV toxicity were reported.

DISCUSSION

GBM accounts for around 25% of primary CNS tumors having a median survival of 12–18 months. The classification of brain tumors has changed moderately over time, the latest one emphasized on molecular and genetic signatures by WHO in 2021 [9]. Significant changes have been introduced in the grading of tumors, namely, use of Arabic numerals, grading within individual tumor types, and combined histological and molecular grading. The terms "Not otherwise specified" and "Not elsewhere classified" can now be used for all tumor types. The WHO CNS 2021 classification also for the first time endorses the use of DNA methylation profiling for the diagnosis of some tumor types/subtypes [10]. There have been studies searching for relevant prognostic markers in Gliomas, but given its complex clinical spectrum and various confounding factors; prognostication in high-grade glioma has not been that easy. Glioma patients and their caregivers will tend to have a very individual experience depending on the prognostic factors discussed above. Our aim should be to treat such patients with optimal care without jeopardizing their quality of life.

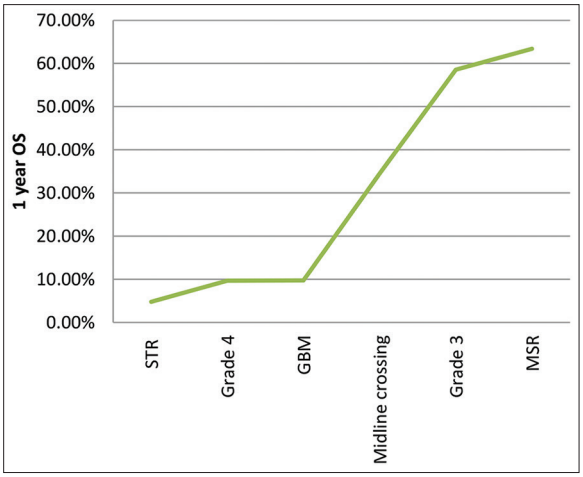

Fig. 5: Correlation of prognostic factors and 1 year overall survival

The available Indian data on CNS tumors suggests that astrocytoma is the most common histology and dominates in the high-grade glioma sections. Contrary to the western world, the median age of incidence is at least a decade earlier in India [11]. In our study, the median age was 48 years and astrocytoma was the most presented case in our experience. Some unique insights were represented by Indian studies in the domain of high-grade adult glioma. Molecular markers such as IDH, PTEN, MGMT, protein phosphatase 1 α, miRNA expression play a significant role in the prognostication of high-grade glioma [12-14]. Baseline MRI and PET CT parameters were also investigated thoroughly seeking relevant correlation [15]. Reviewing Indian literature, we observed that 1p 19q codeletion was found in around 63% patients of with oligodendroglioma and oligoastrocytoma and was associated with a good prognosis [16,17], our study also pointed in that direction. Quality of life has become an essential part of cancer care in the last few decades. In target volume delineation, the RTOG guideline incorporates the tumor edema resulting in a larger planning target volume which leads to a higher dose to the brain. EORTC guideline treats in a single-phase avoiding the edema part in CTV, with less toxicity and equivocal results [18,19]. We observed fewer doses (V60 Brain) in patients treated as per EORTC protocol, which could be a surrogate marker for cognitive function and quality of life. As it was an observational retrospective study we could not further utilize the impact of this dosimetric benefit. MGMT methylation did not translate into a better prognosis in our study cohort. Nearly all patients in high-grade glioma in our series received temozolomide chemotherapy in either concurrent or adjuvant form; this may explain the noted clinical conundrum. We observed that Grade IV tumors, STR, IDH wild type, 1p19q non-codeleted, ECOG PS 3 or more, and tumor crossing midline were significant adverse prognostic factors in our study (Fig. 5). On subgroup analysis, we found Grade 3 oligodendroglioma and oligoastrocytoma patients fared a bit better (but not significant) when treated with adjuvant temozolamide therapy which contemplates the available guidelines and trial results [20].

Our studies have a few limitations also. Retrospective observational design is one of them. Small sample size, recall bias, and non-applicability of quality of life questionnaire are a few areas we need to improve in the future. There has been some special interest in treating glioma patients with Proton or advanced technologies like tumor treating fields [21]. These techniques are quite costly and not available in many tertiary care cancer centers in a developing country like India. Our institute is no exception, but with the precision available at present, we cater to a larger economically poor study cohort with nearly similar results.

CONCLUSION

Although certain markers for positive and negative prognosis exist, it is difficult to truly predict an individual's outcome. A constant re-evaluation and follow-up of all patients are required. More prospective studies with a larger sample size are required to address the unmet needs of adult high-grade glioma.

AUTHORS CONTRIBUTION

AS and AB conceptualized the study hypothesis, AM and BM helped in study design and data collection. AS did the result analysis and the manuscript was drafted by AS and AB. All the authors have approved the final version of the manuscript.

CONFLICTS OF INTERESTS

None.

AUTHORS FUNDING

Nil.

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