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ORIGINAL ARTICLE

Prognostic Significance of Anatomic Origin and Evaluation of Survival Statistics of Astrocytoma Patients—a Tertiary Experience

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Abstract

Astrocytoma constitutes the most noted malignancies of the central nervous system with worse clinical outcomes in grade IV astrocytoma or glioblastoma multiforme. Owing to poor clinical outcomes with existing therapeutic regime, there is a need to revisit the initial course of treatment. Statistical information of clinicopathological parameters could be used to understand the spread of disease and, in turn, to formulate updated treatment management. In the present study, we have seen anatomic distribution of astrocytoma subtypes in a group of 479 patients and correlated it with survival outcomes. Anatomic location was confirmed by MRI (magnetic resonance imaging) images. A registry of patients was maintained with clinicopathological details as tumor type, location, age/sex, and survival after surgery. We have observed overall survival particulars in patients diagnosed with astrocytoma. Our findings highlight that in total cases, tumor location was anatomically dominated by frontal and temporal lobes. Survival analysis in high-grade (grade III, $p = 0.03$; grade IV, $p = 0.01$) astrocytic tumors confirms poor outcomes with temporal, parietal, and occipital location as compared to frontal lobe. Overall survival study demonstrates glioblastoma multiforme (GBM) was associated with worse prognosis as compared to astrocytoma subtypes ($p < 0.0001$). In high-grade astrocytomas, anaplastic astrocytoma was found with 34 months of median survival age while 14 months in the case of patients with glioblastoma multiforme. In conclusion, we report dismal prognosis in parietal, temporal, and occipital lobes in grade II, grade III, and grade IV astrocytoma patients. Among astrocytoma subtypes, patients with glioblastoma multiforme were associated with worse survival outcomes. We uniquely feature the survival of astrocytoma patients for the first time and observe GBM patients have slightly longer survival.

Keywords Astrocytoma · Glioma · Survival · Anatomic origin

Introduction

Astrocytomas are the most common malignancies of the brain. The World Health Organization (WHO) has classified astrocytoma in four grades on account of cellularity, nuclear polymorphism, mitotic index, microvascular proliferation, and extent of necrosis [1]. Grade IV astrocytomas, also referred as glioblastoma multiforme, are the most aggressive primary tumors with worst prognosis and account for nearly 60% of malignant gliomas [1–4]. The overall prognosis for malignant glial tumors have not changed significantly since 1980 despite of advancements in course of diagnosis and mode of treatment [5]. Understanding of prognostic factors affecting survival and clinicopathological statistics can help to evaluate new measures for therapeutic intervention [6]. In previous tertiary study, we observed lower median age and assessed symptoms associated with pathologic progression of astrocytoma patients [7]. Molecular markers such as PTEN, TP53, loss of heterozygosity on chromosome 10q, and EGFR amplification have also been ascertained with poor prognosis [8, 9].

Anatomic origin of tumor is reported to have prognostic importance. Tumors with anatomic origin on the frontal lobe are reported to have enhanced prognosis value than temporal, parietal, or occipital lobe. Preferred anatomy of low-grade astrocytoma in certain areas is explained by functional, developmental, or metabolic aspects. Type of surgery and location are reported as independent factors contributing to prognosis

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of glioblastoma multiforme. Patients with tumor origin at the frontal lobe have been shown to have progression-free survival for 1 year than other locations [10–14]. Relative volume of glial tissue has been shown to influence development of gliomas in different anatomic sites. Functional differences between tissues in the brain have been postulated for certain preferred locations of tumors [15]. Distinct molecular alterations prevalent in subset of glial tumors arising from different anatomic origins have been reported [16–18]. However, there are very few reports evidencing the role of anatomic locations influencing the prognosis.

The aim of the present study was to screen clinical data on account of anatomic origin of tumor, to investigate the survival pattern reflected by tumor anatomy, and to analyze the overall survival among four grades of astrocytic tumors.

Materials and Methods

Selection of Patients

The cases were reported at Krishna Institute of Medical Sciences (KIMS), Secunderabad, India, during the time span of January 2009 to December 2014. Patients were approached after surgical resection. Each patient was assigned with unique ID. Informed consent was obtained from patients and each one was completely anonymized. Pathological distribution of tumor grade was determined by biopsy of surgically resected tissue specimen at pathology department on account of cellularity, nuclear polymorphisms, and MIB-1 staining. The pathology details were confirmed by two independent observations. Registry of patients was maintained with age/sex, grade of tumor, and follow-up details. All patients were Indian citizen.

Anatomic location of tumor was assigned roughly in four lobes on the basis of radiological reports: frontal, parietal, temporal, and occipital (Fig. 1). The treatment for low-grade tumors was dependent on few factors such as age of patients and location of tumors. Treatment (surgical resection, chemotherapy, radiotherapy, or palliative treatment) was designed such that the benefit over fits the possible post-treatment complications. The most common surgical resection procedure was craniotomy; in the case of tumor in the occipital lobe, suboccipital craniotomy was followed. For treating the high-grade tumors, the surgical resection was most commonly followed by chemo and/or radiotherapy. Temozolomide was the most commonly used drug in these patients. MRI scan was practiced every 3 months to trace possible recurrence (Fig. 1).

In tumors with involvement of two lobes (e.g., frontotemporal, predominantly located at the frontal lobe), overlap was ignored and tumor location was designated at one location. In the case with overlap in several areas of the brain, position was designated as per deeper anatomic site. Anterior location was given in the same way with overlapping cases.

In total, our registry reported 42 pilocytic astrocytoma cases, 181 diffuse astrocytoma cases, 78 anaplastic astrocytoma cases, and 178 glioblastoma multiforme cases. Survival information was not available with total of 94 cases (grade $I = 9$, grade II = 50, grade III = 10, grade IV = 25).

Statistical Analysis Survival details were studied using Kaplan-Meier statistics to evaluate overall survival in pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme. Differences between survival in groups were evaluated using logrank (Mantel-Cox) test. p value less than 0.05 was considered to be statistically significant.

Results

Of all cases studied, 8.7% were of pilocytic astrocytoma, 37.7% diffuse astrocytoma, 16.2% anaplastic astrocytoma, and 37.1% cases contributed glioblastoma multiforme. Previously, we reported 15.5 years as median age of diagnosis for pilocytic astrocytoma, 54 years for diffuse astrocytoma, 45 years for anaplastic astrocytoma, and 37.5 years for glioblastoma multiforme in our tertiary experience. We also have reported nearly 60% of male (for grade I astrocytoma, male = 33, female = 18; grade II astrocytoma, male = 124, female = 107; grade III astrocytoma, male = 51, female = 37; and for glioblastoma multiforme, male = 125, female = 78) in our group [7].

In all astrocytoma cases we sorted, 163 were located in the frontal lobe, 57 in the parietal lobe, 191 in the temporal lobe, and 68 in the occipital lobe (Table 1). In pilocytic astrocytoma cases, 3 were found to be located at the frontal lobe, 1 at the parietal lobe, 16 at the temporal lobe, and 22 at the occipital lobe. In diffuse astrocytoma cases, 74 were found to be located at the frontal lobe, 18 at the parietal lobe, 74 at the temporal lobe, and 15 at the occipital lobe. In anaplastic astrocytic tumors, 32 were found to be located at the frontal lobe, 10 at the parietal lobe, 27 at the temporal lobe, and 9 at the occipital lobe. In glioblastoma multiforme cases, 54 were found to be located at the frontal lobe, 28 at the parietal lobe, 74 at the temporal lobe, and 22 at the occipital lobe (Table 1).

We studied survival statistics for each grade of tumor as a function of anatomic location (Fig. 1). We observe variation in survival of patients on account of anatomic origin of tumor. Difference in anatomic location of tumor survival in grade II (Fig. 3), grade III (Fig. 4), and grade IV (Fig. 5) was statistically significant. Here, survival in patients with tumor in the frontal lobe was found to be better than in the occipital or temporal lobes. However, the anatomic details were found to be not significant in the case of grade I astrocytic tumors

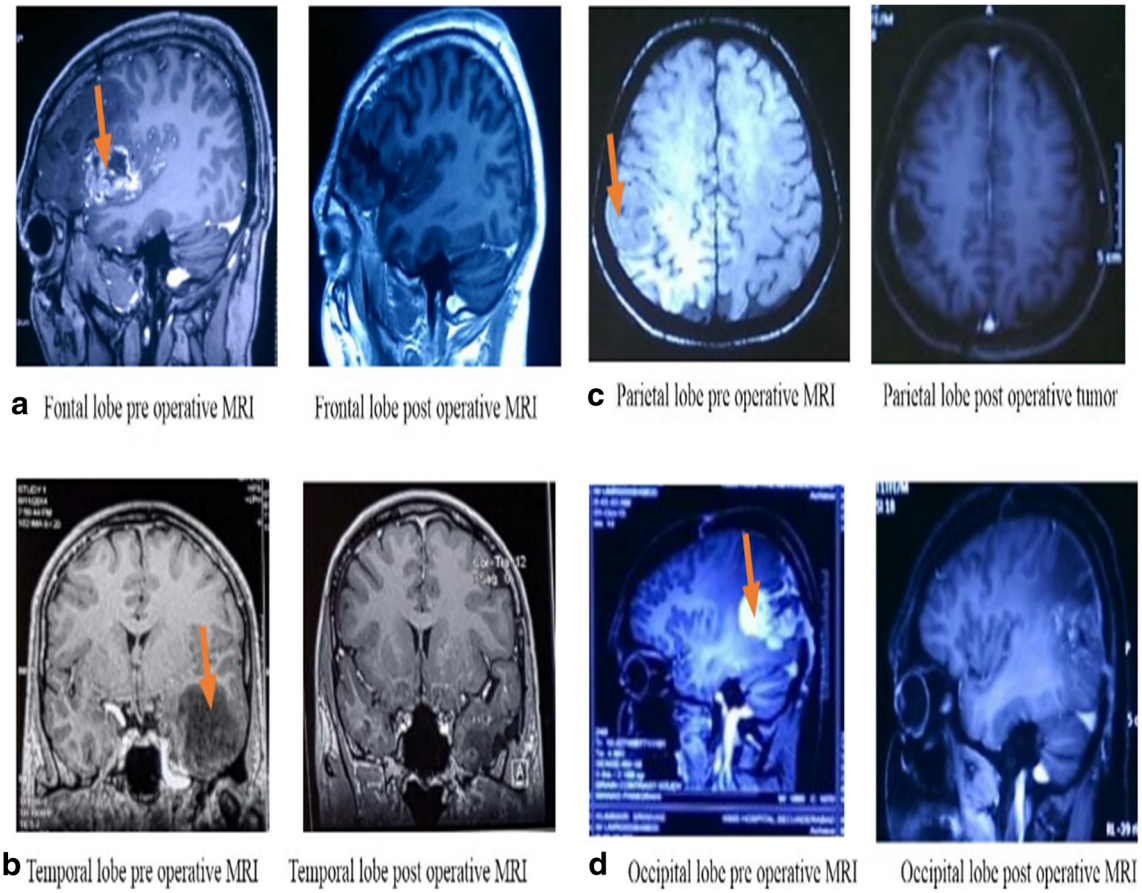


Fig. 1 Representative images showing MRI-based categorization of tumor location: pre- and post-operative MRI images of tumor located at **a** frontal lobe, **b** temporal lobe, **c** parietal lobe, **d** occipital lobe. Visible tumor has been marked by an arrow

(Fig. 2). The median survival for pilocytic astrocytoma cases was undefined for the maximum follow-up time. For diffuse astrocytoma, it was reported to be 59 months; for anaplastic astrocytoma, it was 34 months; while for glioblastoma multiforme cases, the median survival of 14 months was noted. We have also analyzed survival of patients in four astrocytoma subtypes (Fig. 6). Survival in patients with glioblastoma multiforme was worse than other astrocytoma subtypes (median survival = 12 months, mean survival = 11 months) and is found to be statistically significant ($p < 0.0001$).

Table 1 Distribution of anatomic origin of astrocytoma subtypes in a group. Overall, we observed non-uniform distribution dominated by the frontal and temporal lobes ($p = 0.007$)

Lobelocation Astrocytoma grade	Frontal	Parietal	Temporal	Occipital	Total
Grade I	3	1	16	22	42
Grade II	74	18	74	15	181
Grade III	32	10	27	9	78
Grade IV	54	28	74	22	178
Total tissues	163	57	191	68	479

Discussion

The aim of the present study was to clinically screen astrocytoma subtypes by their respective anatomic origin in the brain

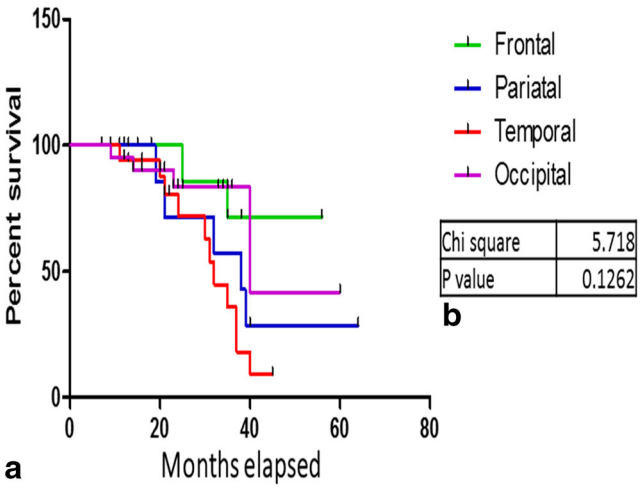


Fig. 2 Anatomic distribution–based Kaplan-Meier survival of grade I astrocytoma patients (**a**, $n = 42$). Anatomic location was not significantly correlated with patients' survival (**b**, $p = 0.12$, chi-square = 5.7)

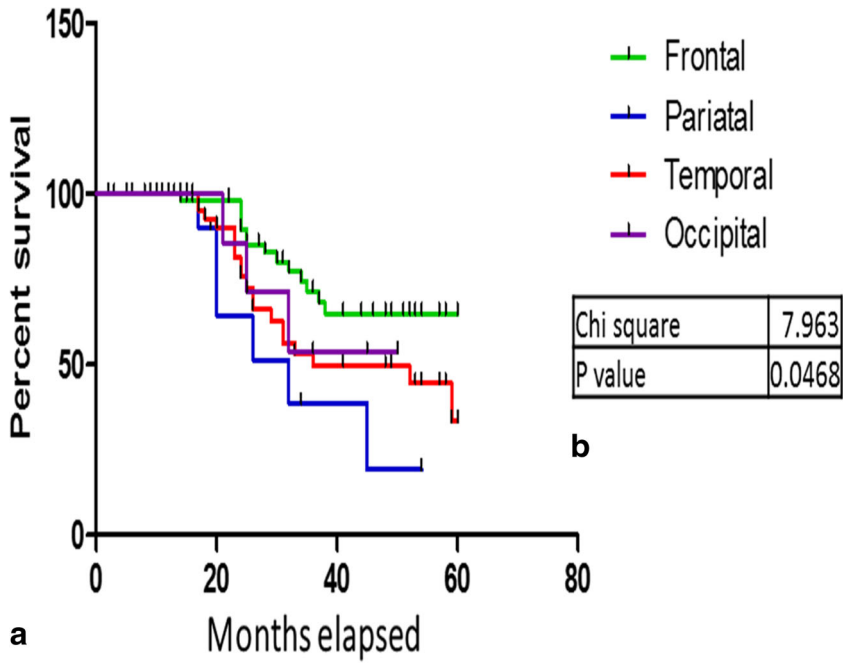


Fig. 3 Anatomic distribution–based Kaplan-Meier survival of grade II astrocytoma patients (**a**, $n = 181$). Comparison of survival outcomes among four anatomic locations was statistically significant (**b**, $p = 0.04$, chi-square = 7.9)

and to study whether selective anatomic origin confers particular survival benefits.

We studied the anatomic location in astrocytomas and found dominated occurrence at the frontal and temporal lobes. Overall, we found tumor anatomic origin at the frontal lobe in 34% of cases, parietal lobe in 11.8% of cases, temporal lobe in 39.8% of cases, and occipital lobe in 14.1% of cases (Table 1, $p = 0.007$), while previous reports claim the frontal lobe as the anatomic origin for 43% gliomas, parietal lobe for 25% of cases, temporal lobe for 28% of cases, and occipital lobe for only 3% of cases [13]. Prominent origin at the frontal and temporal lobes found in our findings is consistent with existing literature [15]. Studies have shown that tumor occurs with more frequent involvement of the right hemisphere in the brain [19]. These reports, however, do not comment on prognostic significance of anatomic origin. We show for the first time that tumors with the frontal lobe as the anatomic origin have better prognostic significance than in the temporal, parietal, and occipital lobes. In grade II (Fig. 3) ($p = 0.04$) and grade III (Fig. 4) ($p = 0.03$) astrocytoma, better survival at the frontal lobe was statistically significant as compared to the parietal and temporal lobes. In glioblastoma multiforme, the temporal, parietal, and occipital lobe as anatomic origin was correlated with poor survival outcomes than the frontal lobe (Fig. 5) ($p < 0.001$). A recent study has shown that tumors located in the right hemisphere are correlated with worst prognosis [20]. Further, it was observed that tumors in this region have larger volume leading to extensive infiltration and tend to be difficult to resect [20, 21]. Previously, tumors located at the subventricular zone (adjacent to right parietal location) are correlated with worse prognosis. These investigations were based on qualitative assessment of tumor location [22, 23]. The association of poor prognosis at the parietal, temporal, and occipital lobes may be related to the underlying tumor biology and neuroanatomy at those particular locations. Along with it, further investigations are necessary to understand the molecular mutations associated with particular locations to know more about origin of tumors and associated pathology. Overall, our findings highlight frontal lobe was associated with significantly better prognostic values in anaplastic astrocytoma and in glioblastoma multiforme.

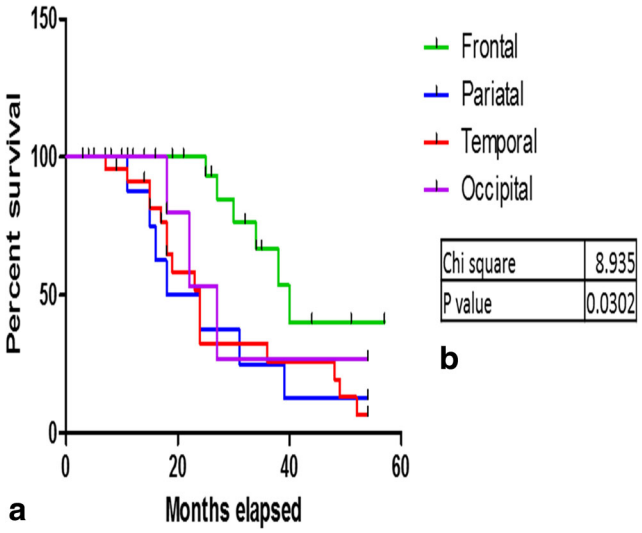


Fig. 4 Anatomic distribution–based Kaplan-Meier survival of grade III astrocytoma patients (**a**, $n = 78$). Comparison of survival outcomes among four anatomic locations was statistically significant (**b**, $p = 0.03$, chi-square = 8.9)

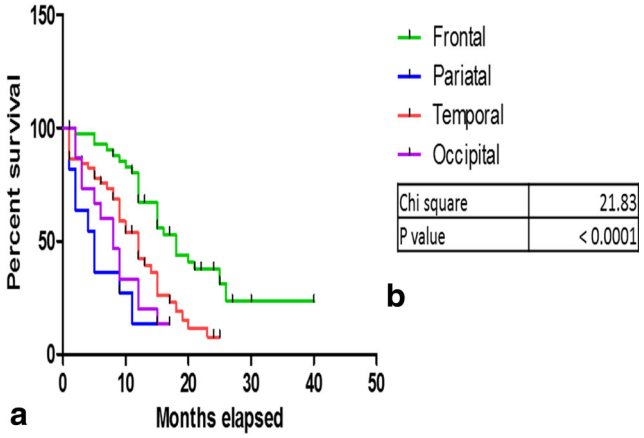
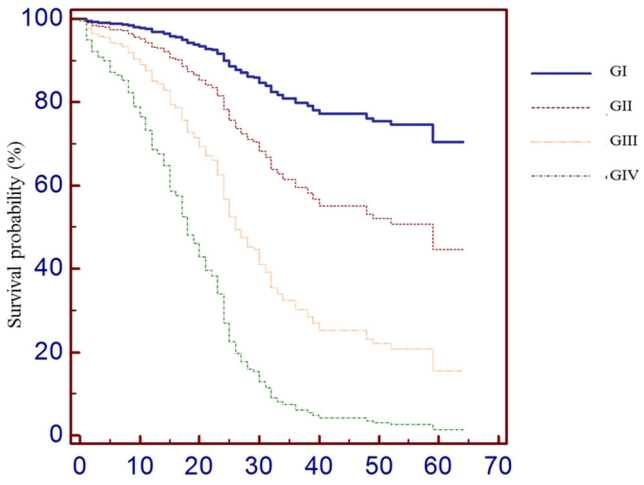


Fig. 5 Anatomic distribution–based Kaplan-Meier survival curve of glioblastoma multiforme patients (**a**, $n = 138$). Survival of patients with temporal, parietal, and occipital origin of tumor was having poor survival outcome as compared to the frontal lobe (**b**, $p < 0.0001$, chi-square = 21.8)

We have further studied retrospectively pattern of survival in patients with astrocytoma. We found that median age of survival (in months) was 59 for diffuse astrocytoma, 34 for anaplastic astrocytoma, and 14 for glioblastoma multiforme. For pilocytic astrocytoma, the median survival was undefined (Fig. 6).

Cancer registry system in developed countries and a developing nation like India differs mainly on ground of uniform collection and reporting of clinicopathological data. The dedicated cancer registry there helps to estimate accurate information about statistical distribution and mortality rate in a population [24]. While in India, epidemiological and clinicopathological study is reported as tertiary experiences [7]. Our study has several advantages; it is for the first time in India we are reporting survival information in a group. Second, we report our data with wide participation of patients and represent a dataset with significant coverage.



Variables	p value	95%CI
Age	0.1649	0.9795 to 1.0035
Treatment	0.6552	0.6326 to 2.0749
Grade	**<0.0001**	1.7236 to 3.1080

b

Fig. 6 Survival pattern of patients with grade I, grade II, grade III, and grade IV astrocytoma (**a**). The values were adjusted according to Cox regression mode where age of patients, treatment given, and grade were considered as variables. Among these variables, the grade of patients was found to have statistically significant association with survival (**b**, $p < 0.0001$)

In conclusion, our findings indicate the frontal and temporal lobes as prominent anatomic origins of tumors. The frontal lobe as anatomic origin was correlated with better prognosis while the temporal, parietal, and occipital origins were significantly associated with worse clinical outcomes in high-grade astrocytoma patients. Among astrocytoma subtypes, glioblastoma multiforme was found with worse survival outcomes with median survival of 14 months, which was slightly higher as compared with existing literature. Further, there was no surgical mortality reported in the cases we observe.

The unique features of our study are (1) the patients were from all parts of India, (2) we note the median survival ages in considerably large cases in India and report the median survival among the four grades of astrocytoma, (3) we found glioblastoma patients to have slightly longer lifespan as compare with the existing literature, and (4) in the cases where the tumor is located on the frontal lobe, the most common surgical procedure followed was complete resection, which may have resulted in favored prognosis.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval The present studies involving human participants were approved by the Institutional Ethics Committee (ICE), University of Hyderabad and KIMS Foundation Research Centre (KFRC), KIMS, Secunderabad, India. All subjects participating were completely anonymized.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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