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Original Research Article

Glial Tumors- Review of Literature and Our Institutional Experience

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Abstract: Tumors of central nervous system (CNS) constitute 1 to 2% of all malignancies. Among these, Gliomas are most common in adults, whereas in children both astrocytomas and medulloblastomas are common. These tumors carry very poor prognosis. We conducted a retrospective and prospective cohort study of 75 patients who underwent surgery for intracranial gliomas in the department of Neurosurgery, Gandhi Hospital, Secunderabad from May 2011 to June 2017. The retrospective data was collected from Department database for the period May 2011 to October 2015 and prospective from November 2015 to June 2017. Patients age at diagnosis, gender, tumor location and biological behavior and histological characteristics were analyzed. All glial tumors (ICD-10; C70-72) included in 2007 WHO classification of central nervous system tumors were included in this study, and metastatic tumors, bony tumors, pineal tumors, pituitary tumors, embryonal and neuroepithelial tumors and all spine and spinal cord tumors were excluded from the study. Molecular study of these tumors, according to recent 2016 WHO Classification of CNS tumors, could not be done due to limited resources in our institute. We analyzed 75 cases of glial tumors operated in Gandhi hospital. Out of these 75 cases, pilocytic astrocytoma were 9, pleomorphic xanthoastrocytoma was one, diffuse astrocytoma were 14, gemistocytic astrocytoma were 2, oligodendroglioma were 4, oligoastrocytoma were 3, anaplastic astrocytoma were 21, anaplastic oligodendroglioma were 3, anaplastic oligoastrocytoma were 2, and glioblastoma were 16. Male dominance was observed in astrocytomas and oligodendrogliomas, and female predominance was observed in pilocytic astrocytomas and anaplastic oligodendrogliomas. Glioblastoma showed equal sex distribution. Most of the WHO grade I tumors were seen in 0-19 years and 20-44 years age groups, WHO grade II tumors were seen in 20-44, 45-54, and 55-64 years age groups, WHO grade III tumors were seen in 20-44 years and 55-64 years age groups and WHO grade IV tumors were seen in 20-44 and 55-64 years age group. Most common initial presentation of glial tumors is headache (33.3%), followed by seizures (25.3), somatosensory loss (21.3%) and motor weakness (20%). Mean duration of illness in low grade gliomas is 10.96 days and in high grade gliomas is 15.5 days. Molecular profiling of gliomas in 2016 WHO classification helps in tumor grading and prognostication beyond histological classification. But many institutions in developing countries have some barriers for molecular and genetic analysis of these distinct brain tumors. However, despite the explosion of molecular era in recent years, we face many challenges in accurately prognosticating and assigning treatment regimes, because of the heterogeneous nature of these gliomas. In future, the use of combined histopathological and molecular criteria coupled with genetic analysis will facilitate the clinical, experimental and epidemiological studies that will lower the mortality and morbidity of patients with glial tumors.

Keywords: Glial tumors, Isocitrate dehydrogenase, Astrocytoma, Oligodendroglioma, Glioblastoma multiforme

INTRODUCTION

Tumors of central nervous system (CNS) constitute 1 to 2% of all malignancies. Among these, Gliomas are most common in adults, whereas in children both astrocytomas and medulloblastomas are common [1]. These tumors carry very poor prognosis.

The incidence and mortality of glial tumors has increased over the past 20 years in all age groups. Their incidence is typically high in developed countries [2]. It is a well known fact that, geographical, genetic and phenotypic differences in the population alter the natural history, biological behavior, and response of these tumors to various management regimes [3].

2016 CBTRUS (Central Brain Tumor Registry of the United States) fact sheet showed that, the overall incidence of all primary malignant and nonmalignant brain and other CNS tumors is 22.36 cases per 1,00,000 population [2], their rate being higher in females (24.46 per 1,00,000) than in males(20.10 per 1,00,000). An estimated 79,270 new cases of primary malignant and nonmalignant brain and other CNS tumors are expected to be diagnosed in United States in 2017. The worldwide incidence of these tumors in 2012 were 3.4 per 1,00,000 using age adjusted world standard population, with 3.9 per 1,00,000 in males and 3.0 per 1,00,000 in females [4].

The average annual mortality rate of these tumors in the US between 2009 and 2013 was 4.32 per 1,00,000 with 73,450 deaths [5]. An estimated 16,947 deaths will be attributed to these tumors in 2017 in the US. The survival rates of these CNS tumors are estimated using the SEER (Surveillance, Epidemiology and End Results) Cancer Incidence Research Database, 1973-2013. The five year relative survival rate following diagnosis of the primary malignant brain and other CNS tumors in The US is 34.7% (36.1% for females and 33.5% for males) [6]. The survival rates after diagnosis significantly vary by age, biological behavior and histological characteristics of the tumor.

The incidence of brain tumors (ICD-10: C70-72) is highest in Bangalore with age adjusted ratio (AAR) of 4.6 with second highest in Delhi with incidence on AAR of 4.3 [7]. An estimated incidence of brain tumors (C70-72) at India level is 30629 in 2015 and 32619 in 2020 in both sexes with relative proportion of 2% [8], and the incidence is higher in males (19300 in 2015 and 20506 in 2020) than females (11329 in 2015 and 12113 in 2020).

Increasing incidence and mortality of CNS tumors in developing countries like India lead the necessity of establishing the Hospital Based Cancer Registries (HBCR) for examining the spectrum of brain tumors within the Indian population. The HBCRs provide information about treatment efficacy and long term survival of patients according to different patient characteristics and treatment modalities and lead to streamlining of management practices and development of hypothesis for future research in this area.

Until recently the Primary central nervous system tumors were classified solely based on histomorphological characteristics and histogenesis of neoplastic cell types, which contains an inherent amount of interobserver variability in interpretation, leading to less predictive clinical outcomes [9]. 2007 WHO classification systems for CNS tumors relied upon conventional histology, which grouped glial tumors as either astrocytomas or oligodendrogliomas. The aggressiveness or higher grades of these diffuse gliomas was further differentiated by histological parameters like nuclear atypia, mitotic figures, microvascular proliferation and necrosis [10, 11].

Recent updates of World Health Organization classification of central nervous system tumors in 2016 incorporates molecular and genetic alterations along with histomorphological characteristics. The molecular biomarkers used in recent WHO classification include IDH, ATRX, and 1p/19q codeletion [12]. Diffuse gliomas are WHO grade II and III astrocytic tumors, WHO grade II and III oligodendrogliomas and WHO grade IV glioblastomas. The WHO grade II diffuse astrocytomas and grade III anaplastic astrocytomas were sub stratified based on Isocitrate dehydrogenase (IDH) enzyme, and divided into IDH-mutant, IDH-wildtype and NOS categories [12]. Glioblastomas (WHO grade IV) were sub stratified into glioblastoma IDH wildtype, IDH mutant and NOS categories. The classification of oligodendroglioma (WHO grade II) and anaplastic oligodendroglioma (WHO grade III) requires demonstration of both IDH mutations and 1p/19q codeletion status with 1p/19q codeletion being unique to oligodendroglial tumors [12]. The Oligoastrocytoma had high interobserver variability in traditional histopathological definition, and it has been reclassified into astrocytoma or oligodendroglioma according to IDH mutation and/or 1p/19q codeletion status [12, 13]. ATRX mutation is most characteristic of astrocytomas and TERT mutation is frequently observed in oligodendrogliomas. In the recent classification variants like diffuse midline glioma, H3 K27M mutant, epithelioid glioblastoma were newly added and entities like gliomatosis cerebri,

protoplasmic and fibrillary astrocytoma were removed [12].

The aim of this study is to analyze clinical and histopathological characteristics of glial tumors. We analyzed the age at the time of diagnosis, tumor location, initial presentation and duration, and overall survival. Finally we tried to compare histological characteristics with recent 2016 WHO classification of central nervous system tumors.

MATERIALS AND METHODS

We conducted a retrospective and prospective cohort study of 75 patients who underwent surgery for intracranial gliomas in the department of Neurosurgery, Gandhi Hospital, Secunderabad from May 2011 to June 2017. The retrospective data was collected from Department database for the period May 2011 to October 2015 and prospective from November 2015 to June 2017. Patients age at diagnosis, gender, tumor location and biological behavior and histological characteristics were analyzed. All glial tumors (ICD-10; C70-72) included in 2007 WHO classification of central nervous system tumors were included in this study, and metastatic tumors, bony tumors, pineal tumors, pituitary tumors, embryonal and neuroepithelial tumors and all spine and spinal cord tumors were excluded from the study. Molecular study of these tumors, according to recent 2016 WHO Classification of CNS tumors, could not be done due to limited resources in our institute.

Our statistical data was compared with the CBTRUS, SEER and ICMR statistics and results were analyzed.

Table 1: WHO 2007 classification versus 2016 classification of Glial tumors

WHO 2007 classification	WHO 2016 classification
WHO Grade I **Astrocytic tumors** Pilocytic astrocytoma (ICD-O 9421/1) Pilomyxoid astrocytoma (ICD-O 9425/3) Subependymal giant cell astrocytoma (ICD-O 9384/1) Pleomorphic xanthoastrocytoma (ICD-O 9424/3)	**WHO Grade I** **Other astrocytic tumors** Pilocytic astrocytoma (ICD-O 9421/1) Pilomyxoid astrocytoma (ICD-O 9425/3 Subependymal giant cell astrocytoma (ICD-O 9384/1) Pleomorphic xanthoastrocytoma (ICD-O 9424/3) Anaplastic Pleomorphic xanthoastrocytoma (ICD-O 9424/3)
WHO Grade II **Astrocytic tumors** Diffuse astrocytoma (ICD-O 9400/3) Fibrillary astrocytoma (ICD-O 9420/3) Gemistocytic astrocytoma (ICD-O 9411/3) Protoplasmic astrocytoma (ICD-O 9410/3) **Oligodendroglial tumors** Oligodendroglioma (ICD-O 9450/3) **Oligoastrocytic tumors** Oligoastrocytoma (ICD-O 9382/3)	**WHO Grade II** **Diffuse astrocytic tumors** Diffuse astrocytoma IDH1 mutant (ICD-O 9400/3) Gemistocytic astrocytoma, IDH1 mutant (ICD-O 9411/3) Diffuse astrocytoma IDH wild type (ICD-O 9400/3) Diffuse astrocytoma, NOS (ICD-O 9400/3) **Oligodendroglial tumors** Oligodendroglioma IDH mutant and 1p/19q codeleted (ICD-O 9450/3) Oligodendroglioma NOS (ICD-O 9450/3) **Oligoastrocytic tumors** Oligoastrocytoma NOS (ICD-O 9382/3)
WHO Grade III Anaplastic astrocytoma (ICD-O 9401/3) Anaplastic oligodendroglioma (ICD-O 9451/3) Anaplastic oligoastrocytoma (ICD-O 9382/3)	**WHO Grade III** Anaplastic astrocytoma, IDH mutant (ICD-O 9401/3) Anaplastic astrocytoma, IDH wild type (ICD-O 9401/3) Anaplastic astrocytoma, NOS (ICD-O 9401/3) Anaplastic oligodendroglioma, IDH mutant and 1p/19q codeleted (ICD-O 9451/3) Anaplastic oligodendroglioma, NOS (ICD-O 9451/3) Anaplastic oligoastrocytoma, NOS (ICD-O 9382/3)
WHO Grade IV Glioblastoma (ICD-O 9440/3) Giant cell glioblastoma (ICD-O 9441/3)	**WHO Grade IV** Glioblastoma, IDH wild type (ICD-O 9440/3) Giant cell glioblastoma (ICD-O 9441/3)

Gliosarcoma (ICD-O 9442/3) Gliomatosis cerebri (ICD-O 9381/3)	Gliosarcoma (ICD-O 9442/3) Epithelioid glioblastoma (ICD-O 9440/3) Glioblastoma, IDH mutant (ICD-O 9445/3) Glioblastoma, NOS (ICD-O 9440/3) Diffuse midline glioma, H3 K27M mutant (ICD-O 9385/3)

RESULTS

We analyzed 75 cases of glial tumors operated in Gandhi hospital. Out of these 75 cases, pilocytic astrocytoma were 9, pleomorphic xanthoastrocytoma was one, diffuse astrocytoma were 14, gemistocytic astrocytoma were 2, oligodendroglioma were 4, oligoastrocytoma were 3, anaplastic astrocytoma were 21, anaplastic oligodendroglioma were 3, anaplastic oligoastrocytoma were 2, and glioblastoma were 16. Male dominance was observed in astrocytomas and oligodendrogliomas, and female predominance was observed in pilocytic astrocytomas and anaplastic oligodendrogliomas. Glioblastoma showed equal sex distribution. Most of the WHO grade I tumors were seen in 0-19 years and 20-44 years age groups, WHO grade II tumors were seen in 20-44, 45-54, and 55-64 years age groups, WHO grade III tumors were seen in 20-44 years and 55-64 years age groups and WHO grade IV tumors were seen in 20-44 and 55-64 years age group. Most common initial presentation of glial tumors is headache (33.3%), followed by seizures (25.3), somatosensory loss (21.3%) and motor weakness (20%). Mean duration of illness in low grade gliomas is 10.96 days and in high grade gliomas is 15.5 days.

Table 2: Age wise distribution of WHO tumor grades I,II,III,IV

S.No	WHO grade	n	0-19 years	20-44 years	45-54 years	55-64 years	65 years or older
1	WHO Grade I	10	4	4	0	0	2
2	WHO Grade II	23	2	6	6	6	3
3	WHO Grade III	26	1	12	2	8	3
4	WHO Grade IV	16	2	5	2	6	1

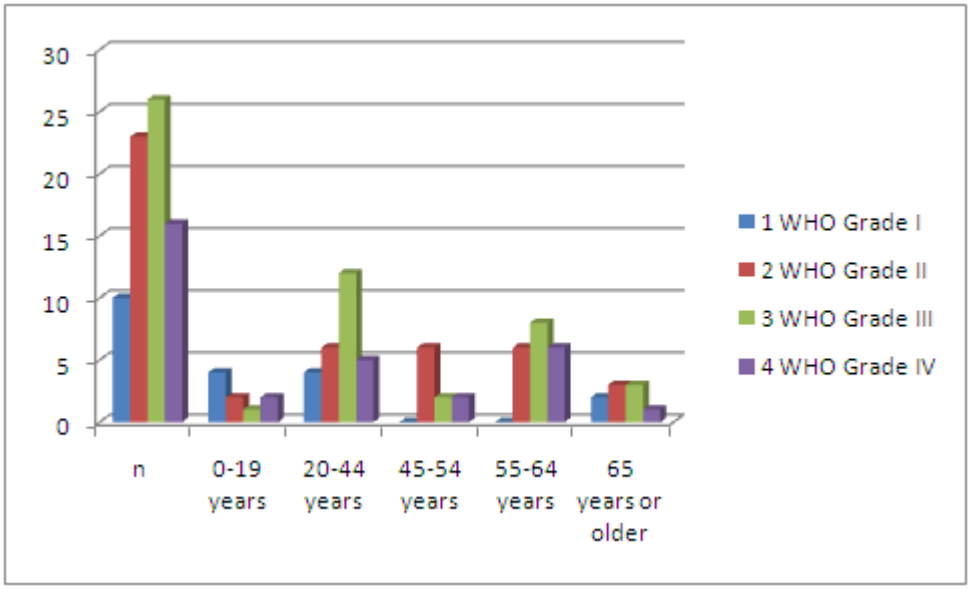

Fig-1: Age wise distribution of WHO tumor grades I,II,III,IV

Table 3: Histological types of glial tumors and sex distribution

S.No	Histology	WHO Grade	n	Male	Female
1	Pilocytic astrocytoma	I	9	3	6
2	Pleomorphic xanthoastrocytoma	II	1	0	1
3	Diffuse astrocytoma	II	14	8	6
4	Gemistocytic astrocytoma	II	2	1	1
5	Olidodendroglioma	II	4	3	1
6	Oligoastrocytoma	II	3	2	1
7	Anaplastic astrocytoma	III	21	13	8
8	Anaplastic oligodendroglioma	III	3	0	3
9	Anaplastic oligoastrocytoma	III	2	2	0
10	Glioblastoma	IV	16	8	8

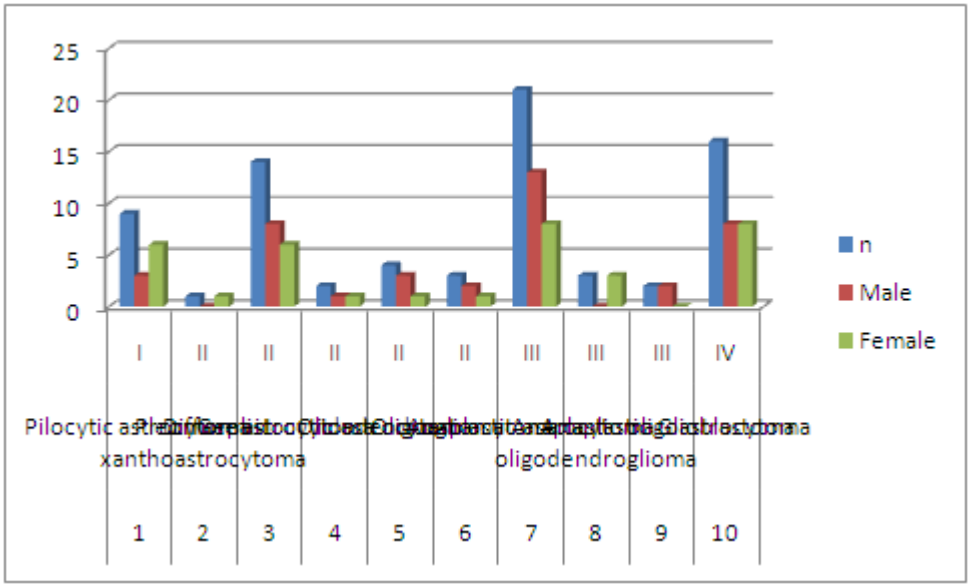

Fig-2: Gender distribution in glial tumors

Table 4: Location of glial tumors

S.No	Histology	n	Frontal	Parietal	Temporal	Frontoparietal	Temporoparietal	Occipitoparietal	Cerebellar
1	Pilocytic astrocytoma	9	1	3	0	0	0	1	4
2	Pleomorphic xanthoastrocytoma	1	1	0	0	0	0	0	0
3	Diffuse astrocytoma	14	6	1	1	1	4	1	0
4	Gemistocytic astrocytoma	2	2	1	0	0	1	0	0
5	Olidodendroglioma	4	2	0	1	1	0	0	0
6	Oligoastrocytoma	3	1	1	1	0	0	0	0
7	Anaplastic astrocytoma	21	4	4	4	1	5	3	0
8	Anaplastic oligodendroglioma	3	1	0	0	2	0	0	0
9	Anaplastic oligoastrocytoma	2	0	0	0	2	0	0	0
10	Glioblastoma	16	3	1	3	4	4	1	0

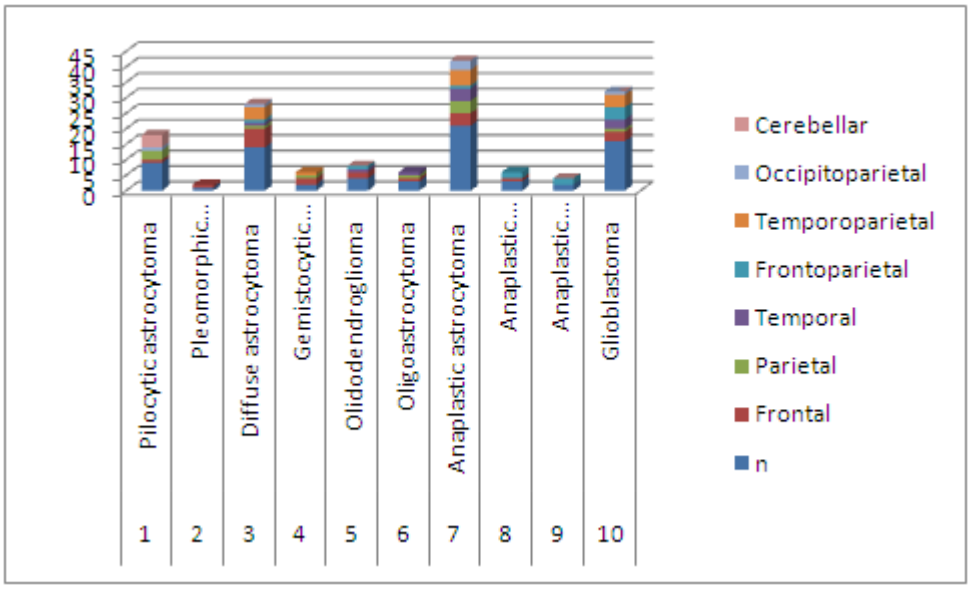

Fig-3: Location of glial tumours

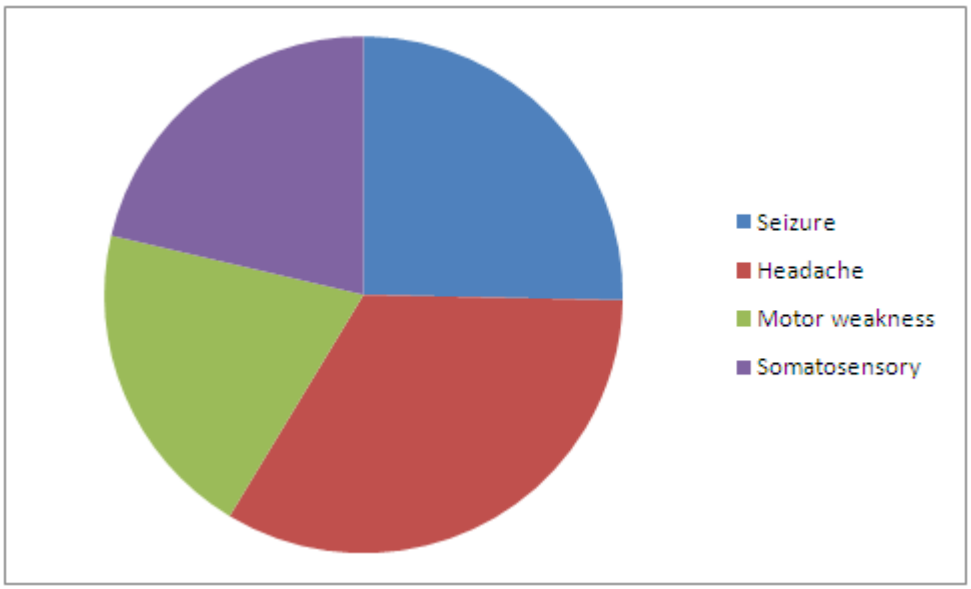

Fig-4: Predominant initial symptom

Seizure :19, Headache :25, Motor weakness :15, Somatosensory :16.

DISCUSSION

Tumors of the central nervous system (CNS) constitute 1 to 2% of all malignancies worldwide and 2% of all malignancies in India. The incidence of central nervous system tumors had been increasing for the past 20 years, and in India their incidence was 5 to 10 per 1,00,000 population [14, 15]. Astrocytomas are more common primary CNS neoplasms in adults, whereas in children both astrocytomas and medulloblastomas are common [1]. In India Astrocytomas accounted for 38.7% of all CNS tumors, with majority being glioblastomas which accounted for 59.5% [16]. Asirvatham JR *et al* reported 47.3% of astrocytomas in South India [17]. The incidence rate of gliomas in the United States is 6.5 per 1,00,000 population which accounted for 28% of all primary

brain and central nervous system tumors [18]. The median age of presentation of glial tumors in India is a decade earlier than that reported in western countries.

The recent 2016 WHO classification of central nervous system tumors brings several new perspectives towards traditional histopathology. This classification emphasizes the role of molecular pathology, which improves the diagnostic accuracy in these heterogeneous brain tumors. The molecular alterations includes IDH 1 and 2 mutations, 1p/19q codeletion status, or hypermethylation of the gene encoding O-6-methylguanine DNA methyltransferase (MGMT). We have analyzed the glial tumors based on histomorphological characteristics, and biological behaviour of the tumors, consistent with 2007 WHO classification (Table 1).

Low grade gliomas (WHO grade I and II tumors) include pilocytic astrocytomas, diffuse astrocytomas, oligodendrogliomas and mixed oligoastrocytomas [9, 11]. Low grade gliomas have better prognosis than their anaplastic counterparts. Their 10 year survival rate is 35% [18]. They are slow growing and diffusely infiltrating masses. These LGGs have high tendency to progress to high grade tumors (WHO Grade III), approximately 50% to 75% transforming within 6 to 7 years of diagnosis [18]. IDH1 and IDH2 mutations are more common in low grade gliomas, and patients with these mutations had a better survival [19]. These tumors primarily localises in frontal lobe, followed by temporal and parietal lobes. Tumors arising from infratentorial region have a better prognosis [20]. In our study also, these tumours showed predilection to frontal lobe (38.4%), followed by parietal, temporoparietal and temporal regions (Table 4 & Figure 3). Pilocytic astrocytomas originate mainly from cerebellar region, followed by parietal region. Seizure (65%-95%) is the most common presentation, followed by headache (40%). In our study, headache is the most common initial presentation (Figure 4). In low grade gliomas the mean age at diagnosis is 39.4 years. The most common histologic subtype is astrocytomas (69.3%). In our study we reported 14 (42.4%) cases of diffuse astrocytoma, 9 cases of pilocytic Astrocytoma, 4 cases of oligodendroglioma and 3 cases of mixed oligoastrocytoma (Table 2&3, Figure 1&2).

Overall survival (OS) and progression free survival (PFS) of LGGs depends on preoperative maximal tumor diameter of 4 cm or larger, histological subtype, maximal postoperative residual tumor diameter of 1 cm or larger. The University of California at San Francisco (UCSF) proposed a scoring system to estimate patient overall survival (OS) and progression free survival (PFS) [21]. A 5 year survival rate of 97% in patients with a UCSF score 0 to 1 and 56% in patients with a UCSF score of 3 to 4 were reported.

High grade gliomas (WHO Grade III and IV) include anaplastic astrocytoma, anaplastic oligodendroglioma and glioblastoma. Approximately 11,000 new cases of high grade gliomas are reported each year in the United States, of these glioblastomas accounts for 9000 cases. In our study we reported 21 (50%) cases of anaplastic astrocytomas, 16 (38%) cases of glioblastomas and 3 cases of anaplastic oligodendroglioma (Table 2&3, Figure 1&2).

In anaplastic astrocytomas, the average age at diagnosis is approximately 40 years. In our study, the average age at diagnosis is 44 years (Table 2). These tumors have an innate tendency to progress to glioblastomas. The local recurrence of these tumors is high. Patients with high grade gliomas present with raised intracranial pressure. Despite optimal treatment, the median survival is 2 to 5 years for anaplastic gliomas [22, 23].

Glioblastomas are the most common primary malignancies of central nervous system in adults. The incidence of glioblastoma is 3.19 per 1,00,000 population [24]. The mean age at diagnosis for glioblastoma is 53 years, with a range between 65 and 74 years [21]. We observed 46 years is the mean age at diagnosis, with a range between 16-69 years (Table 2). Glioblastoma is more common in men (male to female ratio is 1.5:1). In our study we observed equal male to female distribution in glioblastomas (Table 3, Figure 2). Relentless progressive headache is the hallmark of glioblastoma. Approximately 1/3rd of patients may present with seizures. In our study headache (56%) is the most common initial presentation, followed by seizures (25%) (Figure 4). The median survival is less than 2 years for glioblastomas [22, 23]. Some studies reported favourable prognosis of frontal region or surface glioblastomas [25]. In our study we observed 18 months of survival in 65% cases and 22 months of survival in 35% cases.

Anaplastic oligodendrogliomas are rare tumors, accounting for less than 2% of all primary brain

tumors. The incidence in United states is 4 per 1,000,000 per year. Slight male predominance is seen in these tumors [24]. In our study we reported 3 cases, and all were females (Table 3, Histogram 2). The average age at diagnosis is 39 years. Survival in patients with these tumors is better than other high grade glial tumors. Overall survival is 2 to 6 years. The average survival in our patients is 5.4 years.

The optimal management of low grade gliomas is supramarginal resection, followed by adjuvant radiation with or without chemotherapy. The management of high grade glioma is safe maximal resection, followed by adjuvant radiotherapy and concurrent chemotherapy with temozolamide (TMZ).

CONCLUSION

Molecular profiling of gliomas in 2016 WHO classification helps in tumor grading and prognostication beyond histological classification. But many institutions in developing countries have some barriers for molecular and genetic analysis of these distinct brain tumors. However, despite the explosion of molecular era in recent years, we face many challenges in accurately prognosticating and assigning treatment regimes, because of the heterogeneous nature of these gliomas. In future, the use of combined histopathological and molecular criteria coupled with genetic analysis will facilitate the clinical, experimental and epidemiological studies that will lower the mortality and morbidity of patients with glial tumors.

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Conflicts of Interest- Nil

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