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Malignancy Spectrum

ORIGINAL ARTICLE

Multimodal management and outcome of pediatric and adolescent malignant central nervous system tumors: A single-center retrospective study

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Abstract

Objective: There is a paucity of real-world evidence in the Indian context to address the outcome of primary brain tumors (PBTs) in children. This study aimed to describe the demographic profile, clinical characteristics, and histological features of PBTs based on the 2016 World Health Organization classification, assess the efficacy of treatment methods, and identify the factors that influence the outcome.

Methodology: This is a single-institution, hospital-based study. Data were collected for pediatric patients aged 0–19 years, from September 2001 to May 2023 (22 years), who were diagnosed with malignant PBTs. Patients with radiologically or histologically proven tumors were included. Those with metastatic disease to the central nervous system were excluded. The overall survival (OS) and recurrence-free survival (RFS) were estimated using the Kaplan–Meier method.

Results: A total of 251 patients with pediatric brain tumors were included in this analysis. The mean age was 9.10 ± 5.54 years. The male-to-female ratio was 1.20:1. In this cohort, the most common histologies were medulloblastoma and astrocytoma. The mean survival of all patients with PBTs was 141.00 ± 7.90 months with 1-, 3-, and 8-year OS rates of 79.00%, 67.00%, and 60.00%, respectively. Medulloblastoma had 1-, 3-, and 8-year OS rates of 81.00%, 72.00%, and 65.00%, respectively. The 1-year OS rates for glioblastoma and brainstem glioma were 46.00% and 45.00%, respectively. Complete tumoral resection showed longer survival than lesser degrees of resection ($p = 0.001$). Embryonal tumors (ETs) had a better RFS of 133.60 ± 12.70 months ($p \leq 0.001$).

Conclusion: ETs have a better prognosis than glial tumors. With an improved OS, the surgical resection extent has a favorable outcome. As a chemosensitive tumor, medulloblastoma benefits most from systemic treatment and responds well to a multimodal approach.

KEYWORDS

epidemiology, genetic predisposition, symptoms and signs, malignant primary brain tumors, multimodal treatments, patient outcome assessment

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INTRODUCTION

Globally, central nervous system (CNS) tumors in children aged between 0 and 19 years account for 155.8 per million person-years [1]. Primary brain tumors (PBTs) are the most common pediatric malignancy after leukemia. Brain tumors are a significant cause of morbidity and mortality [2]. In India, the incidence of pediatric brain tumors accounts for 8%–12% of total cases of all pediatric tumors [3]. It is currently on an upward trend [4]. The introduction of advanced noninvasive diagnostic imaging methods is the most likely contributor to the increased incidence rate [4]. According to the World Health Organization (WHO), PBTs are classified as low-grade gliomas (LGGs), high-grade gliomas (HGGs), embryonal tumors (ETs), and ependymomas [5]. Clinical manifestation is influenced by the site of the tumor, supratentorial or infratentorial. The prognosis of the PBT patients is based on the age of presentation, histological subtype, and extent of resection. Other factors influencing survival outcomes include tumor size and location, different expression levels of genetic mutations, and treatment-related complications. Brain tumors are treated with multimodal approaches including surgery, radiation, and chemotherapy. The primary mode of treatment for PBTs is surgery, which aims to achieve complete tumor resection, except in the case of diffuse intrinsic pontine gliomas (DIPG) and optic pathway gliomas. The mode of adjuvant therapy varies depending on the histological type of the tumors and the patient's age. Radiotherapy (RT) and chemotherapy are used for all malignant CNS tumors, including optic pathway gliomas and DIPG [6]. The diagnosis and management of PBTs have seen a paradigm shift over the years. The current study aimed to understand the histopathological type, clinical presentation, management, and overall survival (OS) of pediatric and adolescent primary CNS tumors over the past two decades in a single tertiary care center in South India.

Methodology

This is a retrospective study of pediatric and adolescent primary CNS tumors treated at a single tertiary care center between September 2001 and May 2023 (22 years). Data were collected by using the institutional electronic health record. Patients below 19 years of age with primary malignant brain tumors and radiologically and/or histologically proven tumors were included. Those with metastatic disease of the CNS and incomplete medical records were excluded. The study was approved by the Institutional Ethical Committee (ECASM-AIMS-2023-289). Since the data was retrospective, no consent was required. No individual patient identification information had been gathered. Variables collected from the patients' medical records were demographic parameters, including age, gender, and associated hereditary syndromes. The patients were grouped according to age: infants (0–1 month), neonates (4 weeks to 1 year), children (1–9 years), and adolescents (10–19 years). The presentation of signs and symptoms (with or without headache, vomiting, epileptic seizures, neurological deficits [limb weakness, gait abnormalities, dysphagia, dysphonia, cranial nerve palsy, vision abnormality, and bladder and bowel incontinence]), and the duration between symptom onset and radiological/pathological diagnosis were documented. The localization of the tumor origin (supratentorial, infratentorial, and tumors arising from the spine) and the primary diagnosis (for patients who did not undergo surgery) were determined based on neuroimaging. Given that the data were collected in the early 2000s and due to the lack of information on molecular subtypes, the histological features were derived from the pathological report and further classified according to the 2016 WHO classification. Various treatments received by the patients, including surgery, RT, and chemotherapy, were recorded. Operative outcomes were determined based on the operative records by the surgeons and postoperative computed tomography/magnetic resonance imaging performed within 24–72 h after surgery. The extent of surgical resection was classified into four categories based on operative records and postoperative imaging: gross total resection (GTR): complete removal of the tumor with no visible residual on postoperative imaging; near total resection (NTR): removal of > 90% of the tumor volume, leaving minimal residual tissue; subtotal resection (STR): removal of approximately 50%–90% of the tumor; biopsy alone: only a diagnostic tissue sample was obtained, with no attempt at tumor resection. The recurrence rate and survival status were obtained based on follow-up records and calls to patients among those who were lost to follow-up, which were done with the help of the institutional cancer registry. The follow-up records collected included adjuvant therapy, tumor relapse, survival status, and the date of recurrence or death.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 20.0 software. The categorical variables are expressed as frequency and percentage. Continuous variables are presented by mean and standard deviation (SD). To estimate the OS probability, the Kaplan–Meier analysis was used. To compare the mean survival time in different characteristics, the Log-rank test was applied.

RESULTS

Out of 269 patients assessed, 18 patients were excluded, and 251 were identified for final analysis (Figure 1). The mean patient age at diagnosis was 9.10 ± 5.54 years. Among these, 54.60% ($n = 137$) were males, and 45.40% ($n = 114$) were females. The mean duration between symptom onset and diagnosis was 189 days. The most common histologies were medulloblastoma ($n = 57$; 23.00%), LGG ($n = 44$; 17.70%), brainstem glioma ($n = 36$; 14.50%), glioblastoma multiforme (GBM) ($n = 23$; 9.27%), and others. Demographic details are presented in Table 1. Out of the 251 patients, 204 underwent surgery, in which GTR was achieved in 35.00% ($n = 88$) of the patients, followed by STR achieved in 21.00% ($n = 53$), NTR achieved in 13.50% ($n = 34$), and biopsy alone achieved in 12.00% ($n = 29$) of the patients. Forty-seven (18.70%) patients did not undergo surgery due to complex tumor locations and a diffusely infiltrative nature. Among those 47 inoperable patients, surgery was not feasible for 6 patients due to poor general conditions, requiring upfront palliative care support. Radiotherapy (RT) was given to 138 patients, of whom 95.00% had curative intent, and 5.00% received palliative RT. Sixteen patients (6.00%) were not eligible for RT due to age less than 3 years, and others did not receive RT due to various factors such as low-grade histology ($n = 19$), poor general condition ($n = 14$), succumbed due to postoperative sepsis ($n = 7$), referred to local public hospitals ($n = 2$), and planned for RT but failed to report ($n = 14$). Thirty-three percent of patients received chemotherapy, of which neoadjuvant chemotherapy was given to 5 patients with germ cell tumors. Concomitant chemoradiation (CTRT) was given to 28 patients, and 49 patients received adjuvant chemotherapy. Recurrence of disease was noted in 80 (31.90%) patients. Of the 251 patients, 68 (27.00%) patients expired, 119 (47.40%) patients were lost to follow-up or unknown, and 64 (25.50%) patients were still alive at the time of data analysis (Table 2).

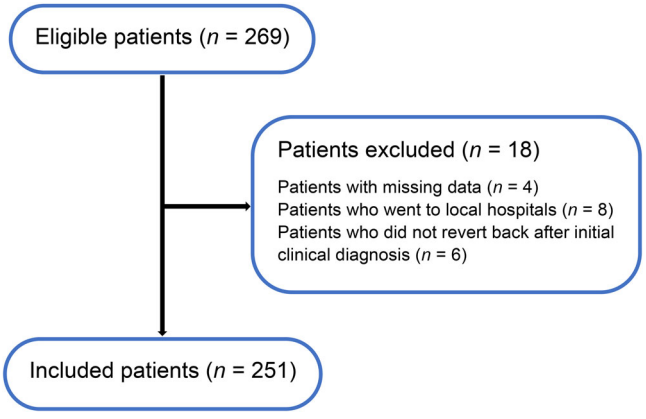

FIGURE 1 Consort diagram of patient population selection.

In this cohort, RT and chemotherapy were given using uniform protocols. Out of 138 patients who received RT, 134 patients completed RT, and 4 patients were unable to complete RT because they developed symptoms of raised intracranial pressure ($n = 2$), hematological toxicity ($n = 1$), and severe fatigue ($n = 1$). Three-dimensional conformal radiotherapy technique (3DCRT) was delivered to 108 patients; 6 patients received volumetric modulated arc therapy (VMAT), 10 patients received TomoTherapy, and the RT techniques were unknown in 14 patients. In this study, a higher percentage of patients received 3DCRT, as the data were collected from 2001. However, the number of patients receiving 3DCRT decreased, and that of patients receiving TomoTherapy/intensity modulated radiation therapy (IMRT) increased with time. TomoTherapy and IMRT provide better dose homogeneity and target coverage than conventional methods. While being more effective than 3DCRT, VMAT and IMRT have a considerable disadvantage of integral dose spillover to surrounding normal structures, which can result in secondary malignancies at later time [7, 8]. In this hospital, TomoTherapy was used the least, as it required general anesthesia [8]. Of the 82 patients who received chemotherapy, 41 patients completed both the induction and maintenance phases according to the protocol, and 41 patients did not complete the recommended treatment. Twenty-six patients failed to complete the induction phase, and 15 patients were unable to complete the maintenance phase. Chemotherapy was provided using uniform, standardized protocol regimens. Patients with medulloblastoma ($n = 29$), primitive neuroectodermal tumor (PNET, $n = 3$), pineoblastoma ($n = 1$), and atypical teratoid rhabdoid tumor (ATRT, $n = 1$) received chemotherapy according to the Pediatric Oncology Group (POG) 9031 [9], 13 patients with GBM received treatment according to the European Organisation for Research and Treatment of Cancer (EORTC) 26981/22981 [10], 5 patients with medulloblastoma received chemotherapy according to Children's Cancer Group (CCG) 9921 [11], the second ATRT patient received chemotherapy according to the American Clinical Neurophysiology Society (ACNS) 0333 [12], each patient with atypical choroid plexus tumor, anaplastic ependymoma, and embryonal tumor with multilayered rosettes (ETMR) received chemotherapy according to POG9233 [13], ACNS0831 [14], and CCG9970 3 [15], respectively, and 2 patients with choroid plexus carcinoma received chemotherapy according to the St. Jude Young Children 07 (SJYC07) [16]. Six patients had germ cell tumors and received the bleomycin, etoposide, and cisplatin (BEP) chemotherapy regimen (Table 3).

The mean OS of all the patients in this cohort was 141.00 months (95% confidence interval [CI]: 125.50–157.00), with 1-, 3-, and 8-year OS rates of 79.00%, 67.00%, and 60.00%, respectively (Figure 2a). Medulloblastoma had 1-, 3-, and 8-year OS rates of

TABLE 1 Demographic parameters.

Characteristic criteria	*n* (%)
Age (mean ± SD, years)	9.10 ± 5.54
Age group	
Neonates (< 1 month)	1 (0.40)
Infants (4 weeks to 1 year)	8 (3.20)
Children (1–9 years)	126 (50.20)
Adolescents (10–19 years)	116 (46.20)
Gender	
Male	137 (54.60)
Female	114 (45.40)
Tumor location	
Supratentorial tumors	84 (33.50)
Infratentorial tumors	156 (62.20)
Spinal tumors	11 (4.40)
Inherited syndromes	
Neurofibromatosis I	5
Neurofibromatosis II	1
Gorlin-Glotz syndrome	1
Foville syndrome	1
p53 mutant	1
Prediagnostic symptoms	
Vomiting	129 (52.00)
Headache	127 (51.20)
Gait abnormality	60 (24.10)
Ocular abnormality	58 (23.30)
Limb weakness	52 (20.90)
Seizure	41 (16.50)
Neck pain	8 (3.20)
Dysphagia	5 (2.00)
Altered sensorium	4 (1.61)
Torticollis	4 (1.61)
Hearing impairment	6 (2.40)
Increased head circumference (in neonate)	4 (1.61)
Behavioral changes	5 (2.00)
Developmental delay	6 (2.40)
Polyuria, polydipsia	5 (2.00)
Dysphonia	3 (1.20)
Vertigo	2 (0.80)

(Continues)

TABLE 1 (Continued)

Characteristic criteria	*n* (%)
Symptom onset diagnostic interval (days) Mean ± SD	188.80 ± 72.50
Range	0–1825
≤ 73	208 (82.90)
> 73	43 (17.10)
Histopathological type (WHO 2016)	
Low-grade glioma	44 (18.00)
Anaplastic astrocytoma	19 (8.00)
Anaplastic oligodendroglioma	4 (1.60)
Glioblastoma multiforme	23 (9.30)
Brain stem glioma	36 (14.50)
Pilocytic astrocytoma	4 (2.00)
Anaplastic pleomorphic xanthoastrocytoma	1 (0.40)
Astroblastoma	1 (0.40)
Ganglioglioma	2 (0.80)
Ependymoma	17 (7.00)
Anaplastic ependymoma	12 (5.00)
Atypical choroid plexus tumor	1 (0.40)
Choroid plexus carcinoma	3 (1.20)
Medulloblastoma	57 (23.00)
Atypical teratoid/rhabdoid tumor	3 (1.20)
Embryonal tumor with multilayered rosettes	2 (0.80)
PNET	11 (4.40)
Pineoblastoma	2 (0.80)
Germinoma	1 (0.40)
Non-germinomatous germ cell tumors (NGGCT)	5 (2.00)
Mixed germ cell tumors	1 (0.40)
Optic nerve glioma	2 (0.80)
Histological grading	
Grade I	10 (4.00)
Grade II	60 (23.90)
Grade III	41 (16.30)
Grade IV	133 (53.00)

81.00%, 72.00%, and 65.00%, respectively. The 1- and 2-year OS rates for GBM were 46.00% and 9.70%, respectively, while brainstem glioma had a 1-year OS rate of 45.00% (Figure 2b). In this study, patients who underwent GTR showed a statistically longer mean survival of 178.80 months (95% CI: 159.00–198.00), compared to those with a lower degree of resections ($p = 0.001$). Among them, the mean survival of patients who underwent NTR, STR, and biopsy alone was 131.00 months (95% CI: 93.70–168.00), 124.60 months (95% CI: 89.50–159.80), and 95.80 months (95% CI: 43.00–143.00), respectively (Figure 3). The mean survival of patients with low-grade tumors was 192.60 months (95% CI: 172.00–213.00), which is significantly longer ($p \leq 0.001$) compared to 109.90 months (95% CI: 91.70–128.00) in patients with high-grade tumors

TABLE 2 Extent of the treatment received and outcome.

Characteristic criteria	*n* (%)
Surgery	
GTR	88 (35.00)
NTR	34 (13.50)
STR	53 (21.00)
Biopsy	29 (12.00)
Not done	47 (18.70)
Radiotherapy (RT)	
Yes	138 (55.00)
Not eligible	16 (6.00)
No	97 (39.00)
Intent of RT	
Radical	131 (95.00)
Palliative	7 (5.00)
Chemotherapy	
Concomitant	28 (34.10)
Adjuvant	49 (59.80)
1st recurrence	80 (31.90)
Overall outcome	
Alive	64 (25.50)
Dead	68 (27.00)
Lost to follow-up/unknown	119 (47.40)

Five patients with germ cell tumor received neoadjuvant chemotherapy, which was not included in the current table.

TABLE 3 Treatment description.

Characteristic criteria	*n*
RT status	
Completed	134
Incomplete	4
Site of RT	
CSI + boost	46
Postoperative site + margin	62
Brainstem	24
Cervical spine + brainstem	1
Tumor + boost	1
Spine	2
Intraventricular	1
WBRT	1
RT technique	
3DCRT	108
VMAT	6
TomoTherapy	10
Chemotherapy status	
Completed	41
Incomplete	41
Chemotherapy regimen	
POG 9031	34
POG 9233	1
CCG 9921	5
ACNS 0333	1
ACNS 0831	1
SJYC 07	2
BEP regimen	6
EORTC 26981/22981	13
CCG 99703	1
Others	18

Abbreviations: ACNS, American Clinical Neurophysiology Society; BEP, bleomycin, etoposide, and cisplatin; CCG: Children's Cancer Group; CSI, craniospinal irradiation; 3DCRT, three-dimensional conformal radiation therapy; POG, Pediatric Oncology Group; SJYC07, St. Jude Children's Research Hospital; VMAT, volumetric arc modulated therapy; WBRT, whole brain radiation therapy.

(Figure 4a). The current study, as expected, showed a significant OS difference between the WHO CNS histological grades I, II, III, and IV tumors ($p \leq 0.001$) (Figure 4b). Based on histology, patients with medulloblastoma showed higher survival rates compared to patients with other high-grade tumors ($p = 0.004$). Patients with medulloblastoma had a mean survival of 135.10 months (95% CI: 111.10–159.00), compared to 83.6 months (95% CI: 59.40–107.70) in patients with non-medulloblastoma high-grade tumors (Figure 5a). Patients with GBM had a poor mean survival of 19.30 months (95% CI: 4.80–33.90) compared to 96.30 months (95% CI: 68.50–124.00) in other high-grade tumors (Grade III and IV), in which medulloblastoma was excluded ($p = 0.004$) (Figure 5b). Patients with brainstem glioma showed poor survival ($p \leq 0.001$), with a mean survival of 11.80 months (95% CI: 7.97–15.68), compared to 149.60 months (95% CI: 133.80–165.40) in patients with the rest of the pediatric CNS tumors (Figure 5c). Patients with LGGs showed better survival with a mean survival of 189.90 months (95% CI: 164.00–215.60), compared to 129.20 months (95% CI: 111.40–147.00) in patients with other pediatric malignancies ($p = 0.005$) (Figure 5d). Based on histological sub-groups, patients with LGGs showed significantly longer OS when compared to patients with ETs, high-grade tumors, and others ($p \leq 0.001$) (Figure 6a). Patients with LGGs had a mean survival of 189.50 months while those with ETs had mean survival of

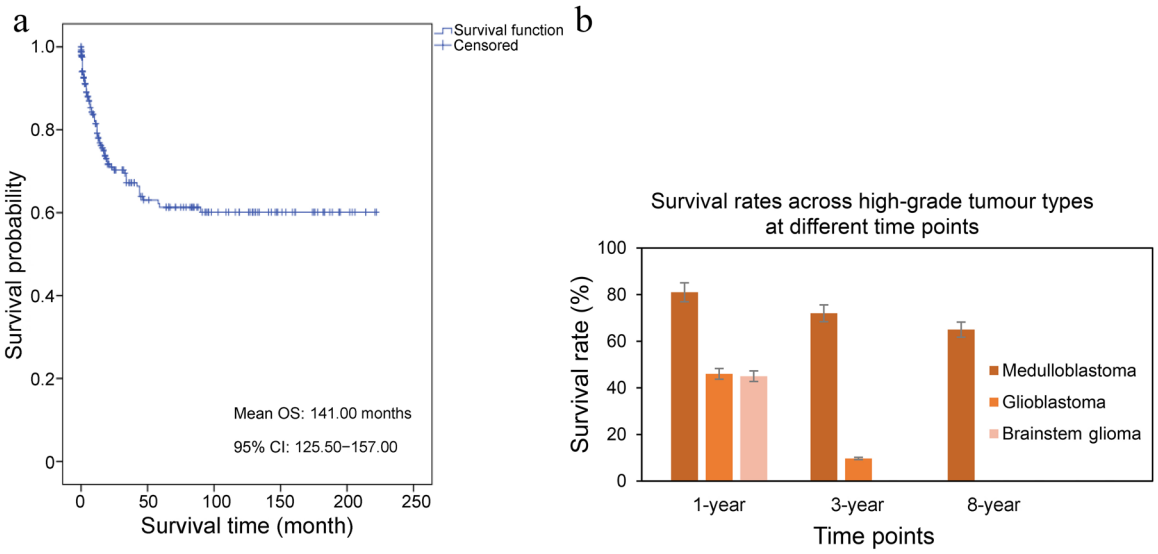

FIGURE 2 (a) Overall survival (OS) for all patients. (b) Survival rates across high-grade tumor types at different time points.

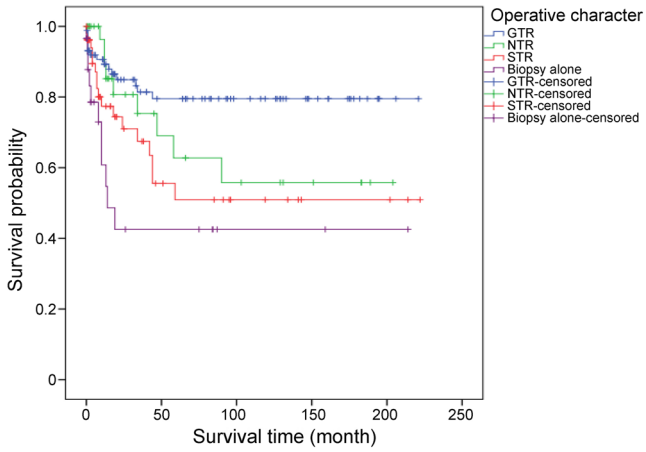

FIGURE 3 Impact of the surgical resection extent of tumor on overall survival.

140.00 months (95% CI: 116.60–163.30), high-grade tumors of 74.35 months (95% CI: 49.10–99.58), and others (ependymoma, atypical choroid plexus tumor, germ cell tumors, etc.) of 185.70 months (95% CI: 153.00–218.40).

Patients with ETs showed longer recurrence-free survival (RFS) when compared to those with LGGs, HGGs, and others ($p \leq 0.001$) (Figure 6b). Patients with ETs had a mean RFS of 133.60 months (95% CI: 12.79–108.60), compared to those with LGGs of 128.10 months (95% CI: 92.44–163.7), HGGs of 65.50 months (95% CI: 39.00–92.00), and other tumors of 79.70 months (95% CI: 79.70–13.39). The OS related to age, gender, tumor location, and symptom-onset diagnosis was not statistically significant. In this study, the impacts of RT and chemotherapy on survival were not analyzed, as these modalities vary according to each histological diagnosis and protocol.

DISCUSSION

This study shows a slight male preponderance with a male-to-female ratio of 1.20:1. This finding is similar to other studies. Shah et al. reported a similar ratio of 1.23:1 [17]. Another large study in South India reported a male-to-female ratio of 1.70:1 [18]. Similarly, a 10-year retrospective study conducted in Serbia [19], as well as studies from various countries, revealed equivalent results [20–24].

The age of the patients at diagnosis ranged from 2 weeks to 19 years, with an average age of 9.05 years. A 5-year study from North Kerala showed a mean age of 8.30 years [25]. A study by Harmouch et al. found an average age of 8.36 years [20]. Globally, various other European datasets (8.90 and 9.20 years, respectively) reported similar results [19, 21].

This study had only one patient (0.40%) who was a neonate (< 1 month of age), which is consistent with the 2017 report of the incidence of neonatal primary CNS tumors being very low, comprising < 1% of patients [26]. The current study had 3.20% infants (4 weeks to 1 year). This correlates with other reports, as overall, 1.40%–8.40% of all brain tumors in the pediatric age group occur under the age of 1 year [27, 28]. This study included 50.20% of children (1–9 years) and 46.20% of adolescents (10–19 years). The frequency was almost the same in the childhood and adolescent age groups. This is in concordance with the study published in 2015, which reported that there are more cases of

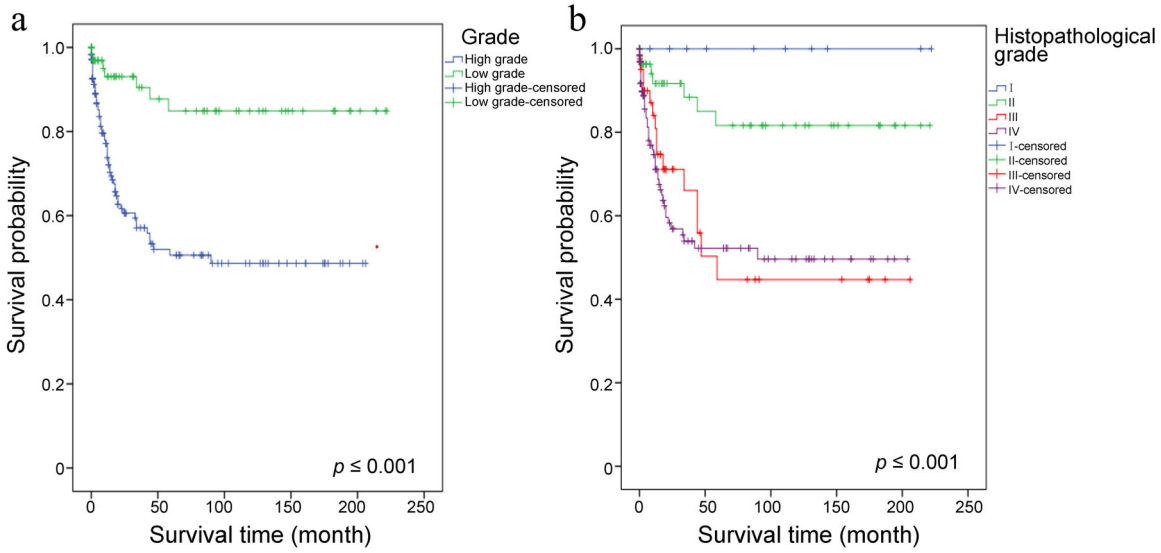

FIGURE 4 (a) Overall survival comparison between high-grade and low-grade CNS tumors. (b) Survival distribution based on different histological WHO CNS grading.

cancer in children (65.80%) than adolescents (34.20%) [17].

Based on clinical presentations and tumor type in patients evaluated for any acoustic disorder, nine (3.60%) patients had inherited genetic disorders in this cohort. The most frequent genetic disorder was neurofibromatosis type 1 (NF1), found in five patients. Those were associated with LGGs and optic pathway gliomas, which is consistent with other studies reported by Hernáiz Driever et al. and Rodriguez et al. [29, 30]. Among them, one patient with the NF1 trait tested positive for the histone H3 lysine 27 (H3K27) methylation mutation and had HGG, which is in agreement with the study done by Spyris et al., and similar cases were reported by Garibotto et al. [31, 32]. One patient with NF2, Foville syndrome, Gorlin-Glotz syndrome (GS), and a p53 mutation was also noted in this study. One patient with GS was diagnosed with a type of variant called desmoplastic medulloblastoma. This is consistent with a study conducted among 173 consecutive cases of medulloblastoma by Evans et al., who reported that only 1%–2% of people with GS develop medulloblastoma [33]. A study reported by Foulkes et al. found that only a small percentage of people with this syndrome (approximately 5%) get this tumor type [34].

The median interval from symptom onset to diagnosis is 73 days (the range being 1–1825 days). A similar retrospective single institutional 7-year study (2009–2016) reported a median interval of 45 days (the range being 0–1673 days) [35]. Another literature reported a mean duration of 133 days (around 4.5 months), while in this study it was 189 days [19].

The most frequent pre-diagnostic clinical presentation in the present study was vomiting (52.00%), followed by headache (51.20%), gait abnormality (24.10%), vision disturbances (23.30%), limb weakness (20.90%), seizure (16.50%), and others. This is consistent with the meta-analysis based on the findings from 74 papers ($n = 4171$) reviewed and reported by Wilne et al. [36]. Similar results were reported by Yang et al. [6].

Tumor location was infratentorial in 62.20%, supratentorial in 33.50%, and spinal in 4.40% of the patients. A study on 633 pediatric cases reported an even distribution among infratentorial and supratentorial tumors, but a similar percentage of spinal tumors (5.00%) [20]. Another study on 115 cases reported a slightly higher incidence of infratentorial tumors (53.00%) than supratentorial tumors (47.00%) [37]. Infratentorial tumors were predominantly higher in this study, which is consistent with prior research in and outside India [19, 38]. However, series from various literatures demonstrated that the supratentorial compartment is the predominant site. A study conducted in China found that the CNS tumors are located predominantly in the supratentorial area, while a smaller proportion are located in the infratentorial area (with the ratio of supratentorial tumors to infratentorial tumors being 1.71:1) [39]. Other Indian studies reported supratentorial tumor location as the predominant site [17, 25, 40]. The difference in tumor location observed in this study may be due to the presence of a dedicated pediatric neurosurgery unit in this hospital, which could have led to referral bias.

Based on the location, infratentorial tumors were commonly located in the posterior fossa (35.50%), cerebellum (16.00%), vermis (1.90%), thalamus (11.50%), hypothalamus (1.30%), tectum (1.30%), intrinsic-brainstem (26.90%), and exophytic-brainstem (5.70%) regions, whereas supratentorial tumors were

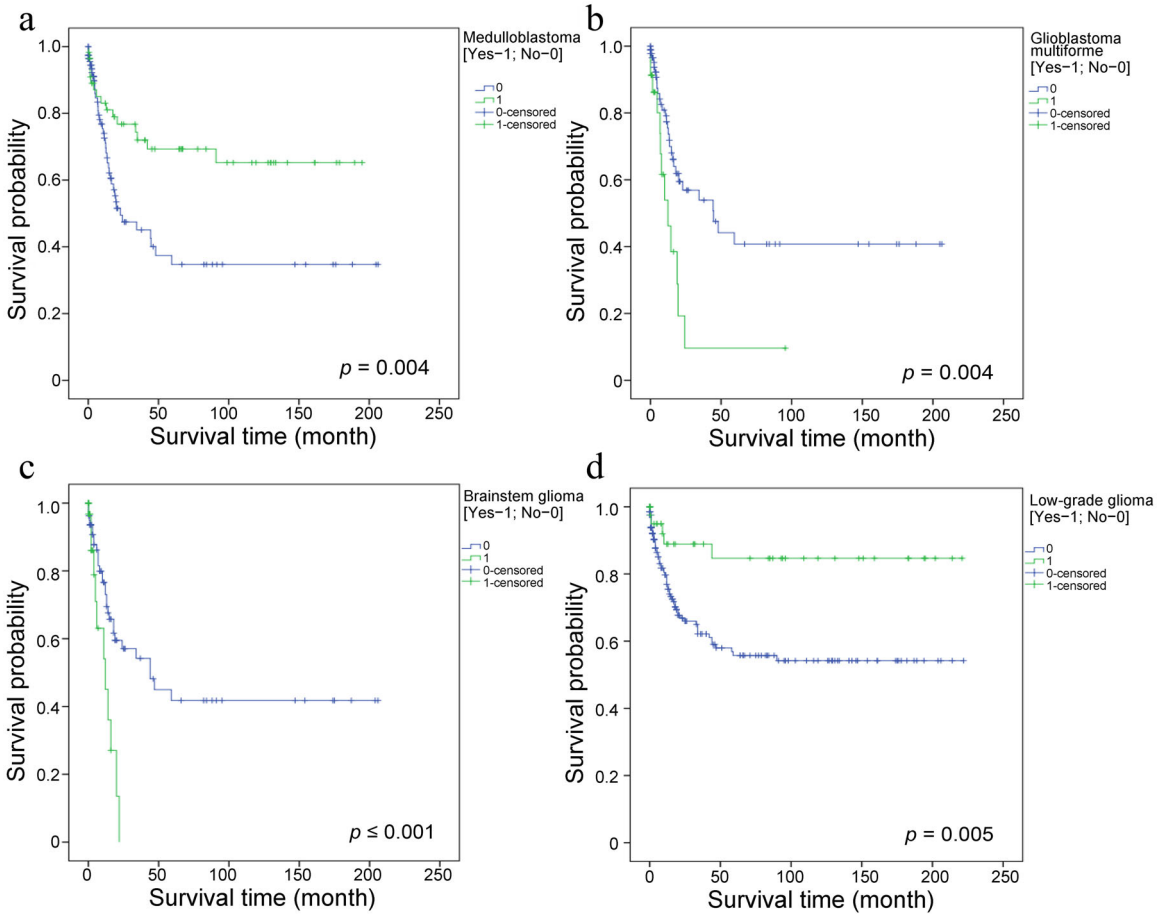

FIGURE 5 (a) Comparison of overall survival between medulloblastoma and other high-grade tumors. (b) Comparison of glioblastoma multiforme with other high-grade tumors while excluding medulloblastoma. (c) Overall survival comparison between brainstem glioma and other pediatric brain tumors. (d) Overall survival comparison between low-grade glioma and other pediatric brain tumors.

commonly located in the lobes of the cerebral hemispheres (67.80%), the sellar and suprasellar regions (11.90%), third ventricle (8.30%), choroid plexus (3.50%), pineal region (2.30%), the optic pathways (1.10%), and others. These results were consistent with the studies from Morocco [20] and Africa [41]. Totally, 72.00% of the spinal tumors were located in the intramedullary region, whereas 9.00% of the tumors were located in the cauda conus medullaris, intradural, and extradural spinal regions, respectively.

The most prevalent brain tumors in this study were medulloblastoma (22.70%), LGG (17.70%), brainstem glioma (14.50%), GBM (9.27%), anaplastic astrocytoma (7.60%), and others. However, a multi-institutional study conducted in India by Jain et al. reported astrocytoma group of tumors as the commonest brain tumors among children, followed by medulloblastomas [42]. The findings of the current study indicate that medulloblastoma is the most common PBT, followed by astrocytoma and brainstem gliomas. This corresponds well with other Indian literatures [37, 40, 43] as well as Moroccan studies [20, 44]. Histopathological distribution also varied according to age groups, as shown in Table 4. Similar findings were reported by another Indian study [38].

Pathological distribution was different within various brain areas. Medulloblastoma was predominantly located in the posterior fossa, including the fourth ventricle ($n = 54$). Similarly, Harmouch et al. reported a higher number of medulloblastomas in their cohort ($n = 145$; 22.90%), all of which were found in the posterior fossa [20]. The majority of the low-grade astrocytoma tumors were found in the cerebrum ($n = 12$), thalamus ($n = 5$), and spinal cord ($n = 4$). Anaplastic astrocytomas were commonly situated in the cerebrum ($n = 7$), thalamus ($n = 6$), and brainstem ($n = 4$). GBM tumors were commonly present in the cerebrum ($n = 9$) and thalamus ($n = 4$). The majority of ependymoma tumors were present in the fourth ventricle ($n = 7$) and posterior fossa ($n = 6$). Pilocytic astrocytomas were commonly located in the suprasellar regions ($n = 2$) and cerebellum ($n = 1$). A study conducted in China on 484 patients reported a similar anatomical distribution [6].

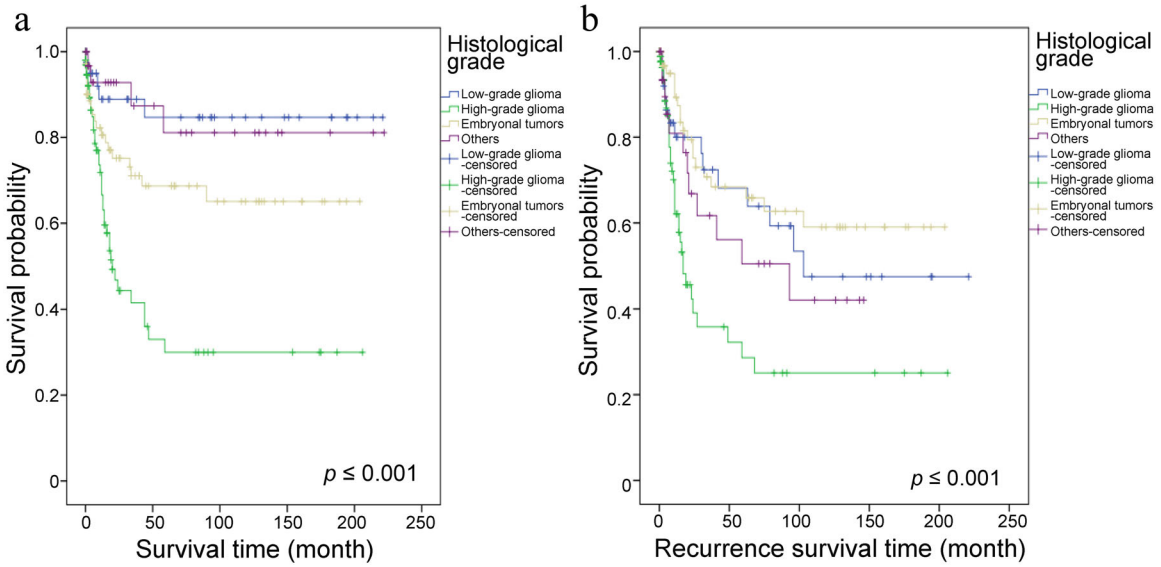

FIGURE 6 (a) Comparison of overall survival between low-grade, high-grade embryonal tumors, and others. (b) Comparison of recurrence-free survival between low-grade, high-grade embryonal tumors, and others.

TABLE 4 The first, second, and third most common histopathological distribution by age group at the occurrence.

Age group (years)	The most common histology	The second and third most common histology
< 1	Medulloblastomas	GBM, ATRT (equal frequencies)
1–9	Medulloblastomas	Brainstem glioma, ependymal tumors
10–14	Medulloblastomas	Astrocytic tumors, low-grade glioma
15–19	Astrocytic tumors	Medulloblastomas, low-grade glioma

In this study, to the extent of initial surgical resection, GTR, STR, NTR, and biopsy alone were achieved in 35.00%, 21.10%, 13.50%, and 11.50% of patients, respectively. Similarly, a Serbian study reported a higher rate of GTR in 40.50% of their patients [19]. Another multi-institutional study reported GTR in 64.00% of cases, which included low-grade tumors [45]. Other literatures from Portugal (63.00%), Nepal (62.90%), and other countries reported higher rates of GTR [21, 46].

Based on histological grading, tumors were classified into four categories: Grade I, II, III, and IV, whereas germ cell tumors ($n = 7$) were excluded as grading cannot be determined. The high-grade (III and IV) tumors ($n = 174$; 71.30%) were comparatively more common in the current study than the low-grade (I and II) tumors ($n = 70$; 28.70%).

In this study, the mean survival time was 141 months. Comparable OS rates were reported from other centers in and outside India [19, 23, 40]. Extended survival was seen in patients who underwent GTR than those with a lesser degree of resection [19]. The complete tumoral resection provides a better outcome; however, this is not feasible in all cases due to the infiltrating nature of brainstem gliomas and other deep-seated lesions.

In this study, the comparison of OS was made among medulloblastoma and other tumors, whereas medulloblastoma showed higher survival than other ETs and HGGs. While comparing GBM with the rest of the high-grade tumors (medulloblastoma excluded), a significantly poorer survival outcome was detected. Brainstem gliomas showed poor survival outcomes among all other tumors. This corresponds with the widely known fact that deep-seated or disseminated tumors have poor outcomes. The strengths of the study lie in the long follow-up period and the uniform treatment protocol. However, this study is limited by its retrospective nature, missing data, and a small sample size. Subset analysis was not feasible in individual histology due to the small number of subsets. This, in turn, affects our ability to prognosticate individual disease subtypes and detail their outcomes based on subgroup analysis, which limits the overall generalizability of this data.

CONCLUSION

In conclusion, ETs have a better prognosis than glial tumors. Early diagnosis and better surgical techniques pave the way for an adequate outcome among children with CNS tumors. The extent of the surgical resection has a favorable outcome with improved OS. Localized residual disease following surgery and disseminated disease have a significant detrimental effect on OS. Medulloblastoma is a chemosensitive tumor that responds well to a multimodal approach and has the most benefit from systemic treatment. GBM has a poorer OS rate. Brainstem gliomas, however, exhibit an exceptionally poor prognosis.

WHAT THIS STUDY ADDS?

This study provides crucial real-world data on pediatric brain tumors in the Indian context, a previously underrepresented area; offers comprehensive information on demographics, clinical characteristics, and histological features of PBTs in Indian children; identifies key factors affecting survival; reveals the impact of tumor type, surgical resection, and treatment modalities on survival outcomes; highlights the effectiveness of multimodal treatment, especially for medulloblastoma, and underscores the need for improved therapies for glial tumors; provides a foundation for further studies to explore specific tumor subtypes, genetic factors, and novel treatment approaches in pediatric brain tumors.

AUTHOR CONTRIBUTIONS

Conceptualization: Wesley M. Jose. Data curation, design: Priyadharshini Veeralakshmanan. Formal analysis and interpretation of results: Wesley M. Jose, Priyadharshini Veeralakshmanan, and Renjitha Bhaskaran. Manuscript preparation: Priyadharshini Veeralakshmanan and Wesley M. Jose. Manuscript editing and review: All co-authors. Final validation: Wesley M. Jose. All the authors reviewed the results and approved the final version of the manuscript.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to privacy/ethical restrictions, the data require a request for access.

ETHICS STATEMENT

This study was approved by the Amrita Institute of Medical Sciences and Research Institutional Ethics Committee (ECASM-AIMS-2023-289).

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