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Recurrent Brain Tumors at The Largest Referral Facility in East and Central Africa- Epidemiology, Patterns and Outcomes: A Descriptive Study

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Abstract
Introduction: The prognosis of brain tumors once treated is variable with outcomes ranging from complete resolution of symptoms to recurrence of the tumor. Different geographical regions worldwide have different recurrence patterns. This paper describes the epidemiology, patterns and outcomes of recurrence in Sub-Saharan Africa. **Methods:** A three-year retrospective study starting January 2014 to December 2016 was carried out at the records department of Kenyatta National Hospital (KNH) following ethical approval. A pre-formed questionnaire was filled in with data from files that fit in the inclusion criteria. Data was analyzed using Statistical Package for Social Sciences (SPSS) Version 20. **Results:** A total of 18 files were retrieved and reviewed. There were 11 male and 7 female patients with the tumors most commonly occurring in the 0-13 and 26-45 years' age groups. Supratentorial tumors accounted for 66.7% and the commonest among these were craniopharyngiomas at 50.0%. The more common recurring infratentorial brain tumors were medulloblastoma and hemangioblastoma. Surgical interventions were carried out in all patients and the recurrence periods ranged from less than 6 months to greater than 5 years. Fifty-five (55%) percent of the recurrent tumors had a Zubrod score of 0-1. **Conclusion:** Craniopharyngiomas were the most common recurrent brain tumors seen in this resource limited setting as shown in this study. Despite the resource scarcity, more than half of our patients had a good outcome. Closer follow up with stringent surveillance and provision of adjuvant chemo and radiation therapy with surgery for treatment of recurrences would lead to better outcomes.

Keywords: *Brain tumors, Kenya, Sub-Saharan Africa, meningioma, glioma, patterns*

Introduction

The overall incidence of brain tumors was 2.2/100,000 and 1.9/100,000 in Kenya for males and females respectively for the period 2004-2008 and is still rising at a rapid rate (1). However, this is still lower than incidences seen in developed nations (2). Once diagnosed, brain tumors are generally treated by surgical, radiotherapeutic or chemotherapeutic interventions or a combination of all. The prognosis after the initial treatment is variable with some patients completely healing, others having residual symptoms whereas others have a recurrence of the tumor leading to a clinical presentation similar to the initial one or even worse thus leading to neurological deterioration. Overall, tumors of the Central Nervous System (CNS) are among the commonest recurring tumors after resection.

Different histological types of brain tumors have various degrees of recurrence with rates varying between 0% to greater than 90 %(3–7). The recurrence patterns differ with a vast majority occurring within 2 cm of the original disease site whereas others show a pattern of distant recurrence(8). Notably, different regions worldwide have different recurrences and outcomes of brain tumors. Tumor recurrence increases the strain on the already limited resources in developing countries considering the issues of patient re-admission and re-strategizing the treatment modalities which might include re-operation and other socio-economic burdens to the family, patient and public health facilities.

Currently, there is no study that describes the recurrence patterns in our local setting. In this paper, we illustrate the epidemiology, patterns and outcomes of recurrent brain tumors in our local geographical setting. Notably, this is a descriptive retrospective study of 3 years and the classification system used is the 2007 WHO Central Nervous System classification which does not incorporate the molecular and genetic basis incorporated in the 2016 update (9,10).

Materials and methods

Following ethical approval by the Kenyatta National Hospital/ University of Nairobi Ethical Review Committee (KNH/UON-ERC), a descriptive retrospective study was carried out at Kenyatta National Hospital (KNH), the largest teaching and referral hospital in East and Central Africa with a bed capacity of over 2000 patients. Patients' records were retrieved and reviewed for the period January 2014 to December, 2016.

The inclusion criteria were patients who were treated for recurrent brain tumors at Kenyatta National Hospital (KNH) and had complete file records at the registry. Patients' bio data, initial presentation of the tumor and its management, period of remission, diagnosis at recurrence and its management and the overall outcome according to the Eastern Cooperative Oncology Group (ECOG)/WHO/Zubrod score were entered in to a pre-formed questionnaire.

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 20 and frequencies were calculated for the variables. Data was presented as tables, pie charts and bar graphs.

Results

A total of 198 patients with brain tumors were operated on at Kenyatta National Hospital (KNH) during the period 2014-2016. During the same period, 18 patients had recurrences, all of whom were re-operated.

Histologic classification

Meningiomas were the most frequent tumor, accounting for 44.8% of all cases, followed by gliomas (glioblastoma, astrocytoma, ependymoma, and oligodendroglioma), which accounted for 34% of all cases (Table 2). Medulloblastomas made up 6.9% of the total, whereas primitive neuroectodermal tumors (PNET) comprised 3.4%. Brain metastases accounted for 3.0 percent of all tumors.

Bio data and initial diagnosis

A total of 18 patients fit the inclusion criteria and their records were retrieved and reviewed. There was a slight male predominance with 11 (61.1%) being male patients and 7 (38.9%) being female patients. Majority of the patients with recurrent brain tumors were aged between 0-13 years and 26-45 years which accounted for 33.3% each. Only one patient with a recurrent brain tumor was in the 61-70 years age group. Notably, we did not have any patient older than 70 years in our data set with a recurrent brain tumor (Figure1).

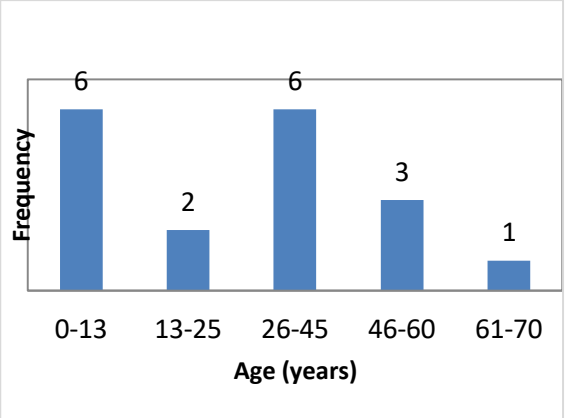

Figure 1: Age distribution of patients with recurrent brain tumors

The modal level of education was primary school that was at 44.4% of the study population and about 39% of the patients had post-primary education. The rest of the patients had informal (16.7%) or tertiary education (16.7%). Fifty percent (50.0%) of our patients came from counties neighboring Nairobi County, 27.8% from Nairobi County and the rest of our patients came from other counties in the country.

Tumor characteristics

With regards to location of the tumors, supratentorial tumors accounted for 66.7%, while 33.3% were infratentorial tumors. Of the supratentorial tumors, half (50%) were craniopharyngiomas while other histological subtypes encountered included, glioblastoma, pituitary macroadenoma, hemangiopericytoma, anaplastic oligodendroglioma, and pineal region tumor (Table 1). Half of the patients with recurrent craniopharyngioma were aged younger than 13 years (Table 2). Thirty-three percent (33%) of patients with recurrent supratentorial tumors were aged 0-13 years and a similar number was seen in the 26–45-year age-group.

Medulloblastoma and hemangioblastoma were the most common recurrent infratentorial tumors with 2 patients each. Other infratentorial tumors that were recurrent included; astrocytoma, and papillary adenocarcinoma (Table 1). All patients with recurrent medulloblastoma were aged less than 13 years whereas all recurrent hemangioblastomas were seen in patients in the 26–45-year age group (Table2).

Time interval to Recurrence

Sixty seven percent of recurrences occurred before 2 years after initial surgical extirpation (Table 3). Craniopharyngioma recurrence was seen at less than 6 months in 2 patients, at 1-2 years in 2 patients and at more than 5 years in 2 patients. Glioblastoma recurred at 2 years in one (1) patient and after more than 5 years in another patient whose initial diagnosis was an anaplastic astrocytoma. The patients who had medulloblastoma and hemangioblastoma all had recurrences within 1-2 years (Figure 2).

Management

All patients had initially undergone surgical intervention by craniotomy. Additionally, 2 patients (11.1%), a male with a glioblastoma and a female with an anaplastic astrocytoma, had adjuvant chemotherapy and radiation therapy and 4 patients (22.2%) underwent a combination of radiotherapy and surgery.

Diagnosis at recurrence and subsequent interventions

At the time of recurrence, 77.8% of the tumors were supratentorial, while 22.2 % were infratentorial. Except for one male patient in the 0-13 age range, whose initial histological analysis was an infratentorial medulloblastoma, whereas the recurrence was a primitive neuroectodermal tumor (PNET) in the supratentorial region, the histologies were similar to the first presentation. Another female patient was diagnosed with anaplastic astrocytoma at first, but had a histological diagnosis of glioblastoma at recurrence, which was 8 years after the initial diagnosis.

At recurrence, 14 patients (77.8%) underwent surgical intervention, 1 patient had no intervention as they were on hormonal replacement therapy for pan-hypopituitarism, and 1 other patient underwent palliative care whereas 2 patients (11.1%) died before any intervention could be carried out (Table 4).

Table 1: Histological types of recurrent supratentorial brain tumors during the initial diagnosis

Tumor Histology	**n**	**%**		**n**	**%**
Surpratentorial tumors			**Infratentorial tumors**		
Glioblastoma	1	8.3	Medulloblastoma	2	33.3
Craniopharyngioma	6	50.0	Astrocytoma	1	16.7
Pituitary macroadenoma	1	8.3	Hemangioblastoma	2	33.3
Hemangiopericytoma	1	8.3	Papillary adenocarcinoma	1	16.7
Anaplastic Oligodendroglioma	1	8.3	*Total*	***6***	***100***
Pineal gland tumor	1	8.3			
Anaplastic Astrocytoma	1	8.3			
Total	***12***	***100 .0%***			

Table 2: Recurrent brain tumors at various age groups

Histology	Age groups (years)				
	0-13	13-25	26-45	46-60	Total
Supratentorial tumors					
Glioblastoma	0	0	1	0	1
Craniopharyngioma	3	1	2	0	6
Pituitary macroadenoma	0	0	1	0	1
Hemangiopericytoma	0	0	0	1	1
Anaplastic Oligodendroglioma	1	0	0	0	1
Pineal gland tumor	0	1	0	0	1
Anaplastic Astrocytoma	0	0	0	1	1
Infratentorial tumors					
Medulloblastoma	2	0	0	0	2
Astrocytoma	0	0	1	0	1
Hemangioblastoma	0	0	2	0	2
Papillary adenocarcinoma	0	0	0	1	1
Total	**6**	**2**	**7**	**3**	**18**

Table 3: Time to recurrence of the brain tumors

	n	%
0-6 Months	4	22.2
6-12 Months	1	5.6
1-2 years	7	38.9
3-5 Years	3	16.7
> 5 years	3	16.7
Total	18	100

Table 4: Interventions carried out post-recurrence on brain tumors

	n	%
Surgery	14	77.8
Palliative Care	1	5.6
Death before intervention	2	11.1
Hormone replacement therapy	1	5.6
Total	18	100

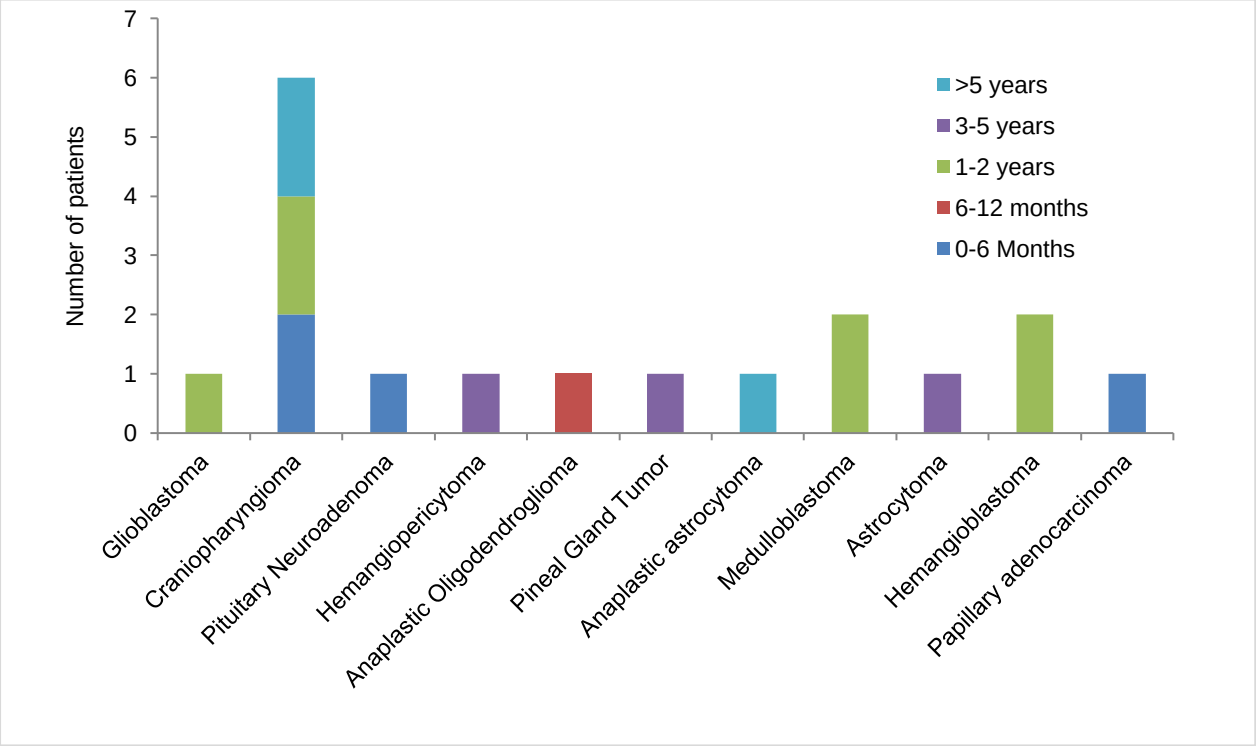

Figure 2: Periods before recurrence of various histological types of brain tumors

Table 5: Results of the exact test conducted between age and outcome

Age (years)	Outcome n (%)			Total
	Good	Poor	Death	
0 – 25	3 (100.0)	3 (27.3)	2 (50.0)	8 (44.4)
26 – 60	0 (0.0)	8 (72.7)	1 (25.0)	9 (50.0)
>60	0 (0.0)	0 (0.0)	1 (25.0)	1 (5.6)
Total	3 (100.0)	11 (100.0)	4 (100.0)	18 (100.0)

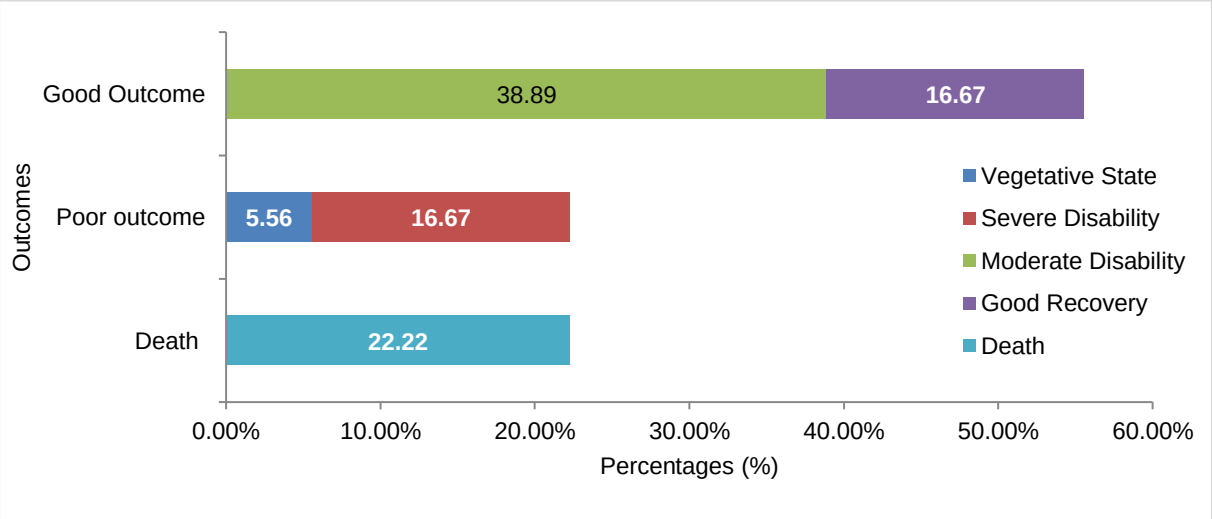

Figure 3: Outcomes on the ECOG/WHO/Zubrod scale

Outcomes post recurrence

The outcomes of the patients post recurrence were evaluated using the Eastern Cooperative Oncology Group (ECOG) / WHO/ Zubrod score. An outcome of 0-1 was defined as a good outcome, 2 as moderate outcome, 3 as severe outcome, 4 as vegetative state and 5 as death. The most frequent outcome was moderate at 38.89% (Figure 3).

Two patients died before intervention at recurrence. One patient presented with an infratentorial papillary adenocarcinoma whereas the other patient had a pineal gland tumor. The outcome of death was equal in both males and females and was significantly more if the tumor recurred within the first 6 months. Surgical intervention post recurrence resulted in patients having better outcomes relative to other patients who underwent other therapies.

Analysis of data

There was significant difference (p = 0.047) between age and outcome as assessed by Fisher-Freeman-Halton exact test. The significance tests carried out between the other variables were not significant. The results of the exact test are displayed in Table 5.

Discussion

Tumor recurrence is defined as, a change from a previous interval of tumor absence or a loss of prior complete tumor control, and thus are a nightmare to practitioners who treat them. The patterns of recurrence vary worldwide and the likelihood of recurrence varies with the histological identification of the brain tumor. Several factors including; the grade of tumor resected, extent of resection, intraventricular dissemination, and repeated needle aspiration leading to implantation and

seeding determine the risk of a tumor recurring(11,12).

Male patients treated at our center were 1.5 times more likely than female patients to have a brain tumor recurrence. Notably, men have poorer health-seeking behavior than women, which may explain why male patients have higher recurrence rates (13).Furthermore, males not only develop more cancers, but they also respond to therapy less well (14).These variations could be attributed to differences in fundamental mechanisms of tumor initiation, tumor promotion, and therapeutic response(14).The level of education also influences health-seeking behavior and income levels. The majority of patients treated had a primary level of education and thus comparable incomes. They sought treatment at KNH because it was relatively inexpensive and affordable based on their incomes.

Brain tumors are the most common form of solid tumors among children under the age of 15 and represent about 20% of all childhood cancers (15). In our study, the age groups 0-13 and 26-45 had the highest number of recurrent brain tumors. Patients aged 0 to 13 years are typically primary school-aged children who rely on their parents/guardians. This increases the burden on parents/guardians, who must invest significant time and financial resources, contributing to the vicious cycle of poverty that exists in several Sub-Saharan African countries, including Kenya. The 26–45-year age group is the driving force behind developing countries' social and economic power, yet in this study, they had the highest recurrence rate of brain tumors. This implies that the formative years and active working age group are the most affected, and thus a greater emphasis should be placed on reducing tumor recurrence and/or improving the facilities for caring for this population.

Certain tumor types such as medulloblastoma, craniopharyngioma and germ cell tumors, ependymoma, and pilocytic astrocytoma, have an incidence that decreases with age (16). Our patients in the age group, 0-13 years exhibited recurrent craniopharyngiomas and medulloblastomas as the most common recurrent tumors which correlate well with other studies.

Supratentorial tumors accounted for 66.7% of the overall recurrence rate in our study. Fifty percent of the supratentorial recurrent tumors were craniopharyngiomas in this study which correlates well with other studies that showed they are the most common form of non-neuroepithelial neoplasms in the pediatric population with a high recurrence rate after primary treatment(17–19).

In this study, all patients with recurrent craniopharyngiomas were aged less than 45 years. The reported recurrence rates of craniopharyngiomas are 6.8% with patients less than 9 years more likely to suffer recurrence relative to those aged 9-13 years (20). Other studies report that the recurrence rates may be as high as 25% to 70% even after the administration of radiotherapy (21). The most significant risk factor for recurrence is incomplete resection of the tumor (19).

The standard treatment for craniopharyngiomas is complete surgical resection, or partial resection followed by adjuvant radiotherapy (22).When managing a recurrence, the primary treatments for craniopharyngioma should be considered when choosing the surgical strategy (18). Considering the high recurrence rates of craniopharyngiomas in our setup and the complicated neurosurgical management, with or without radiotherapy and chemotherapy in this setup, there is need for a localized management protocol in developing countries. This protocol will define the extent of tumor resection, radio- and chemotherapy that is affordable, available and easily accessible to patients in public health facilities in developing countries. In Kenya, there is only one public health facility countrywide offering radiotherapy services and this is the KNH. There are long waiting times, occasionally up to 2 years, associated with accessing radiotherapy services in the public sector and thus this protocol will define localized management strategies for recurrent brain tumors.

One patient had primary glioblastoma seen in our study. The other patient had records that showed an initial diagnosis of anaplastic astrocytoma that later recurred as glioblastoma after more than 5 years, however, the initial results were not analyzed using immunohistochemistry to confirm the histological diagnosis. The cells of GBM due to their infiltrative nature make it difficult to eliminate microscopic disease despite gross total resection macroscopically(23).GBM accounts for more than 50% of all gliomas and thus it is surprising that our dataset only yielded two recurrent GBMs in a period of three years. It therefore appears that in our setup patients with GBM are either lost to follow up or die before presentation to our health facility at tumor recurrence. There is need to educate the patients that despite recurrence of tumor, there is still a protocol for re-operation, re-irradiation and chemotherapy.

The majority of glioblastomas are destined to recur less than 6 months after resection (24,25). The median interval from initial diagnosis to evidence of tumor recurrence is 12 months (4). In our patient population, all patients who had a recurrence of GBM underwent surgical intervention. Despite this intervention, one patient died whereas the other patient who had a recurrence after 5 years had moderate recovery after intervention post recurrence. None of these patients had any other intervention aside from surgical resection. Maximum resection in newly diagnosed GBM appears to provide a significant survival advantage though this is less certain in resection of recurrent GBM, nonetheless some data shows that maximum resection at recurrence also prolongs survival (26).The efficacy of repeated resection alone remains controversial due to the lack of randomized controlled trials evaluating this intervention independently (23). Despite this, repeat craniotomy relieves mass effect and gives the chance for delivery of in situ chemotherapy or brachytherapy.

The more commonly recurrent infratentorial tumors in our series were medulloblastoma and hemangioblastoma. In a study by Weintraub et. al., the rate of recurrence of pediatric medulloblastoma is between 35% and 40% (27).In our study, 33.3% of the infratentorial tumors that recurred were medulloblastomas. Current therapy for patients older than 3 years, consists of maximal surgical resection followed by craniospinal irradiation with supplemental “boost” treatment of the post-operative tumor bed, followed by platinum-based chemotherapy (28).The prognosis for relapsed patients still remains poor, with a median overall survival of less than 1 year(29,30). The expected 2-year overall survival after disease progression is less than 25% while probability of 5 year survival for medulloblastomas is reported at 26.3% (28,31). Despite these dismal outcomes, one patient in our study had a recurrence whose outcome was moderate disability whereas another patient’s outcome was good recovery.

Two patients in our study with recurrent medulloblastomas had recurrence despite being subjected to surgery and craniospinal irradiation during the initial disease phase. None of them received chemotherapy before and after recurrence. Both patients in our study had good outcomes after recurrence. Poorer prognosis in medulloblastomas is associated with loss of chromosomes6, 8, 9q, 10q, 11, 16q and 17p or gain of chromosomes 1q, 7 and 17q, loss of genes controlling methylation of histone 3, lysine 9 (H3K9) and activation of the PDGFRA, Erbb2, or Myc oncogenes(32,33). Consequently, there is need for immunohistochemistry, genetic and molecular studies in our setting to differentiate between nodular, anaplastic, medulloblastoma with extensive nodularity and large cell type medulloblastomas(9) and define the specific types that will recur more often, their prognosis and outcomes in a resource limited setting with a low number of radiotherapy facilities and a less number of patients who can afford chemotherapy..

Hemangioblastomas occur more commonly in men with the peak age of incidence noted to be between 20 and 50 years. They rarely

occur in children(34).Hemangioblastoma may also recur in women who are pregnant as the tumor increases in size during pregnancy despite earlier surgical resection (35).Our study reveals that all the patients at our centre with recurrent hemangioblastoma were male and aged between 26 and 45 years old. Their outcomes post re-craniotomy was of moderate disability.

All the other histological entities that were recurrent at our center were in single patients. Patients with recurrent brain tumors have a wide affect in their social, emotional and economic sphere in their life. The effects of recurrent brain tumor in young children are different relative to the effects in the young working age group. The insight of the recurrence of the brain tumor in the young children (0-13 years) is poor and therefore the overall impact on the parent/guardian is burdensome. The impact of recurrent brain tumors on young adults and their lifestyle is devastating. However, the overall quality of life in patients with recurrent brain tumors is controversial and in a study by Lamperti et. al it is shown to be significantly higher than those with a first time diagnosis of a brain tumor because of highly preserved coping strategies in the emotional sphere despite intact judgment and disease awareness (36).

Despite the recurrence of tumor, our study still showed good outcomes in more than 50% of the patients in this resource strained environment. However, there is need for other studies that find out mechanisms of reducing the rates of patients who had poor outcomes and death in our region.

In this study, there were a small number of patients that fit the inclusion criteria due to poor follow up of patients with recurrent brain tumors and lack of presentation to the hospital at recurrence. There were also incomplete records at the registry prior to three years and the cohort of patients is from a single center. It is proposed by the authors that this study should be replicated in multiple centers so as to be more reflective of the patterns of recurrent brain tumors in this region.

Conclusion and recommendations

This study identifies that the greater burden of recurrent brain tumors are craniopharyngiomas Glioblastomas were not as common in recurrence as shown in other literature and there is need to have a subsequent study that focuses on GBM and identify the loop holes in follow up of these patients. It is hence recommended that sophisticated microscopes be used intra-operatively so as to increase the levels of acceptable resection rates. The government, public and private insurance should also assist in sourcing for funds in helping patients with recurrent brain tumors to access better healthcare.

Competing interests

The authors declare that they have no competing financial or personal interests.

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Authors' contributions

JGK conceptualized and developed the concept, and participated in overall study organization. MAO developed the concept, collected and analyzed data, and drafted the manuscript. ANW developed the concept, and collected data. CNK developed the concept, and collected data. All authors participated in revising the article and final approval of the submitted version.

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