Child's Nervous System (2019) 35:2347–2353
https://doi.org/10.1007/s00381-019-04260-7

ORIGINAL ARTICLE

Intracranial tumors in children: a 10-year review from a single tertiary health-care center

Quratulain Riaz[1] · Ehsun Naeem[2] · Zehra Fadoo[1] · Mahadev Lohano[3] · Naureen Mushtaq[1]

Received: 8 February 2019 / Accepted: 10 June 2019 / Published online: 2 July 2019

Abstract

Objective Brain tumors are the second most common pediatric malignancy and the most common cause of cancer-related mortality and morbidities. Major advances in terms of surgery, radiation, and chemotherapy have led to better outcomes in developed countries. Delayed diagnosis, advanced disease at presentation, late referrals, nosocomial infections, delays to radiotherapy, and poor support services are the major reasons for poorer outcomes in developing countries. Little is known about the profile of brain tumors in Pakistan. This study aims to evaluate the epidemiology, management, and clinical outcomes of children with brain tumors in Pakistan in a single tertiary care center.

Methods/materials All children (0–16 years) with primary CNS tumors from 2004 to 2014 at Aga Khan University Hospital were reviewed retrospectively for clinical data, demographics, radiological findings, management, and outcome.

Results One hundred seventy-five children were included in the study. Male to female ratio was 1.4:1. Most of the patients were in 5–10 years age group (38.9%). Most common presenting complains were headache 115 (65.7%) and vomiting 100 (57.1%). Predominant site was infratentorial 93 (53%). Glial tumors were 105 (60%) followed by embryonal 40(22.9%), craniopharyngiomas 25 (14.3%), and germ cell 1 (0.6%). Astrocytomas (25.7%) were the most common glial tumors while medulloblastoma (15.4%) was the most common embryonal tumor. Majority of the patients underwent surgical resection (78.8%). Radiation was given to 47 (26.8%) patients. A half of the patients, 89 (50%), were lost to follow-up. Forty-two (24%) patients expired, 20 (11.4%) are alive with residual disease while 15 patients (8.5%) were cured with no evidence of recurrence and regular follow-ups.

Conclusion This is the only study from Pakistan showing demographics of the childhood brain tumors. Significant improvement needs to be made for timely diagnosis, early referrals, and collaborated team efforts with multidisciplinary tumor board to improve outcome.

Keywords Childhood · Brain tumor · Surgery · Outcome · Lost to follow-up · Developing country

✉ Quratulain Riaz
Quratulain.riaz10@gmail.com

Ehsun Naeem
Ehsnnaeem@gmail.com

Zehra Fadoo
Zehra.fadoo@aku.edu

Mahadev Lohano
mlohano76@gmail.com

Naureen Mushtaq
Naureen.mushtaq@aku.edu

[1] Department of Oncology, Aga Khan University, Karachi, Stadium Road, PO Box 3500, Karachi 74800, Pakistan

[2] Department of Medicine, Aga Khan University, Karachi, Stadium Road, PO Box 3500, Karachi 74800, Pakistan

[3] Specialist Pediatric Haematology/Oncology, Sultan Qaboos University Hospital, Muscat, Oman

Introduction

Brain tumors are the most common solid neoplasm and leading cause of malignancy-related death in children. Central nervous system (CNS) malignancies represent approximately 15–20% of all childhood malignancies [2, 15, 18, 19]. Approximately 30,000–40,000 new cases are diagnosed worldwide each year [9]. Children with brain tumors do not have as favorable outcome as non-CNS malignancies nor has their survival dramatically improved in the recent decades, as we did see with other types of malignancies. Nearly 88% of the world's children live in developing countries and 80 to 90% of the 250,000 new cases of pediatric cancer each year are diagnosed in a lower and middle income countries

(LMIC). In general, pediatric oncology represents a substantial challenge for developing nations due to inadequate access to pediatric oncologists, a shortage of trained experts in pediatric cancer histology and imaging, scarcity of dedicated pediatric cancer units, and inadequate diagnostic and imaging techniques. There is also shortage of antineoplastic medications and limitations in supportive care combined with lack of facilities for specific treatments such as high-dose chemotherapy and major financial constraints.

Childhood brain tumors in particular, depends on large teams of highly specialized individuals, including neuro-oncologists, neurosurgeons, neurologists, radiologists, radiation oncologists, pathologists, palliative care specialists, oncology nurses, physical therapists, occupational therapists, speech therapists, pediatric intensivists and social workers to establish the correct diagnosis, deliver appropriate and effective treatments, and maximize patient outcomes.

Even though there is a lot of data published from West about the epidemiology of brain tumors in children but there are only few reports available from LMIC [3, 8, 14, 20]. In Pakistan, the lack of comprehensive national cancer registry, we mainly depend on our hospital based registry for evaluating the incidence of children with brain tumors.

This study aims to describe the clinical profile and outcome of primary brain tumors in children at a single tertiary center in Pakistan.

Materials and methods

This is a retrospective observational study. It was conducted at Aga Khan University Hospital and institutional ethics committee approval was obtained. The charts were reviewed of all patients aged between 0 and 16 years, admitted with the diagnosis of primary CNS tumors, between January 2004 and December 2014. The topographic codes of all registered patients during this time frame were thoroughly upgraded. All codes for CNS tumors were reported including C71.0–C71.9 (brain), C70.0–C70.9 (meninges), and C72.0–C72.9 (spinal cord, cauda equine, cranial nerves, and undetermined parts of CNS) with the exclusion of metastatic lesions. The details of patients were recruited from the medical record regarding the age, gender, presenting complaints, site, histological classification, management including type and duration of chemotherapy, and outcome were recorded.

Statistics

Data recorded from patients charts included age at the time of presentation, gender, histological diagnosis, and tumor locations. Categorical data were described in terms of frequencies and percentages. It was analyzed by using SPSS (statistical package for social science for window version 19.0). Tables and charts were created on SPSS version 19 and Microsoft Excel version 2010. Data will be presented as mean ± standard deviation for quantitative variables and frequency (percentage) for qualitative variables. Difference in mean will be assessed by using sample *t* test. *P* value less than 0.05 will be considered as statistically significant.

Results

A total of 175 children were admitted in our institute from emergency department and outpatient clinics. There is slight male preponderance with male to female ratio of 1.4:1. There were 102 (58.3%) males and 73 (41.7%) females. We have

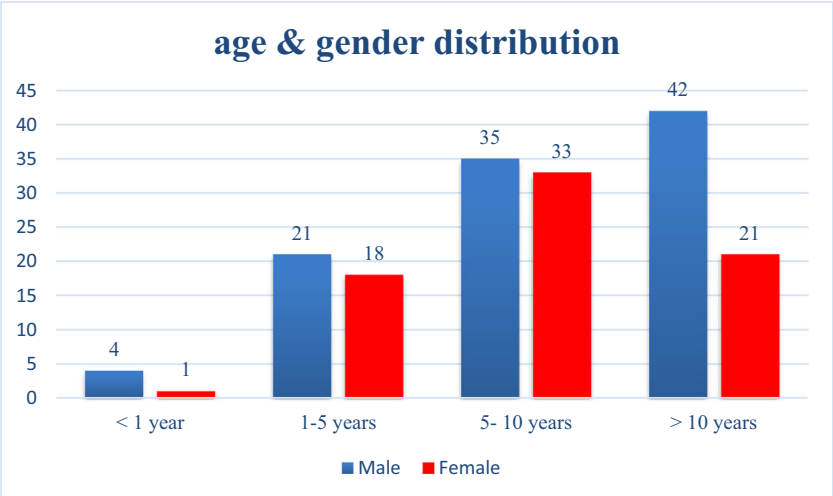

Table 1 Presenting Complains in Children with Primary CNS Tumors

Presenting Complains	
Symptoms	n (%)
Headache	115 (65.7)
Vomiting	100 (57.1)
Visual changes	59 (33.7)
Cranial nerve palsies	50 (28.6)
Cerebellar signs	49 (28)
Drowsiness	48 (27.4)
Seizures	44 (25.1)
Weakness	38 (21.7)

subdivided our patients in four age subgroups 1, less than 1; 2, between 1 and 5 years; 3, between 5 and 10 years; and 4, between 10 and 16 years. Most common age at presentation was between 5 and 10 years with a mean of 8 years. A total of 68 patients (38.9%) included in this category followed by 63 (36%) children between 10 and 16 years of age, 39 (22.3%) children fell in 1–5 years' age group and only 5 (2.9%) children were less than 1 year of age as shown in Fig. 1. Among the most common symptoms we came across in our institute were headache 115 (65.7%) and vomiting 100 (57.1%) followed by visual disturbances 59 (33.7%) and cranial nerves palsies in 50 (28.6%) patients as shown in Table 1. Majority of the patients (68.6%) presented within 6 months of symptoms but the time duration between the appearance of symptoms and presentation to a tertiary care facility was prolonged with mean interval of 4–9 months as we only have few tertiary care centers dealing with brain tumors in Pakistan and scarcity of knowledge among primary health-care provider. The family history of cancers was found to be present in only 3 (1.7%) patients as per the medical charts of patients although this seems to be misleading as consanguinity is widely prevalent in our part of the world. Ninety-three (53%) of brain lesions were found at the infratentorial area and 82 (46.8%) at supratentorial. Regarding the broad classification of primary CNS tumors, there were 105(60%) glial tumors, followed by embryonal 40 (22.9%), craniopharyngiomas 25 (14.3%), and germ cell tumors 1 (0.6%) as given in Fig. 2. Biopsy was not considered in 22 (12.5%) patients of whom 18 were radiologically proven diffuse intrinsic pontine glioma (DIPG).

The most common histopathological subtypes we have found in our data were astrocytomas, commonest being pilocytic astrocytomas in 34 (19.4%) patients, diffuse astrocytomas 3 (1.7%), anaplastic astrocytomas 1 (0.5%), and glioblastoma multiforme (GBM) 7 (4.6%) as shown in Fig. 3. Ependymomas was diagnosed in 15 (8.5%) while oligodendrogliomas in 13 (7.4%). The most common malignant brain in our study was medulloblastoma in 27 (15.4%) patients followed by CNS PNET in 10 (5.7%) patients as seen in Table 2.

Metastatic workup was not done in 35 (20%) patients. We have only found metastatic disease in 7 (4%) children more common with medulloblastoma. Majority of the patients underwent surgical resection 138 (78.8%) of whom nearly one-third (32.6%) achieved gross total resection while 67% had a subtotal resection. Eleven (6.2%) patients had a biopsy only due to tumor being in the suprasellar or pontine region or the family did not give consent for the surgical resection. Twenty six (14.8%) patients did not undergo any sort of surgical intervention as shown in Figs. 4 and 5. A VP shunt for CSF diversion was needed in 72 (41%) children of whom 47 (63.5%) patients were with posterior fossa tumors (medulloblastoma, low and high grade gliomas, and ependymomas). Radiation was given to 47 (26.8%) patients. Nearly half of the patients 89 (50.8%) were lost to follow-up of whom

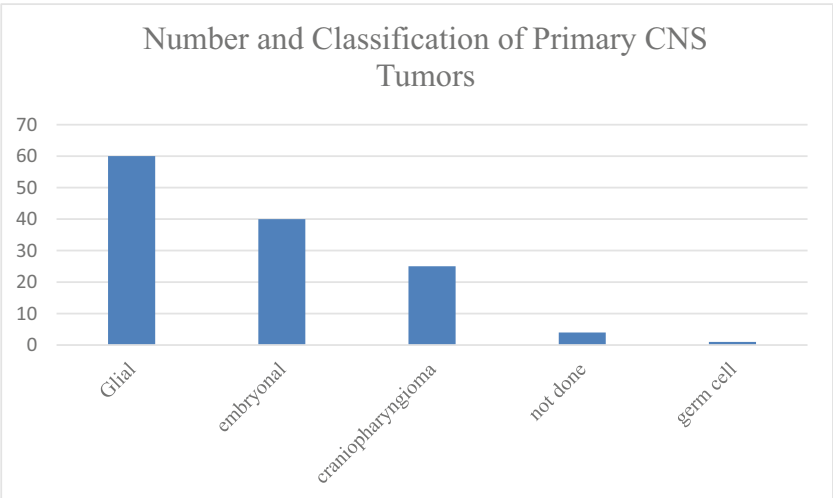

Fig. 2 Number and classification of primary CNS tumors

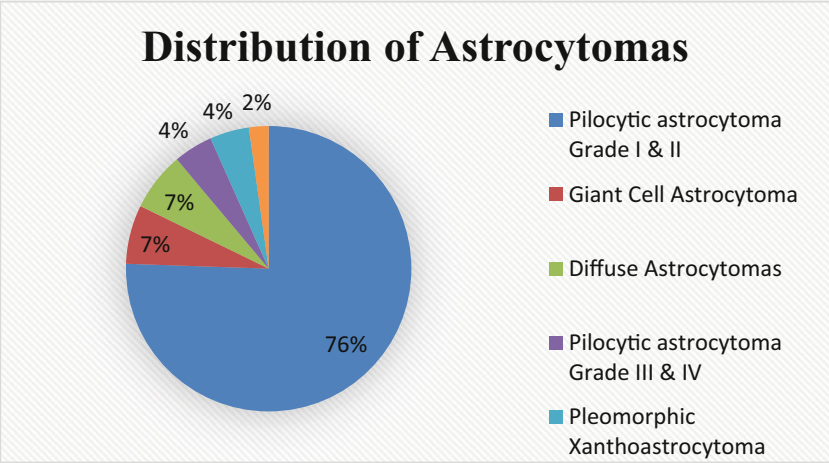

Fig. 3 Distribution of astrocytomas

54% were males. There were 42 (24%) patients who expired as shown in Fig. 6. A majority of the patients (64.6%) had at least one visit to an oncologist during their treatment in our hospital.

Discussion

Childhood primary CNS tumors are a heterogeneous group of neoplasms which differs not only in their specific cell of origin

Table 2 Histological classification of Primary CNS tumors with Age Groups

Histology n (%)	Age Groups			
	< 1 year	1 – 5 years	5 – 10 years	>10 years
Astrocytomas 45 (25.7)	2	15	12	16
DIPG 19 (10.2)	-	2	10	6
Ependymoma 15 (8.5)	3	4	7	1
Oligodendroglioma 13 (7.4)	-	2	4	12
GBM 7 (4)	-	-	4	3
Ganglioglioma 2 (1.1)	-	1	-	1
Nonspecific glial tumors 3 (1.7)	-	-	-	3
Gliosarcoma 1 (0.5)	-	1	-	-
Medulloblastoma 27 (15.4)	-	5	13	9
CNS PNET 10 (5.7)	-	3	3	4
Ependymoblastoma 1 (0.5)	-	-		1-
Pinealoblastoma 1 (0.5)	-	-	1	-
Astroblastoma 1 (0.5)	-	1	-	-
Craniopharyngioma 25 (14.2)	-	3	11	11
Germinoma 1 (0.5)	-	-	-	1
Not done 4 (2.8)	-	2	3	-

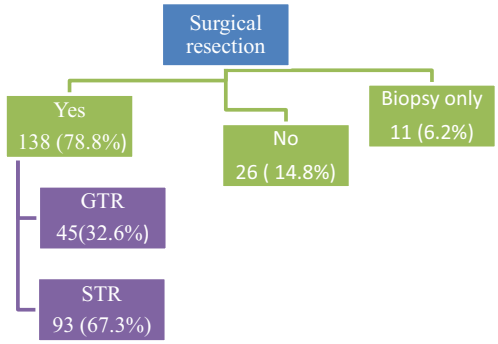

Fig. 4 Surgical management of primary CNS tumors, CNS, central nervous system; GTR, gross total resection; STR, subtotal resection

and cellular pathways but also in their diversified clinical features and survival outcome. World has seen significant improvement in the outcome of acute lymphoblastic leukemia but there is no improvement. Our retrospective single center study is the only one in Pakistan with all the histopathological and clinical features of brain tumors in children with the management strategies and survival outcome. There were only few studies encompassing childhood brain tumors and majority of them only revealed basic histopathology; no clinical data has been provided.

The total number of patients in our study was 175 over a period of 10 years which seems to be less in number considering Pakistan a populated developing country and despite of our institute being the only referral center here with multidisciplinary teams for pediatric neuro-oncology including neuro surgery, pediatric neuro-oncology, histopathology, neuro-radiology, physiotherapy, and pediatric neurology under one roof. This depicts relative lack of access to health-care systems in LMIC.

Our study has revealed male predominance with male to female ratio of 1.4:1. This is in accordance with various other studies which have shown similar results [1, 4, 10]. In a study of 81 children with primary brain tumors from tertiary care center in Pakistan, the mean age was 8.8 years with the greatest number of children in 5–9 years age group [10, 11]. In our study also the majority of the children were in 5–10 years age group followed by > 10 years. It is assumed that children more than 5 years age group are more able to complain of their headache, visual complains or endocrinopathies like increased thirst or urination. This is also supported by studies from Seoul, Spain, and Canada [5, 6, 13]. In our cohort of patients headache (65.7%) was the most common presenting complain followed by vomiting (57.1%), visual changes (33.7%), and cerebellar signs (28%). The other common presenting symptoms of brain tumors like personality change and symptoms of endocrinopathies like polyurea, polydispsia, and weight gain were mentioned in only 5 to 12% of patients. This can be due to deficiencies in documentation in patients' records considering this to be a retrospective data. Majority of the patients in our cohort presented within 6 months of experiencing the symptoms. A family history of cancers was present in only 3 (1.7%) patients. One patient had medulloblastoma with family history of breast cancers and genetic testing being positive for Li Fraumeni Syndrome, while 2 patients had clinical stigmata of neurofibromatosis I. Considering this is a retrospective data, documentation deficiencies are considered an intrinsic bias in three such studies. Awareness of genetic predisposition syndromes among oncologists will lead to more thorough probing of family history of malignancies and testing for germline genetic mutations. This can be done through collaboration between the oncology centers of the developing countries with the developed centers. The tumor site classification showed slightly higher frequency of infratentorial tumors making 52% and

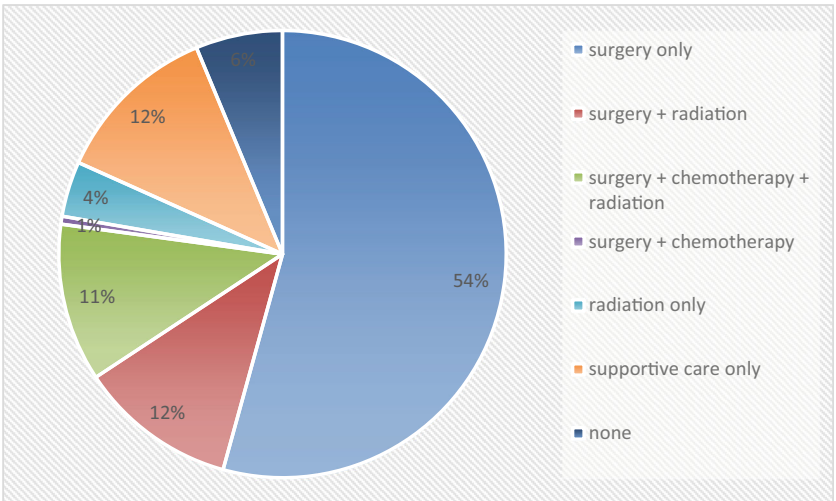

Fig. 5 Management of children with primary CNS tumors

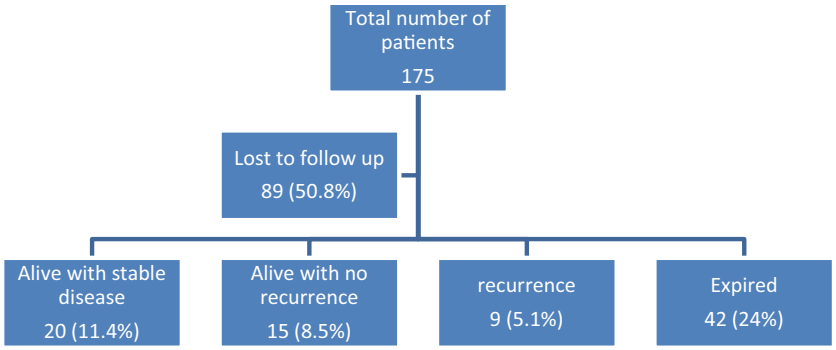

Fig. 6 Outcome of primary CNS tumors

supratentorial tumors present in 48% patients. These findings are in line with various other studies [12].

Regarding morphological classification of the tumors, the most common tumors were glial tumors (53%), including both low- and high-grade gliomas collectively representing half of the tumors. This is in accordance with previously published data which shows that pilocytic astrocytomas are the most common childhood brain tumor representing approximately 17% of all CNS tumors in children less than 14 years [16]. This is followed by low- and high-grade ependymomas and oligodendroglioma. This again is in accordance with international data where ependymomas represent 5–10% of intracranial neoplasms [12]. Fifteen patients in our cohort were diagnosed as DIPG based on their classic radiological findings. All of them were treated with supportive care only and now of them survived. Medulloblastomas are the most common embryonal tumors and our study had similar findings. A study done in Iran showed that medulloblastoma to be the second most common brain tumor and was found in 18.4% of all children. Only one patient was diagnosed to have primary germ cell tumor while one patient had non-specific histopathological findings.

A major point of concern is that a metastatic workup was needed in around 30% of patients but not done for reasons not known. Regarding the management, majority of the patients underwent some sort of intervention including surgery, radiation, chemotherapy, or a combination of all of them. Around 34% of the patients had achieved subtotal resection. The clinical outcome of majority of the brain tumors is dependent mainly on safe surgical resection of the tumors.

We could see in our study that nearly half of our patients were lost to follow-up. This is in accordance with data from other resource limited settings where rate of treatment abandonment is very high irrespective of the type of malignancy [7, 17]. We need to strengthen the follow-up practices as this has a strong impact on overall treatment failure, mortality, and poor prognosis. The major reason for abandonment is assumed to be poor socioeconomical support, unavailability of lodging for patients who are coming from the far flung areas, fear of neurosurgery and radiation. Lack of coordination between the various teams involved in management of children with brain tumors is also one the major factor for abandonment. The main limitation of our study is the retrospective nature of our study with many deficiencies in the documentation. We strongly feel that such single center institution–based studies can contribute strongly to the better understanding and management plan of brain tumors in developing countries.

In conclusion, this study depicted that childhood primary brain tumors presented in our institute has consistent frequency and demographic (age, gender, and histopathology) with those reported by most of the studies done in developed and Middle Eastern countries. We assume that a majority of children with brain tumors go unrecognized in our country due to lack of access and availability of trained centers. The data warrants for more prospective and multi-institutional epidemiological studies in children with brain tumors.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Ahmed N, Bhurgri Y, Sadiq S, Shakoor KA (2003) Pediatric brain tumours at a tertiary care hospital in Karachi. Asian Pac J Cancer Prev 8:399
2. Baldwin RT, Preston-Martin S (2004) Epidemiology of brain tumors in childhood—a review. Toxicol Appl Pharmacol 199:118–131
3. Bleyer WA (1999) Epidemiologic impact of children with brain tumors. Childs Nerv Syst 15:758–763
4. Brown S, Belgaumi A, Ajarim D, Kofide A, Al Saad R, Sabbah R et al (2004) Loss to follow-up of patients with malignant lymphoma. Eur J Cancer Care (Engl) 13:180–184

5. Cho KT, Wang KC, Kim SK, Shin SH, Chi JG, Cho BK (2002) Pediatric brain tumors: statistics of SNUH, Korea (1959–2000). Childs Nerv Syst 18:30–37
6. El-Gaidi MA (2011) Descriptive epidemiology of pediatric intracranial neoplasms in Egypt. J Neurosurg Pediatr 47:385–395
7. Ferlay J, Heanue M, Boyle P (2007) Cancer incidence in five continents, Volume IX. IARC Scientific Publications
8. Horner M, Ries L, Krapcho M, Neyman N, Aminou R, Howlader N, et al (2009) SEER cancer statistics review, 1975-2006, National Cancer Institute. Bethesda, MD
9. Kadri H, Mawla AA, Murad L (2005) Incidence of childhood brain tumors in Syria (1993–2002). J Neurosurg Pediatr 41:173–177
10. Keene DL, Hsu E, Ventureyra E (1999) Brain tumors in childhood and adolescence. Pediatr Neurol 20:198–203
11. Luo XQ, Ke ZY, Huang LB, Guan XQ, Zhang YC, Zhang XL (2009) High-risk childhood acute lymphoblastic leukemia in China: factors influencing the treatment and outcome. Pediatr Blood Cancer 52:191–195
12. Magnani C, Aareleid T, Viscomi S, Pastore G, Berrino F, Group EW (2001) Variation in survival of children with central nervous system (CNS) malignancies diagnosed in Europe between 1978 and 1992: the EUROCARE study. Eur J Cancer Care (Engl) 37:711–721
13. Memon F, Rathi SL, Memon MH (2007) Pattern of solid paediatric malignant neoplasm at LUMHS, Jamshoro, Pakistan. J Ayub Med Coll Abbottabad 19:55–57
14. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y et al (2013) CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. J Neuro-Oncol 15:ii1–ii56
15. Parkin D, Kramarova E, Draper G, Masuyer E, Michaelis J, Neglia J, et al (1998) International incidence of childhood cancer, Volume II. IARC Scientific Publications
16. Peris-Bonet R, Martínez-García C, Lacour B, Petrovich S, Giner-Ripoll B, Navajas A, Steliarova-Foucher E (2006) Childhood central nervous system tumours–incidence and survival in Europe (1978–1997): report from automated childhood cancer information system project. Eur J Cancer Care (Engl) 42:2064–2080
17. Madhavan R, Kannabiran B, Nithya A, Kani J, Balasubramaniam P, Shanmugakumar S (2016) Pediatric brain tumors: an analysis of 5 years of data from a tertiary cancer care center, India. Indian J Cancer 53:562–565
18. Suresh SG, Srinivasan A, Scott JX, Rao SM, Chidambaram B, Chandrasekar S (2017) Profile and outcome of pediatric brain tumors–experience from a tertiary care pediatric oncology unit in South India. Eur J Paediatr Neurol 12:237
19. Bellil S, Limaiem F, Mahfoudhi H, Bellil K, Chelly I, Mekni A et al (2008) Descriptive epidemiology of childhood central nervous system tumours in Tunisia. J Neurosurg Pediatr 44:382–387
20. Ezzat S, Kamal M, El-Khateeb N, El-Beltagy M, Taha H, Refaat A et al (2016) Pediatric brain tumors in a low/middle income country: does it differ from that indeveloped world? J Neuro-Oncol 126: 371–376