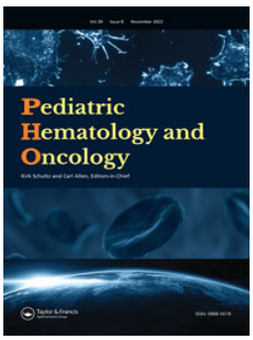

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The clinicopathological profile and value of multidisciplinary management of pediatric brain tumors in a low-income setting

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ABSTRACT

Brain tumors are the most common solid tumors in children and a leading cause of cancer-related mortality in children worldwide. Data on the epidemiology and management of pediatric brain tumors in Uganda are limited. We aimed to assess the clinicopathological profile and management of pediatric brain tumors at the national oncology center in Uganda since the inception of weekly multidisciplinary meetings. Records of children younger than19 years diagnosed with primary brain tumors at Uganda Cancer Institute between 2017 and 2021 were retrospectively reviewed. Patient and tumor characteristics were collected with multidisciplinary team management treatment plans for analysis. There were 35 patients evaluated, most of whom were males (57.1%). Craniopharyngioma (n = 9, 25.7%) was the most common brain tumor, followed by astrocytoma (n = 5, 14.2%) and medulloblastoma (n = 4, 11.4%). Management included surgical resection in 28.5% of patients, chemotherapy (28.6%), radiotherapy (17.1%) and palliative care (20.0%). Over the last five years, there were increasing trends in the number of cases discussed in the multidisciplinary team and the number for whom the multidisciplinary management decisions were implemented. The majority (n = 18, 51.4%) of the children with brain tumors were alive and active in care, 34.2% abandoned treatment/lost to follow-up, and 8.6% died. The relative distribution of pediatric brain tumors types in Uganda Cancer Institute differs slightly from international reports, and there has been a notable increase in the number of cases over the years. Implementing multidisciplinary management decisions benefited patients and decreased abandonment and patient loss to follow-up.

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In light of the inception of weekly multidisciplinary team management meetings.

LEARNING POINTS

- Multidisciplinary team management for pediatric neuro-oncology is a sustainable resource for improved patient care and outcome in resource-limited settings.
- Pediatric neuro-oncology patients have lower rates of treatment abandonment and loss to follow-up when managed according to multidisciplinary team meetings.

Background

Pediatric brain tumors are the most common solid tumors in children with an estimated incidence of1.7 to 4.1 per 100,000,[1] accounting for about 15–25% of all pediatric neoplasms in children.[2] They are the leading cause of childhood cancer-related deaths and remain one of the most challenging tumor groups to treat in low and middle-income countries.[3,4] In resource-constrained settings, including sub-Saharan Africa, the true epidemiology of pediatric central nervous system (CNS) tumors is not well documented and is likely undiagnosed.[5] In Uganda, the annual incidence of pediatric brain tumors is not known, though estimated to be less than 0.1–0.2 per 100,000 children aged under 19 years based on a historical, single-facility report.[5]

The survival rate for pediatric brain tumors in high-income countries (HICs) has consistently increased, approaching 70–80% as a result of advancements in diagnosis and treatment, including new and improved surgical techniques, imaging studies, histopathologic classification and radiation therapy.[6–9] In LMICs, with nearly 80% of the global pediatric cancer burden, the treatment outcomes of pediatric CNS tumors are considerably lower, with 5-year survival rates in the range of 0–40%.[7,8,10–12] Neuro-oncological care is often inadequate in many African pediatric oncology units as a result of infrastructural challenges, deficient human resources and evidence-based treatments, and a lack of interdisciplinary teams trained in neuro-oncology, compounded by late diagnosis.[7,8,10,13,14] Effective management demands a multimodal management approach, including surgery, chemotherapy, and/or radiation therapy delivered through a complex interdisciplinary approach.[3,15–17] Improving outcomes with good quality of life requires correct diagnosis, staging, and timely access to neurosurgery, radiation oncology, neuro-oncology, and endocrinology, among others, that are not often available in LMICs.[18,19] Therefore, the available resources should be managed efficiently in a coordinated manner starting with multidisciplinary team meetings.

In Uganda where data are scarce because of inadequacies in tumor registration, hospital-based studies have an important role in estimating the disease burden that contributes to the planning of healthcare infrastructure for improved disease outcomes. The Uganda Cancer Institute is the largest national reference cancer treatment facility treating the majority of children with cancers in Uganda. It also receives patients from other East African countries including South Sudan, Burundi and the Democratic Republic of Congo. Before 2017 few children with brain tumors were referred to oncology centers and multidisciplinary management of patients with brain tumors was non-existent.

At the Uganda Cancer Institute, the on-site capacity includes pediatric oncologists, pediatric oncology nurses, radiation oncologists, pathologists and radiologists; but no on-site neurosurgeons. While the pediatric solid tumor multidisciplinary team management was established in 2012, and neuro-oncology services in 2017, a dedicated pediatric neuro-oncology multidisciplinary management was only established in 2020 in collaboration with the CURE specialist neurosurgery hospital.[20] The pediatric neuro-oncology service, however, continues to be challenged by the lack of rehabilitation services, intensive care services and inadequate supportive care at the institute.

The primary objective of the study was to determine the clinicopathological profile and evaluate the management of brain tumors in children at the national cancer treatment center in Uganda, in light of the multidisciplinary management.

Methodology

This was a retrospective analysis of case records of children and adolescents below 19 years diagnosed with brain tumors, treated and followed up at the Uganda cancer institute, between January 2017 and December 2021. All accessible records within the study period were retrieved, and data regarding age, sex, tumor location, clinical features, histology, management, and treatment outcome were collected and analyzed. The diagnosis of brain tumor was based on histopathological analysis, except for four cases (2 diffuse intrinsic pontine gliomas, 1 optic pathway glioma, and 1 low-grade glioma) where the diagnosis was made based on clinical and radiological features. The pathology classification was based on the World Health Organization (WHO) 2007 classification of brain tumors.[21] Immunohistochemistry, cytogenetic or molecular analysis was not done due to the paucity of resources. Data were abstracted from the medical records into the data abstraction forms and then entered into, and analyzed, using Statistical Package for Social Sciences (SPSS) software package (SPSS for Windows, Version 23.0. Chicago, SPSS Inc.). Descriptive statistics were summarized as proportions for categorical variables, while continuous variables were summarized as means with standard deviations (SD) or medians with interquartile ranges (IQR), including the comparison of the mean interval of symptoms within the subgroups of gender, age, tumor location, and WHO grade.

Results

Demographic characteristics of the study population

Of the 35 neuro-oncology cases reviewed –accounting for 68.6% (35/51) of the registered cases over the study period, 15 (42.9%) were in the age group of 5–9 years and about one-third (31.4%) were in the 10–17 years age group, with a median age of 8.0 years (IQR 4–11 years). Over one-half, 20/35 (57.1%) of children were males. There was an increasing trend in pediatric neuro-oncology cases over the study period (Table 1). Males predominated over females in the 5–9-year age group while the sex distribution was similar in the 0–4 years and 10–17 years age cohort (Figure 1).

Table 1. Demographic characteristics of children diagnosed with central nervous tumors between 2017 and 2021 in the Uganda Cancer Institute.

Characteristics	N (%)
Age (years)	
0–4	9 (25.7)
5–9	15 (42.9)
10–17	11 (31.4)
Total	35
Gender	
Male	20 (57.1)
Female	15 (42.9)
Total	35
Referral facility	
CURE hospital*	20 (57.1)
Other facilities	13 (37.2)
Self-referral	2 (5.7)
Total	35
Year	
2017	3 (8.6)
2018	5 (14.3)
2019	4 (11.4)
2020	9 (25.7)
2021	14 (40.0)
Total	35

*Specialist neurosurgery hospital in eastern Uganda (>224 km from the capital, Kampala).

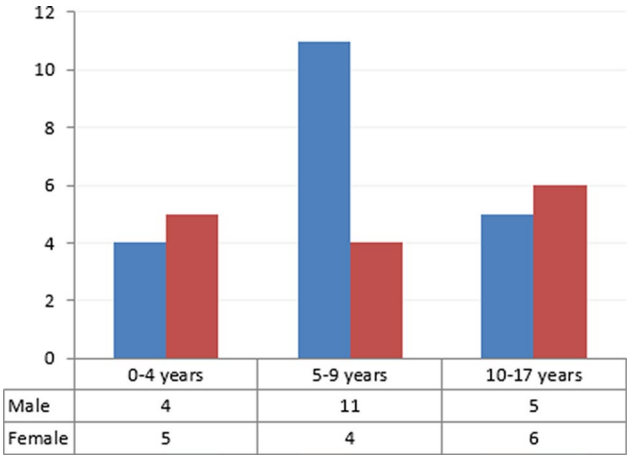

Figure 1. Age-sex distribution of children diagnosed with central nervous tumors between 2017 and 2021 in the Uganda Cancer Institute.

Histopathology and anatomic location

Of the 35 brain tumors, 22 (62.9%) were supratentorial while 13 (37.1%) were infratentorial. The most common brain tumor was craniopharyngioma (n = 9, 25.7%), followed by astrocytoma (n = 5, 14.3%), medulloblastoma (n = 4, 11.4%), and ependymoma and pineoblastoma (n = 3,8.6% each) (Table 2). Astrocytoma and ependymoma were more commonly seen in females than males, while medulloblastoma, craniopharyngioma and pineoblastoma were more in males than females, with all the cases of medulloblastoma occurring in males below 10 years of age.

Table 2. Tumor type, location and grade between 2017 and 2021.

Characteristic	N (%)
Location	
Supratentorial	22 (62.9)
Infratentorial	13 (37.1)
Total	35
Tumor type	
Astrocytoma	5 (14.3)
DIPG	2 (5.7)
Ependymoma	3 (8.6)
Medulloblastoma	4 (11.4)
CNS PNET	2 (5.7)
Craniopharyngioma	9 (25.7)
Haemangioblastoma	1 (2.9)
Oligodendroglioma	1 (2.9)
Pineoblastoma	3 (8.6)
Pituitary adenoma	1 (2.9)
Optic pathway glioma	1 (2.9)
No histology	3 (8.6)
Total	35

DIPG: Diffuse intrinsic pontine glioma; CNS PNET: Central nervous system primitive neuroectodermal tumor.

Table 3. Common clinical presentations and time to the presentation of pediatric neuro-oncology tumors (n = 35) between 2017 and 2021.

Characteristic	N (%)
Clinical symptom	
Headache	22 (62.9)
Vomiting	14 (40.0)
Ataxia	6 (17.1)
Impaired vision	13 (37.1)
Seizures	6 (17.1)
Impaired speech	5 (14.3)
Paraplegia	8 (22.9)
Problem feeding	3 (8.6)
Regression of milestones	6 (17.1)
Hydrocephalus	4 (11.4)
Time to presentation	
<3 weeks	1 (2.9)
3–6 weeks	4 (11.4)
7–24 weeks	12 (34.3)
>24 weeks	18 (51.4)
Total	35

Clinical presentations

The most common clinical presentation was headache (n = 22, 62.9%) followed by 14 (40.0%) with vomiting, 13 (37.1%) with impaired vision, and eight (22.9%) with paraplegia (Table 3). The median time from onset of symptoms to seeking medical care was 6.0 months (IQR 3.0–8.5 months). The majority (n = 18, 51.4%) of the children had symptoms for more than 6 months before presentation, and only one (2.9%) child presented within less than 3 weeks of symptoms.

Operative characteristics and multimodal management

Only over a quarter (n = 10, 28.5%) of the children underwent surgical resection, of which 6 (17.1%) were gross total resections (GTR) and 4 (11.4%) were subtotal

Table 4. Multi-modal treatment of childhood neuro-oncology patients diagnosed between 2017 and 2021.

Characteristic	N (%)
Surgical intervention:	
Surgical extent:	
GTR	6 (17.1)
STR	4 (11.4)
Biopsy only	2 (5.7)
Conservative	7 (20.0)
Total	19
CSF diversion:	
VPS	7 (20.0)
ETV/EVD	8 (22.9)
Total	15
Other treatment modalities*	
Chemotherapy (curative)	10 (28.6)
Radiotherapy	6 (17.1)
Total	16
Multimodality management:	
Surgery/chemotherapy/radiotherapy	4 (11.4)
Surgery/chemotherapy	4 (11.4)
Surgery/radiotherapy	2 (5.7)
Chemotherapy/radiotherapy	1 (2.9)
Total	11
Palliation:	
Palliative chemotherapy	4 (11.4)
Total palliation	3 (8.6)
Total	7

GTR: Gross total resection; STR: Subtotal resection; VPS: Ventriculo-peritoneal shunt; ETV: Endoscopic third ventriculostomy; EVD: External ventricular drain; Conservative = cyst decompression/Ommaya reservoir.
*Includes multimodal therapy.

resections (STR). Seven (77.8%) of the children with craniopharyngioma had a cyst decompression procedure. Cerebrospinal fluid (CSF) diversion procedures to relieve intracranial pressure were performed in 15 (42.9%) of the cases, of which seven (20.0%) were ventriculoperitoneal shunts (VPS) and eight (22.9%) were endoscopic third ventriculostomy/external ventricular drain (ETV/EVD). A total of 10 (28.6%) of the children received chemotherapy, 6 (17.1%) received radiotherapy and 7 (20.0%) palliative treatment as part of multimodal therapy. As expected, multimodality treatment was also a common practice as shown in Table 4.

Multidisciplinary management

Over the five years, the number of cases increased from 3 to 14 per year. In 2017 no cases were discussed in the multidisciplinary tumor board but this increased over the years. In 2018, 3 out of 5 patients were discussed, 2/4 were discussed in 2019, 6/9 in 2020, and 11/14 patients in 2021 – with up to 81.8% of the management decisions being acted upon (Figure 2).

Outcomes

The majority (n = 18, 51.4%) of children with brain tumors were alive and receiving treatment, 12 (34.2%) had abandoned treatment or were lost to follow-up, and three

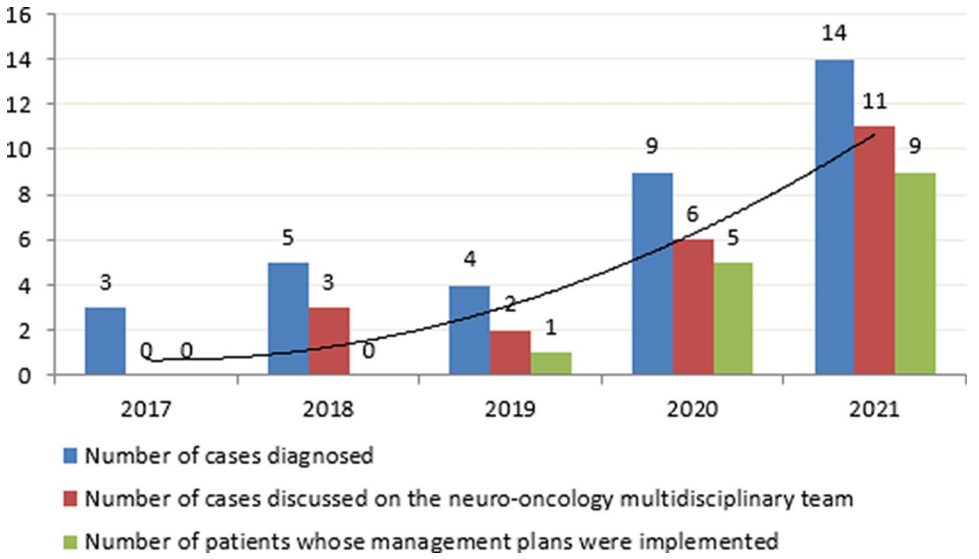

Figure 2. Trends in cases, multidisciplinary meetings and implementation of decisions in children diagnosed with central nervous system tumors between 2017 and 2021.

Table 5. Patients outcome and multidisciplinary management.

Characteristic	Number of cases overall (%)	Number Discussed in MDT	Multidisciplinary management recommendation implemented	
			Yes n (%)*	No n (%)*
Active	18 (51.4)	12	12 (80.0)	0 (0.0)
Lost to follow-up	6 (17.1)	4	2 (13.3)	2 (28.6)
Treatment abandonment	6 (17.1)	4	0 (0.0)	4 (57.1)
Transfer out	2 (5.7)	1	1 (6.7)	0 (0.0)
Dead	3 (8.6)	1	0 (0.0)	1 (14.3)
Total	35	22	15	7

MDT = multidisciplinary team; *Outcome according to implementation of multidisciplinary management recommendations.

(8.6%) died (Table 5). Of the patients that died, two (66.7%) were diagnosed with astrocytoma and one (33.3%) was diagnosed with craniopharyngioma. The majority of the 12/15 (80.0%) of the cases for whom the multidisciplinary recommendations were implemented were alive and active in care compared to none 0/7 (0%) of those for whom the multidisciplinary management decisions were not executed. Of the twelve surviving active cases above, 5 were craniopharyngioma and 2 were medulloblastoma, while astrocytoma, haemangioblastoma, oligodendroglioma, pituitary adenoma and optic pathway glioma were 1 case each (Table 5).

Relation between time to presentation with child and tumor characteristics

There was no statistically significant difference in the time to the presentation by the child's gender, age, tumor grade or anatomic location. However, the time to presentation was longer for males than females ($F = 0.045$, $p = 0.833$; not significant) and shorter

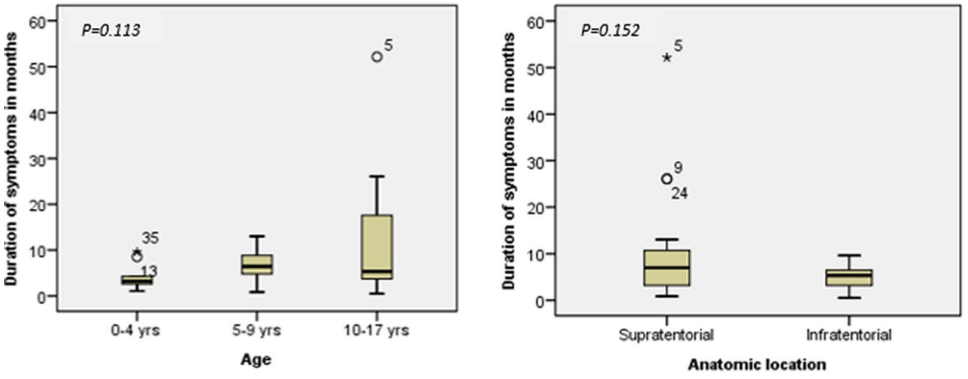

Figure 3. Box plot of duration of symptoms by age group and tumor location.

for children aged 0–4 years than for older children (F = 2.341, $p = 0.113$; not significant). The time to presentation was longer for low-grade tumors than for high-grade tumors (F = 0.121, $p = 0.886$; not significant) and for supratentorial tumors than infratentorial tumors (F = 2.149, $p = 0.152$; not significant) (Figure 3).

Discussion

We found that the relative frequency of childhood brain tumor types at the Uganda cancer institute does differ from historical hospital-based reports and other international reports.[1,2,22] We demonstrated that with concerted efforts and recommendations from multidisciplinary team management, outcomes could be improved in a low-income setting as indicated by a marked reduction in the loss to follow-up and treatment abandonment rate from 58.3% in the three years before multidisciplinary management to 21.7% thereafter, notwithstanding that the treatment abandonment/loss to follow-up rates among pediatric brain tumor cases remain a point for improvement.

In LMICs, the epidemiological and treatment data for pediatric brain tumors are limited, occasioned by the lack of reporting from population-based cancer registries. A common finding between India and Uganda was that most pediatric brain tumors were of supratentorial origin.[2,5,8] Yet, India reported predominantly embryonal tumors with medulloblastoma constituting 34.6% of the cases, followed by astrocytoma (28.8%) and ependymoma (9.6%).[2,18] This contrasted with the predominance of craniopharyngioma and astrocytoma in the Ugandan population.[5] We postulate that the difference could be attributed to the varying sample sizes and age groups of the cohorts in the different studies in combination with the underreporting, poor health-seeking behavior and missed diagnoses for those that do seek care in the Ugandan population.[5] The low frequency of pediatric brain tumors presented in this study is not representative of the pediatric oncology population. The frequency suggests, as asserted by Stagno et al, the possibility that more than 90% of pediatric brain tumors in Ugandan children go undiagnosed,[5] and underscores the critical gaps in the referral pathways between medical centers to ensure comprehensive pediatric neuro-oncology care. A possible

contributing factor may be the nonspecific signs and symptoms of brain tumors in children such as headaches, vomiting, ataxia, lethargy, or seizures that are more likely to be misinterpreted[5] as infection-related etiologies or that patients die without the central nervous tumors being detected.

The identification of just over fifty registered children with brain tumors in the five years at the current study setting (35 of which were accessed) in comparison to the 172 cases reported in a retrospective operative series at a pediatric neuro-surgical facility (Cure hospital) in eastern Uganda over 10 years from 2002 to 2012[5] highlights a gap in the continuum of care. The big difference in numbers at the two sites could be attributed to the fact that Cure Hospital, located approximately 225 km away from Uganda Cancer Institute, is a neuro-surgical hospital which serves as a point of first contact for many children with neurological symptoms due to brain tumors. Many of these children, however, do not end up in the cancer treatment center after surgical resection of their tumor, underscoring the critical gaps in the referral pathway for pediatric brain tumors in the country. The apparent improvement following surgical resection of the tumor seems to provide a negative motivation for the caretakers as regards the need/urgency of the continuum of care at the cancer treatment center even when properly referred. This is compounded by the socio-economic and transport challenges and the delayed turnaround of histopathology results.

The higher male-to-female ratio with brain tumors in other LMICs, such as Morocco, was reproduced in our study.[2,18,23,24] The mean age at diagnosis of patients in our study was 8.1 years (SD4.4 years) which is similar to a Pakistani report,[23] but lower than reports from China (12.68 years) and India (10.69 years).[2,25,26] The differences in the study age groups could be due to tumor biology, symptom presentation and referral dynamics. A higher proportion of patients presented late with symptoms lasting more than six months. The time to presentation was longer in low-grade tumors and supratentorial tumors in keeping with the higher incidences in these tumors in the current study. This is in keeping with the generally slow-growing nature of these tumors that present later with neurologic deficits compared to more aggressive biology in high-grade tumors where patients tend to deteriorate more rapidly.[27] Tumor-unrelated factors such as the lack of infrastructure, misdiagnosis or non-diagnosis by untrained health providers, as well as cultural practices that delay healthcare seeking further hinder improving survival outcomes.[28–30]

The degree of tumor resection, perioperative complications and poor communication with families contribute to poorer outcomes.[30] In our study, the surgical resection rate was low (28.5%), with 17.1% achieving GTR and 11.4% STR compared to India, for example, where more than two-thirds of patients are operated on with GTR and STR rates of 52.7% and 37.7% respectively.[18] The Ugandan statistics reflect the whole study period, but after establishing multidisciplinary team management and dedicated neuro-oncology service in 2021, the resection rate has already increased to 63.4% in 2021 with improved treatment retention rates. The completeness of brain tumor resections is a significant predictor of overall survival, especially in medulloblastoma and low-grade gliomas.[3,31–33] We suppose that the critical lack of neuro-surgery expertise, infrastructural resources and defined referral pathways identified and addressed by the neuro-oncology team contributed to the observed recent improvement.

Globally only 15% of pediatric neurosurgeons operate in LMICs with a ratio of one pediatric neurosurgeon to 3.6 million children.[34] While countries lack neurosurgeons to augment their neuro-oncology management, the pediatric oncology teams should utilize established resources to improve services by joining regional multidisciplinary team meetings. East African pediatric oncology units can join the Ugandan meetings, online meetings arranged by the Society of neuro-oncology in Sub-Saharan Africa (SNOSSA) or other international discussion platforms.[35,36] These pediatric oncology units could base management on adapted management guidelines such as those developed by the International Society of Pediatric Oncology-Pediatric Oncology in Developing Countries (SIOP-PODC) working groups on medulloblastoma, low-grade glioma and craniopharyngioma.[4,37,38]

The multidisciplinary management of pediatric neuro-oncology cases and the rate of implementation of the multidisciplinary management decisions have only shown an increasing trend over the two years immediately preceding the current study. Likewise, we noted a higher proportion of ongoing care among children whose multidisciplinary management decisions were implemented compared to those whose multidisciplinary management decisions were not acted upon, supporting the importance of multidisciplinary management in the continuum of care among childhood brain tumor patients. In the current study, we could only confirm a mortality rate of 9.7%. While this is lower than the 15.3% mortality rate reported in India,[18] we postulate that since brain tumor is a progressive disease, those that abandoned treatment are more likely to have died in the absence of continued management; therefore, meaning the mortality rate as reported may be an underestimate.

There are a few focuses for improvement: (1) the high treatment abandonment/loss to follow-up rate of 34.2%, which is higher than the 25% treatment abandonment rate by other LMICs.[18,35] Failure to complete treatment is problematic in manyLICs.[39] This could be addressed by including referral hospitals in the multidisciplinary management, establishing financial and social support for financial hardships experienced by the families of the children who are unable to travel to treatment centers, and increasing pediatric neuro-oncology advocacy to communities and families to increase awareness.[36,39] (2) Establishing rehabilitation services for children with tumors or treatment-related complications to increase the quality of life. (3) Include late effects surveillance, including an endocrinologist, especially in the Ugandan service with a predominance of craniopharyngeomas.[40] (4) A neuro-oncology-focused palliative care plan since the mortality rate is still high.[41] (5) Improving the quality and effectiveness of the multidisciplinary management meetings themselves, as well as streamlining the implementation of management decisions and communication to the relevant stakeholders in the care of the patients.[42]

Our study was limited by the small sample size and single-center, retrospective design and may not entirely reflect the true burden and the relative frequency of pediatric brain tumors in Uganda. This, however, brings out the critical challenges as well as the opportunity to improve pediatric brain tumor recognition, referral, diagnosis, treatment, and care in a resource-limited context. A population-based study may be required to determine the true burden and epidemiology of pediatric brain tumors in the country, which calls for a comprehensive national cancer registry. The current

status of all the patients who had abandoned treatment/were lost to follow-up could not be verified.

Conclusions

The relatively low frequency of pediatric brain tumors found in this study suggests that the majority of children with brain tumors in Uganda go untreated, and possibly die, without being diagnosed. There is also a high rate of treatment abandonment/loss to follow-up among children managed for brain tumors. There is a need to further strengthen the neuro-surgical services, follow-up practices and multidisciplinary team management to further limit treatment abandonment/loss to follow-up and provide rehabilitation and long-term care in Uganda. Multidisciplinary team management for pediatric neuro-oncology is a sustainable resource for improved patient care and outcome in resource-limited settings. Pediatric neuro-oncology patients have lower rates of treatment abandonment and loss to follow when managed according to multidisciplinary team meetings.

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Authors' contributions

RN and JVH initiated the study and contributed to the study design, data collection, and interpretation of results. JBK, RA, HS, SK, and FG contributed to the revision and drafting of the manuscript. All authors have read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Disclosure statement

The authors declare that they have no competing interests

Ethical approval

This evaluation was undertaken as part of the quality improvement process and so did not require ethical approval.

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