A Comparative Retrospective Survival Analysis Study of Brain Tumor Patients in Age Less Than or Equal to 50 Years versus More Than 50 Years of Age

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Abstract

Introduction Approximately 2.5% of fatalities from cancer are caused by brain tumors. Even though there is literature regarding prognostic factor of adult brain tumor, studies often resort to Western demographics. Hence, we conducted this retrospective observational study to compare the demographic characteristics and prognosis in patients of glial tumors in Indian population with histological diagnosis with respect to age.

Materials and Methods A single-center retrospective observational study with 76 patients of glioma who had been treated with surgery combined with radiotherapy with or without chemotherapy was conducted. Group I patients were aged less than or equal to 50 years and group II more than 50 years of age. There were 28 patients in group I and 48 in group II. Postoperatively, external beam radiation therapy was delivered in a conventional fraction (1.8 Gy/fraction, five fractions/week) using tele-cobalt 60. Ill patients who presented with grade III and IV gliomas received oral chemotherapy temozolomide at a dose of 100 mg daily during course of radiotherapy.

Results The median age of the patients at the time of diagnosis was 45.0 years. More cases of hematologic toxicity occurred in group I than in group II. Total 55 patients were alive at 1-year follow-up (11 in group I and 44 in group II).

Conclusion Grade I and II gliomas were predominant in less than 50 years of age and grade III and IV were predominant in more than 50 years age. Male preponderance was seen in age group of more than 50 years (68%). Overall survival and disease-free survival were better for patients aged less than 50 years.

Keywords
► brain tumor
► cancer
► glioma
► prognosis
► radiotherapy

Introduction

About 1.4% of all malignancies and 2.5% of cancer-related fatalities are caused by brain tumors. The majority of brain tumors are malignant, and thus have a poor prognosis. The brain functions required for daily tasks might nevertheless be affected by tumors, even if they are benign. We conducted an audit of patients with gliomas who had received care at our facility and observed their prognosis and histologic grade in correlation with age. Primary brain tumors are categorized according to their histological features, where they are located, and then according to their invasiveness and malignant potential.[1] The frontal, temporal, and parietal lobes of the brain account for the majority of adult tumors that are supratentorial in origin. Astrocytoma, glioblastoma, oligodendroglioma, and other unclassified gliomas make up the majority (86%) of cases. Despite years of research, brain tumors remain the most deadly type of cancer. The average survival time for adults with glioblastoma, the most aggressive type of cancer, is less than 2 years after diagnosis.[2,3] Numerous studies suggest that age affects health prognostically. Patients of different ages have different prognoses despite having the same diagnosis. According to a single institute evaluation of 70 patients with cerebral anaplastic oligodendroglioma, the median survival length of patients under 50 years old was significantly longer than that of patients over 50 years old.[4] These tumors are sometimes too far away for even the most expert neurosurgeon to approach. These tumors are present behind the blood–brain barrier, which shields them from exposure to systemic chemotherapy.[5,6] Although a patient with a brain tumor may initially undergo computed tomography, magnetic resonance imaging (MRI) is typically the main imaging technique used on patients with brain tumors. Even though there is abundant literature on adult brain tumor prognostication, the studies resort to Western demographics. Hence, we propose this study to compare the demographic characteristics and outcome in patients of gliomas in Indian population of more and less than 50 years of age.

Materials and Methods

Patient Selection
This study was conducted in the Department of Radiotherapy of Moti Lal Nehru Medical College, Prayagraj, UP, India. Data was collected retrospectively after approval from institutional ethics committee from the records of 76 consecutive patients of glioma who had been treated with surgery combined with radiotherapy with or without chemotherapy from August 2019 to August 2021. The following inclusion criteria were included for this study: histological diagnosis of primary brain tumor, patients who completed treatment with 6 months of follow-up post-treatment or before if event occurred within 6 months. The patients included in this study presented with grade I or II gliomas with residual disease or grade III and IV gliomas with or without residual disease, with good performance status (Eastern Cooperative Oncology Group 0 [asymptomatic], or 1 [symptomatic but

ambulatory]), 2[Unable to carry normal activity or to do active work]).

Exclusion criteria included patients with uncontrolled concomitant disease, connective tissue disease, and history of prior irradiation.

For evaluation, we divided our cohort into two age groups: Group I patients aged more than50 years and group II aged less than or equal to 50 years There were 28 patients in group I and 48 in group II. All patients had provided written consent for treatment.

Procedure
All patients had gone with pre- and postoperative brain MRI scans. All of them underwent maximal safe resection. Tissue diagnosis was confirmed histopathologically in all patients. Postoperatively, external beam radiation therapy was delivered in a conventional fraction (1.8 Gy/fraction, five fractions/week) using telecobalt 60. A total dose of 54 Gy was administered to grade I or II tumor with residual disease with 1 to 2 cm margin, and for grade III and IV gliomas total 59.4 Gy with 2 to 3 cm margin with reducing field were administered. External beam radiation therapy was interrupted if the white blood cell count fell below 4,000/mm3 or if platelets fell below 1,00,000/ mm3 and was resumed once counts rose above these levels. All patients who presented with grade III and IV gliomas received oral chemotherapy temozolomide at a dose of 100 mg daily during course of radiotherapy. No chemotherapy was given to grade I and grade II glioma and it was only administered to grade III and grade IV gliomas. Patients were seen weekly by a physician for a physical examination and a complete blood count test. Chemotherapy was interrupted if patients had the total white blood cell count less than 4,000/mm3, or platelets were less than 100,000/mm3. Adjuvant chemotherapy with temozolomide 150 to 200 mg/m^2 D1 to 5 at 4 weeks interval for six cycles was administered for grade III and IV gliomas.

Toxicity
During treatment, toxicities were assessed weekly and graded in accordance with the National Cancer Institute Common Terminology Criteria of Adverse Events: 1 mild; 2 moderate; 3 severe; and 4 life-threatening or disabling.[7]

Statistical Analysis
The data were collected, and information were analyzed with the IBM SPSS 18.0. The results are considered significant at 5% level of significance under logrank test. Chi-squared test was applied. Overall survival (OS) and disease-free survival (DFS) was calculated by Kaplan–Meier curve.

Results

Patient Characteristics
In total, 76 patients were included from August 2019 to August 2021. The median age of the patients at the time of diagnosis was 45.0 years (in group I 61 years and in group II 38 years; range: 19–68 years). Thirty patients presented with grade I and II tumor (7 in group I and 23 in group II). Forty-six

Table 1 Patients characteristics

Particulars	Group I[a]	%	Group II[b]	%	p-Value
Hemoglobin level					
≥10 g/dL	10	35.71	29	60.42	0.03768
<10 g/dL	18	64.29	19	39.58	
ECOG performance status					
0 or 1	11	39.29	30	62.50	0.050165
>1	17	60.71	18	37.50	
Sex ratio					
Male	19	67.86	27	56.25	0.317988
Female	9	32.14	21	43.75	
Grade of tumor					
I and II	7	25	23	47.92	0.048656
III and IV	21	75	25	52.08	

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]Patients >50 years, $n = 28$.
[b]Patients <50 years, $n = 48$.

patients presented with grade III and IV (21 in group I and 25 in group II).

Thus, grade I and II tumors were predominant in group II (≤50 years) and grade III and IV were predominant in group I (>50 years). The p-value came out to be 0.048 that is significant for age. Total 46 patients were male (19 in group I, 27 in group II) and 30 were female (9 in group I and 21 in group II). p-Value for sex in relation to age came out to be 0.32 (not significant). Patient characteristics are outlined in ►**Table 1**.

Survival of Patients

Total 55 patients were alive at 1 year follow-up (11 in group I and 44 in group II). Among 11 patients in group I, six patients were with residual disease. In group II among 44 alive patients,

11 had residual disease. At 2 years, total 32 patients were alive (seven in group I and 25 in group II). In group I, three patients were free from disease, while in group II, 24 out of 25 alive patients were free from disease (►**Figs. 1** and **2**, ►**Table 2**).

Toxicities

Anemia, neutropenia, and thrombocytopenia were found in 42, 9, and 7 patients, respectively. In group I, 20, 6, and 4 patients developed anemia, neutropenia, and thrombocytopenia, while in group II, 22, 3, and 3 patients developed these side effects. The differences in acute hematologic toxicity between the two patient groups were significant ($p = 0.03$ for anemia, $p = 0.04$ for neutropenia) (►**Table 2**). More cases of hematologic toxicity occurred in group I than in group II. In
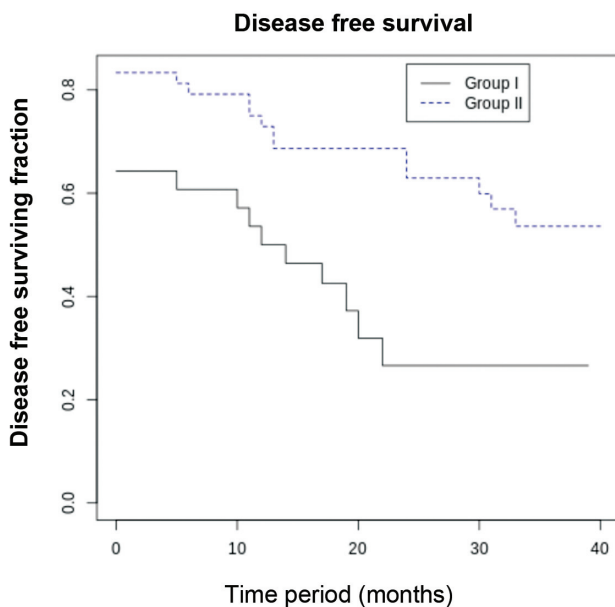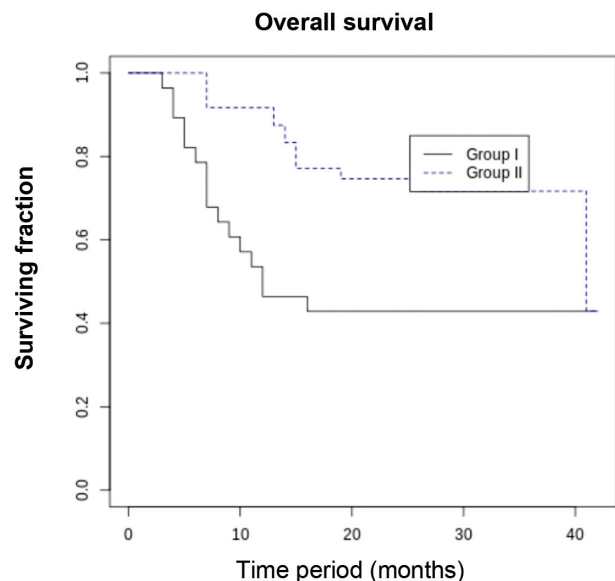

Fig. 1 Disease-free survival curve.

Fig. 2 Overall survival curve of both groups of patients.

Table 2 Toxicities, overall, and disease-free survival rates stratified by patient group

Toxicities	Group I[a]	Group II[b]	p-Value	Chi-squared test	Significance
	%	%			
Anemia	71.43	45.83	0.030409		Significant
Neutropenia	21.43	06.25	0.048211		Significant
Thrombocytopenia	14.29	06.25	0.242574		Not significant
Grade I and II CNS toxicity	35.71	27.08	0.429489		Not significant
Grade III and IV CNS toxicity	25.00	20.83	0.674135		Not significant
Overall survival (1 year)	44.44	83.33	0.0025	9.1098*	Significant
Disease-free survival (1 year)	20.00	57.14	0.0063	7.4478*	Significant
Overall survival (2 years)	25.00	52.08	0.0223	5.2199*	Significant
Disease-free survival (2 years)	14.29	50.00	0.0559	3.6528*	Not significant

Abbreviation: CNS, central nervous system.
[a]Patients >50 years, $n = 28$.
[b]Patients <50 years, $n = 48$.
*Logrank test at 95% confidence level.

group I, anemia, neutropenia, and thrombocytopenia incidences were 71.43, 21.43, and 14.29%, respectively; while for the group II, anemia, neutropenia, and thrombocytopenia incidences were 45.83, 6.25, and 6.25%, respectively (►**Table 2**). Total 40 patients developed central nervous system (CNS) toxicity (17 in group I and 23 in group II). Grade I and II CNS toxicities were present in 35.71 and 27.08% patients among group I and II, respectively, (p-value= 0.42), while grade III and IV toxicities were present 25 and 20.83%, respectively, in both groups (p-value= 0.67). The difference in CNS toxicities was not significant (►**Table 2**).

Discussion

Adults with high-grade brain tumors are frequently diagnosed after middle age. For the majority of brain tumors, the extent of resection performed before radiation therapy is a prognostic indicator. In several histological subgroups, radical resection should be taken into consideration due to the possible benefit it may offer. Radiation oncologists should collaborate with their surgical counterparts thereby concentrating on a team approach for patient optimization toward radiation therapy.

Due to the elective nature of the technique, which takes advantage of the brain relaxation brought on by the initial debulking, second surgeries performed prior to radiation therapy are frequently performed with limited morbidity. It is sometimes preferable to leave residual disease rather than "pushing" the initial resection because the most technically challenging aspects of tumor resection are frequently performed at the end of a lengthy surgical procedure in a patient who is already debilitated from the events leading to diagnosis, in the absence of a certain histological diagnosis, and in the presence of an edematous brain. The histology and possible resectability of the residual disease have an impact on the choice to attempt a second resection.

MRI is performed within 72 hours of surgery to plan subsequent treatment, to acutely assess hemostasis, to distinguish between ischemia and retraction injury, to evaluate residual tumor, and amenability of further resection. This also allows for improved interpretation of residual enhancement from hemostatic products placed in the operative tumor bed. However, we currently lack the specific dataset related to immediate postoperative MRI measurements comparing to disease-free outcome within the stipulated timeframe.

Since 1973, the recorded incidence of malignant brain and CNS tumors has climbed by 1.2% annually, while the death rate has increased by 0.7% annually.[8] This increase has been notably noticeable among people 65 years and older. Although primary malignant brain tumors in the elderly are on the rise, only a small number of studies[9–13] have focused on clinical trends in this age range.

In a research by Jeanette et al,[14] the proportion of patients diagnosed with glioblastoma multiforme increased progressively with age, from 23% of patients in the 18 to 24 years age range to 73% of patients in the 75 year or older age range. In our study, 75% of the patients had grade III or IV gliomas in age group more than 50 years. In a study by Patel et al,[15] total 82.5% cases had grade III and IV astrocytoma in all age groups. In a research by Lin et al, 44.4% of patients had grade I or II gliomas and 55.6% had grade III or IV gliomas.[16] In our study, majority (60.5%) of patients were grade III and IV, while 39.5% patients were grade I and II. In our study, 63.2% patients were in the age group of 19 to 50 years and 36.8% were aged more than 50 years (►**Fig. 3**).

There were 60.5% male patients and 39.5% female patients in our study overall. Similar male preponderance was seen in various studies.[14–16] In a study by Wang et al,[17] out of all glioma patients, 44.1% were female and 55.9% were male. Glioma incidence was often higher in men. Male-to-female incidence peaked between the ages of 50 and 59, having been lowest between 0 and 9 years.
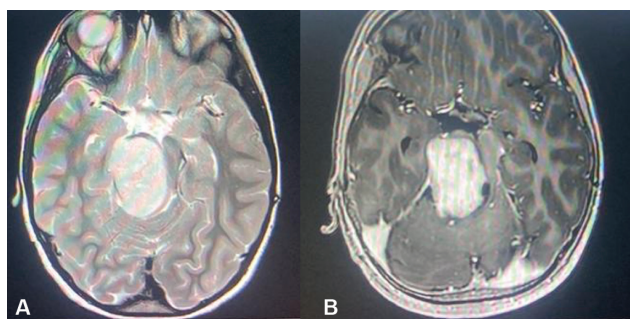
Fig. 3 A 46-year-old male with a history of headache and dizziness. (**A**) Fluid-attenuated inversion recovery image showing well-defined homogeneously hyperintense lesion involving midbrain. (**B**) T1-weighted post-gadolinium contrast image showing homogeneous enhancement of lesion, no calcification or necrotic area seen. Patient underwent biopsy with radiotherapy and pathologically was glioma grade II.

In a study by Jeanette et al,[14] survival was significantly reduced in older patients, and appeared to worsen significantly in patients aged 45 years and older. In our study, the 1-year survival for patients under the age of 50 was 83.33%, whereas it was only 44% for patients more than 50 year of age. According to a study by Lin et al,[16] patients under the age of 50 had an OS that was significantly longer than those over the age of 50 (median: 8.8 vs. 4.1 months, $p = 0.001$).

Conclusion

In our study, grade I and II gliomas were predominant in less than or equal to 50 years of age and grade III and IV were predominant in more than 50 years age. Male preponderance was seen in age group of more than 50 years (68%). OS and DFS were better for less than or equal to 50 years of age. Hematological toxicities were more in group of more than 50 years. Further evaluation for other cofactors like regarding the potential correlation between postoperative residual tumor volume and disease-free outcome based on postoperative MRI needs to be considered in future studies.

Limitations of Study

(1) Limited retrospective dataset and small study sample.
(2) Limited dataset related to immediate postoperative MRI measurements.

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