



# Patterns, treatments, and outcomes of pediatric central nervous system tumors in Sudan: a single institution experience

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Received: 9 October 2018 / Accepted: 17 December 2018 / Published online: 4 January 2019  
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## Abstract

**Purpose** Studies of epidemiology, treatment modalities, and outcomes of childhood central nervous system (CNS) tumors in Sudan are scarce. To address this shortcoming, we evaluated baseline information about the epidemiology, treatment types, and outcomes of childhood CNS tumors at the National Cancer Institute, University of Gezira (NCI-UG) in Wad Madani, Sudan.

**Methods** We performed a retrospective health facility-based study of children with CNS tumors who were treated at the NCI-UG from January 2000 to December 2015.

**Results** A total of 62 (5.4% of all childhood cancers) pediatric patients with CNS tumors were identified over the study period. Tumors were more common among male children and involved the infratentorial compartment in 58% of cases. The median age at diagnosis was 9 years (range, 2–14 years). Approximately 60% ( $n = 37$ ) of the study population had histology-determined diagnoses. Astrocytomas and medulloblastomas were the most common tumors in these cases. The mean time to diagnosis was 6 months (SD, 9). During the study period, the number of children with CNS tumors who were referred for treatment at the NCI-UG increased every year. Of the 37 patients who received surgical interventions, 8 received gross total resections, 20 received partial resections, and 24 received postoperative radiotherapy. The treatment abandonment rate was 11%. The 2-year and 5-year survival rates were 33% and 13%, respectively.

**Conclusion** Our findings reveal a high incidence of poor outcomes for patients with CNS tumors in Sudan, which is most likely due to many distinct factors.

**Keywords** Brain tumors · Child · Epidemiology · Survival · Sub-Saharan Africa · Sudan

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**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s00381-018-04032-9>) contains supplementary material, which is available to authorized users.

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## Introduction

Worldwide, approximately 30,000 to 40,000 new cases of primary central nervous system (CNS) tumors are diagnosed each year [1]. The international age-standardized incidence rate of CNS tumors is 28.2 per million person-years in children aged 0 to 14 years [2]. Considerable variation is prevalent in the reported incidence rates among different regions and countries [3, 4]. In high-income countries (HICs), primary CNS tumors are the most common solid neoplasms in children and typically account for 20 to 25% of all childhood cancers [5, 6]. In low- and middle-income countries (LMICs), CNS tumors are rarely reported and are generally outnumbered by leukemias and lymphomas [5]. In sub-Saharan Africa, the incidence rate of CNS tumors is quite variable but generally very low, rarely exceeding 15 per million [7]. At the National Cancer Institute-University of Gezira (NCI-UG) in Wad Madani, Sudan, primary CNS tumors are the fifth most

frequent cancer among children [8]. Relatively poor access to neuroimaging and neurosurgical facilities, resulting in missed diagnoses in children with headaches, seizures, and altered levels of consciousness, may contribute to the low incidence rates of CNS tumor diagnoses in LMICs [9, 10].

Survival and cure rates for childhood CNS tumors in HICs have greatly improved over the past decades but remain poor in many LMICs. In Sudan, like that of most of LMICs, treatment of children with CNS tumors is restricted by the availability of adequate healthcare infrastructures. Little information of the epidemiology and treatment outcomes of pediatric CNS tumors is available for Sudan [11, 12]. To address this shortcoming, we describe the epidemiology, clinical presentations, survival rates, and modalities of treatment for pediatric patients with CNS tumors who were treated at the NCI-UG in central Sudan, as an example of a limited-resource African setting. We also compare our findings with those previously reported by others.

## Materials and methods

### Setting

The population of Sudan is approximately 40 million, and children comprise 40% of the total population. Children with cancer are treated either at Khartoum Oncology Hospital (KOH) in the Sudanese capital Khartoum or at the NCI-UG in Wad Madani, which are the only two centers in Sudan that offer cancer treatment for children. Referral to one of these centers after cancer diagnosis depends on the proximity the center to the patient's residence or family choice. The annual number of new cancer cases referred to KOH and the NCI-UG ranges between 8000 to 8500 and 2000 to 2300, respectively. Childhood cancers represent 4.5% and 5.4% of the total cases referred to KOH and NCI-UG, respectively.

The NCI-UG, located in the central Sudanese state of Gezira, was established in 1989 in the Gezira capital Wad Madani. The NCI-UG began treating patients with cancer in 1999. The cancer treatment modalities available at the NCI-UG include radiotherapy (RT), chemotherapy, and palliative care. For RT, two cobalt-60 RT machines are available. A complete clinical workup generally consists of an ultrasound, X-rays, blood tests, bone marrow examination, tumor marker analysis, and nuclear imaging. Neurosurgical operations are performed by two neurosurgeons at the Gezira Center for neurosurgery, which is also located in Wad Madani. Computed tomography (CT) is available there and at the Gezira Diagnostic Center, both of which are governmental institutions. In the state of Gezira, only one magnetic resonance imaging (MRI) scanner is available, and it is located in a private hospital. The National Health Insurance Program covers the cost of MRIs. For uninsured patients, charges for

medical MRIs matter greatly. The Sudanese Zakat Chamber and charity organizations, such as The Friends of Cancer Patients Society cover MRI and other investigational expenses for poor patients.

Histopathologic and cytopathologic studies are provided by the University of Gezira Medical Laboratory Center. In Sudan, chemotherapy and RT are free of charge to Sudanese citizens at government institutions. No local protocols are in place at the NCI-UG for the management of CNS tumors in children. Pediatric and radiation oncologists make treatment decisions based on international guidelines, such as the treatment practice guidelines published by the Pediatric Oncology in Developing Countries Committee of the International Society of Pediatric Oncology (PODC-SIOP).

### Study design

We performed a retrospective study of data extracted from the medical records of all children younger than 15 years with CNS tumors that were diagnosed on the basis of imaging and/or histologic confirmation and who were treated in the Oncology department at the NCI-UG between January 2000 and December 2015. The data extracted included demographics, clinical presentation, pathology reports, radiology reports, treatment modalities, and outcomes. Only cases with complete data were included in the study. Four patients with CNS tumors were excluded because of incomplete data. Exclusion criteria included cases of brain metastases and brain tumors as a second cancer.

### Statistical analysis

We analyzed statistical data as frequencies and percentages for categorical variables or as both mean  $\pm$  SD and median (range) for continuous variables.

### Ethical considerations

Ethical approval for this retrospective study was obtained from the ethical committee at the NCI-UG.

## Results

### Treatment modalities at NCI-UG in Wad Madani, Sudan

Surgical resection without severe morbidity is the primary treatment of choice for surgically accessible tumors. Immediate postoperative MRI for assessment of the extent of resection was not performed for any cases. Of the 37 patients who received surgical interventions, only 8 received gross total resection of their tumors, 20 received partial

resections, and 5 received only biopsies. In four cases, the extent of surgery was missing from their medical charts.

Although the minimum requirement for RT for CNS tumors is conformal RT, in which a CT-based 3D technique is used for treatment planning, all cases during the study period planned for RT treatment with 2D techniques, despite their limitations. For low-grade astrocytomas, RT was reserved for residual tumors that were symptomatic or demonstrated progression in neuroimaging analyses. The RT doses comprised 50.4 Gray (Gy) at 1.8 Gy/fraction with 5 fractions/week. For high-grade astrocytomas, RT was generally administered as adjuvant treatment or an upfront modality for inoperable tumors. Treatment doses comprised 60 Gy at 2 Gy/fraction with 5 fractions/week in 2 phases: an initial phase (treatment of primary tumor and associated edema, 40 Gy in 20 fractions administered over 4 weeks) and a reduced volume phase (treatment of primary tumor + 2-cm margins, 20 Gy in 10 fractions administered over 2 weeks). For medulloblastoma, patients received craniospinal irradiation (CSI) of 30 to 36 Gy, with a boost to the posterior fossa (total dose = 50–55 Gy), and weekly vincristine treatment during RT. For localized ependymoma, patients received 54 Gy at 1.8 Gy/fraction for a total of 30 fractions. For metastatic ependymoma, patients received CSI in the same treatment regimen described for medulloblastoma. For brainstem tumors, patients received either 54 Gy in 30 fractions (1.8 Gy/fraction) or 30 to 36 Gy in 10 to 12 fractions (3 Gy/fraction) as palliation.

For low-grade glioma, chemotherapy was administered for children less than 3 years (frontline therapy) for partially resected tumors in some cases or during disease progression as postradiation therapy. Chemotherapy for these patients consisted of carboplatin and etoposide. For high-grade astrocytoma, children less than 3 years old received carboplatin and etoposide as a neoadjuvant treatment, with the objective of delaying RT. For children older than 3 years, temozolomide was given as an adjuvant therapy.

### Patient characteristics

Of the 1159 pediatric patients with cancer who were registered at the NCI-UG during the study period, 62 (5.4%) had primary CNS tumors. The mean and median ages at diagnosis were 8.83 years (SD, 3.4) and 9 years (range, 2–14 years), respectively. Most patients were male, with a male-to-female ratio of 1.38. The mean age was 8.03 years (SD, 3.45) for boys and 8.42 years (SD, 3.52) for girls. We divided the study population into three age groups (0–4 years, 5–9 years, and 10–14 years). Patient characteristics, including demographics, tumor locations, and types of treatment, are shown in Table 1. The age frequency, sex distribution, and tumors sites among the three age groups are presented in Table 2. The number of children with CNS tumors who were referred for treatment at the NCI-UG increased every year during the study period (Fig. 1).

**Table 1** Demographic data at diagnosis and pattern of treatment

Variable	Number (%)
Age (years)	
0–4	7 (11)
5–9	26 (42)
10–15	29 (47)
Sex	
Male	36 (58)
Female	26 (42)
Residence	
Rural	42 (68)
Urban	20 (32)
Tumor location	
Infratentorial	36 (58)
Supratentorial	21 (34)
Spinal cord	5 (8)
Treatment	
Surgery followed by adjuvant RT	22 (35)
RT alone	14 (23)
Surgery only	13 (21)
No treatment	9 (14)
Surgery followed by CRI	2 (3)
Surgery followed by adjuvant chemotherapy	1 (2)
Chemotherapy alone (palliative)	1 (2)

*CRT* craniospinal irradiation, *RT* radiotherapy

### Tumor characteristics, presenting symptoms, and survival

To determine changes in the incidence of childhood CNS tumors, symptom duration before diagnosis, and availability of neuroimaging and neurosurgical facilities in central Sudan, we categorized these variables according to three specific time periods: 2000–2005, 2006–2010, and 2011–2015 (Table 3). The most common tumor locations in our study population were brainstem (30%), cerebellum (27%), and cerebral hemispheres (19%). Other less commonly found locations included the spinal cord (8%), pituitary gland (6%), pineal body (4%), third ventricle (4%), and thalamus (2%). Thirty-seven (60%) patients with CNS tumors received histology-determined diagnoses, whereas 25 (40%) received diagnoses based on clinical and imaging findings. In the histologically determined diagnosis group, the following tumors were diagnosed: astrocytomas ( $n = 17$ ), medulloblastomas ( $n = 11$ ), ependymomas ( $n = 3$ ), adenomas ( $n = 3$ ), craniopharyngioma ( $n = 1$ ), ganglioma ( $n = 1$ ), and germinoma ( $n = 1$ ). The following tumors were found in the clinical/imaging findings-determined diagnosis group: typical diffuse pontine gliomas ( $n = 18$ ), cerebral tumors ( $n = 2$ ), cerebellar tumors ( $n = 2$ ), pineal body tumor ( $n = 1$ ), hypothalamic tumor ( $n = 1$ ), and spinal cord tumor ( $n = 1$ ).

**Table 2** Distribution of children with CNS tumors according to age groups, place of residence, tumor location, and sex

Sex	Age group (%)			Place of residence (%)		Tumor location (%)		
	<5 years	5–9 years	10–15 years	Rural	Urban	ST	IT	SC
Male	4 (57)	15 (62)	17 (57)	24 (57)	12 (60)	12 (55)	20 (56)	5 (100)
Female	3 (43)	10 (38)	13 (43)	18 (43)	8 (40)	10 (45)	16 (48)	0 (0)
Total	7 (100)	25 (100)	30 (100)	40 (100)	20 (100)	22 (100)	36 (100)	5 (100)

IT infratentorial, SC spinal cord, ST supratentorial

Cranial nerve palsy was the most frequently reported clinical presentation ( $n = 28$ , 45%), followed by headache ( $n = 24$ , 39%), vomiting ( $n = 23$ , 37%), motor weakness ( $n = 18$ , 29%), abnormal gait ( $n = 12$ , 19%), seizures ( $n = 11$ , 18%), and altered level of consciousness ( $n = 9$ , 15%). Among those with headache and/or vomiting, neurologic abnormalities were not present in six patients. Only 11 (18%) patients had a single presenting symptom, and 32 (37%) had three or more signs and symptoms. The mean prediagnostic symptomatic interval (PSI) was 6 months (SD, 9). The median PSI was 2 months (range, 2 weeks to 3 years). In two cases of pituitary adenomas, the history of symptoms was 3 years. The median PSI for children with infratentorial and supratentorial tumors were 2 and 4 months, respectively. Children at least 10 years old had longer PSIs (2.5 months) than did children younger than 10 years (2 months).

The rate of treatment abandonment was 11%. The 2-year and 5-year survival rates were 33% and 13%, respectively. Survival rates varied according to tumor location, sex, place of residence, histopathology, and mode of diagnosis (Tables 4 and 5). Only eight patients were alive and in remission at their last follow-up (Table 6).

### Comparison of findings with those of other African countries

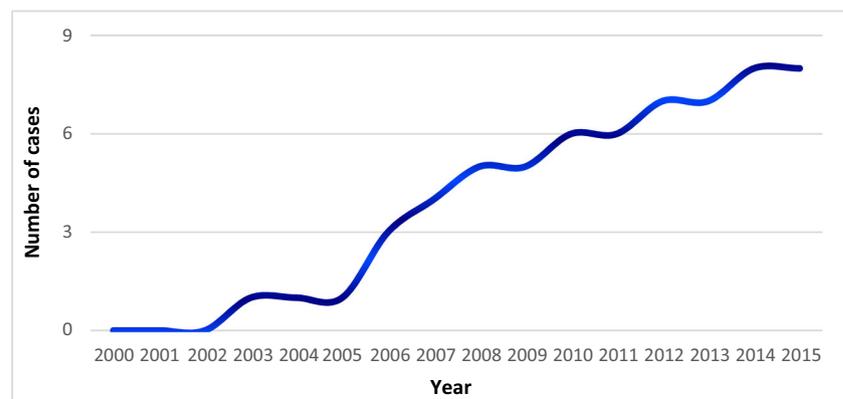
A limited number of studies of childhood CNS tumors have been reported in Sudan [11, 12]. To determine whether our findings are unique to Sudan, we compared our findings with those reported from other African countries (Table 7). The

largest discrepancy between our findings and those of other African countries was the frequency of astrocytomas, as the percentage of patients with astrocytomas was considerably higher at the NCI-UG than in all other African countries. In addition, the ratio of supratentorial to infratentorial tumors was markedly different from our findings in all studies except one relatively recent report from Nigeria.

### Discussion

In accordance with findings from reports of CNS tumors in other countries, including Western and Asian countries, we found that the greatest number of CNS tumors occurs in children aged 5 to 9 years, and the overall male-to-female ratio is approximately 1.3 similar [17, 19, 22–25]. However, some studies, albeit with smaller numbers of patients, have reported a slight female predominance [15, 26]. The anatomic location of pediatric CNS tumors appears to widely vary according to country. A predominant infratentorial location of tumors was reported in such countries as Denmark, South Africa, and Syria, as we also observed in Sudan [14, 27, 28]. Conversely, other studies reported a predominance of supratentorial tumors in Brazil, Uganda, and China [20, 25, 29]. These differences are most likely related to varying inclusion criteria, accuracy of pathologic analyses, and the rate of histologic confirmation of diagnoses among the different countries. We also noted that the number of children with CNS tumors was lower than expected. It is not clear whether these tumors are indeed rare in Sudan or whether their

**Fig. 1** Number of children with central nervous system tumors treated at the National Cancer Institute, University of Gezira in Wad Medani, Sudan during the study period



**Table 3** A time line describes the development in neuroimaging and neurosurgical services in the state of Gezira in central Sudan

Time span	Resources		No. of cases	Median PSI	Mean PSI		
	CT	MRI				Neurosurgeons	Neurosurgical centers
2000–2005	0	0	NA	NA	3	12	8.3
2006–2010	1	1	1	NA	27	2	6.3
2011–2015	2	1	2	Yes	32	2	5.3

CT computed tomography, MRI magnetic resonance imaging, NA not available, PSI presymptomatic interval

diagnoses are overlooked because of a paucity of neuroimaging tools and specialized neurosurgical centers. It is very likely that many children with CNS tumors in Sudan and other LMICs die before diagnosis.

Suspicion of CNS tumors are classically raised by symptoms such as intracranial pressure, focal deficits (including seizures), or papilledema. A meta-analysis of 4171 children with intracranial tumors found that headache (33%), nausea and vomiting (32%), abnormalities of gait and coordination (27%), and papilledema (13%) are the most frequent clinical presentations of childhood CNS tumors [30]. In our study, we found that approximately half of patients presented with cranial nerve palsy, followed by headache, vomiting, and motor weakness. Although fundoscopy is an important examination tool to identify deficits that should prompt imaging studies, none of the patients in our study population received fundoscopy examinations. The strikingly high incidence of brain

stem tumors in our limited-resource setting may be due to the fact that the symptoms associated with brainstem tumors are more obvious and concerning. Therefore, a child with cranial nerve palsy may receive a more thorough investigation than a child with headache would.

We observed that the number of children with CNS tumors who were treated at the NCI-UG increased during the study period. In addition, PSI lengths improved over the course of the study period. These findings most likely reflect improved patient referral patterns as a result of increased availability of neuroimaging and neurosurgical facilities in the region. The time to diagnosis is critical in the effort to provide the best treatment for children with CNS tumors. Several factors affect PSIs, including severity of symptoms, age, tumor grade, and anatomic location. Delays in diagnosis may lead to neurologic, developmental, intellectual, and neuroendocrinologic morbidity [31]. Short PSIs commonly reflect rapid tumor progression and are correlated with high-grade tumors [32]. In our study, we found that the median PSI length was 2 months, which is consistent with other studies [33, 34]. This was a particularly surprising finding because it is similar to the PSIs reported in developed countries [35–38]. We predicted that the many local challenges our cohort experienced would contribute to longer PSIs. However, it is possible that many of the considerably delayed cases did not reach our center. It is also possible that the retrospective nature of our study and a lack of proper documentation of PSIs contributed to the reduced PSI lengths we observed. Because the NCI-UG is a referral cancer center that receives patients after cancer diagnoses, the PSIs recorded during data collection may not reflect precise PSI lengths.

We found that older children generally have longer PSIs than do younger children, and children with infratentorial tumors have shorter PSIs than do those with supratentorial tumors. This is similar to findings reported in a recent study conducted in Morocco [33]. Furthermore, most of our study population lived in rural areas, requiring travel of long distances and great expenses to reach the nearest referral hospital. Many families in Sudan and other LMICs seek medical treatment only during the later stages of disease, when their child experiences pain and disability. Our findings suggest that improved access to neuroimaging and neurosurgical services in

**Table 4** Relation between survival rates, tumor locations, sex, and place of residence

Characteristics	Survival rate (%)	
	2-year	5-year
<b>Location</b>		
Supratentorial	48	10
Infratentorial	20	13
Spinal cord	60	20
<b>Sex</b>		
Male	31	11
Female	35	15
<b>Residence</b>		
Rural	36	12
Urban	25	15
<b>Pathology</b>		
Confirmed	45	20
Not confirmed	12	4
<b>Pathologic subtypes</b>		
Astrocytoma (G1/G2)	37	25
Astrocytoma (G3/4)	25	0
Medulloblastoma	36	9

G1/G2 grade 1/2 tumors, G3/G4 grade 3/4 tumors

**Table 5** Outcomes of patients with central nervous system tumors treated at the National Cancer Institute, University of Gezira in Wad Madani, Sudan

Outcomes	Cases with pathology confirmations (%)	Cases without pathology confirmations (%)	All cases number (%)
Alive	7 (19)	1 (4)	8 (15)
Dead	17 (49)	13 (52)	30 (48)
Abandonment	2 (5)	5 (20)	7 (11)
Lost to follow-up	10 (27)	6 (24)	16 (26)
Total	37 (100)	25 (100)	62 (100)

central Sudan played an important role in reducing PSI lengths of CNS tumors in children.

The various histologic subtypes of CNS tumors occur with various relative frequencies among children. In our study cohort, histopathologic-determined diagnoses were provided for 60% of cases because biopsies were avoided for all children with diffuse brainstem tumors and those with terminal-stage tumors. Because of the paucity of resources and financial constraints in central Sudan, histopathologists depend largely on their skills in morphology to classify tumors on the basis of routine H&E staining of tumor specimens. Among the pathology-confirmed cases, we found that most frequent cases were astrocytoma followed by medulloblastoma. This finding is similar with other published data [19, 20, 27].

Most children in our study, regardless of age and tumor type, received surgery or RT. Only 14% received no specific therapy. Chemotherapy, with or without surgery and/or RT, was administered in 4% of cases. Because of a lack of advanced neurosurgical equipment, such as operating microscopes and the advanced stage of tumors at presentation, only eight patients received complete gross total tumor resections. In addition, RT, when delivered, was planned with 2D-imaging technology, which is limiting. Treatment abandonment is a major challenge facing the care of children with cancer in Sudan. Treatment abandonment is defined as the failure of starting or completing therapy, and it is a major cause of cancer mortality in children in the LMICs [39–41]. In a study by Fredrich et al., treatment abandonment was reported to contribute to a third of the survival gap in the

LMICs compared with that of HICs [41]. Factors contributing to treatment abandonment include tumor type (e.g., retinoblastoma), rural residence, lack of insurance, lack of employment, low parental education, HIV diagnosis, travel burden, and fear [39–41]. We did not specifically investigate the causes of treatment abandonment in our study, but we expect that they are similar to those of other LMICs, especially those in Africa [40, 42, 43].

The overall 5-year survival in our study was 13%, which is considerably lower than that reported in Germany (64%), Italy (68%), Uganda (60%), and Tunisia (45%) [3, 16, 20, 22]. We found that supratentorial tumors were associated with higher 5-year survival rates than were infratentorial tumors. Similar results were reported in a Tunisian study [16]. We also found that low-grade astrocytomas were associated with higher 5-year survival rates than were high-grade astrocytomas and medulloblastoma. An advanced stage of disease at presentation, prevalence of brainstem tumors, lack of a multidisciplinary treatment approaches, and poor access to appropriate operative management are the most likely contributing factors for the poor survival observed in our study population. The PODC-SIOP has generated treatment practice guidelines that provide adapted treatment strategies for the management of pediatric CNS tumors in limited-resource countries [44–46].

The retrospective nature of our study and its reliance on medical records are potential limitations to consider. Moreover, our study was limited to a single institution and included a relatively small patient cohort size, which have introduced selection and measurement biases to our study.

**Table 6** Demographic data, pathology, and treatment of patients alive 5 years or more

Patient no.	Age (years)	Sex	Site	Histopathology	Type of surgery	RT	Survival (months)
1	11	Male	Cerebellum	Pilocytic astrocytoma	GTR	Yes	132
2	5	Female	Cerebellum	Pilocytic astrocytoma	GTR	No	108
3	9	Male	Cerebral	Grade II astrocytoma	STR	No	144
4	10	Male	Spinal cord	Grade I meningioma	STR	Yes	65
5	14	Female	Pituitary	Adenoma	GTR	No	70
6	14	Female	Cerebellum	Medulloblastoma	GTR	Yes	76
7	10	Male	Cerebellum	Medulloblastoma	GTR	Yes	72
8	7	Male	Brainstem	No histopathology	No	Yes	64

*GTR* gross total resection, *RT* radiotherapy, *STR* subtotal resection

**Table 7** Comparison of common pediatric brain tumors between various series from different African countries

Reference	Country	Years of study	<i>n</i>	Mean age (years)	M:F	ST	IT	AST	MED	EPD	CPG
Current study	Sudan	2000–2015	62	8.83	1.38	34	58	52	18	3	1.6
[13]	Nigeria	1960–1982	89	NA	1.62	53	47	51.5	17.6	5.9	11.9
[14]	South Africa	1979–1985	145	NA	1.16	47	53	24.8	26.2	10.3	8
[15]	Nigeria	1980–1990	75	NA	0.75	NA	NA	40	10	NA	16
[16]	Tunisia	1990–2004	492	8 (median)	1.01	50.2	49.8	38	16.2	6.9	5.3
[17]	Morocco	2003–2007	542	9.3	1.08	NA	NA	31.6	28.9	10.3	6.6
[18]	Egypt	2005–2008	541	NA	1.06	46.6	49.7	35	18.8	10	11.3
[19]	Morocco	1991–2009	633	8.36	1.22	47	48	23.1	22.9	10.4	9
[20]	Uganda	2002–2012	172	6.5	1.4	62.2	37.8	32.8	8.1	16.3	9.9
[21]	Nigeria	1994–2006	40	9.75	1.2	40	60	25	25	2.5	12.5

AST astrocytoma, CPG craniopharyngioma, EPD ependymoma, IT infratentorial, MED medulloblastoma, M:F male-to-female ratio, NA not available, ST supratentorial

Consequently, we cannot make generalized conclusions regarding the status of childhood CNS tumors in all of Sudan. However, the NCI-UG is the only cancer treatment facility in central Sudan. Therefore, these data may be generally representative of the burden and pattern of childhood CNS tumors in central Sudan. In addition, the current study provides valuable information that may be applicable to the treatment of pediatric CNS tumors in other limited-resource settings and lays the foundation for improvements in cancer care in Sudan.

**Acknowledgements** We thank Nisha Badders, PhD, ELS for providing scientific editing of the manuscript.

### Compliance with ethical standards

**Conflict of interest** None of the authors have any conflict of interest to declare or any financial disclosure.

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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