

Clinical-Pathological Features and Treatment Modalities of Primary Brain Tumors in Tanzania—4 Years of Institutional Experience

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Abstract

Background: The profile of primary brain tumors and treatment modalities employed in Tanzania remains largely unknown. The study aimed to describe the baseline clinical-pathological profile and treatment modalities for primary brain tumors in adults treated at the Ocean Road Cancer Institute (ORCI) from 2017 to 2020. Materials and Methods: This was a retrospective study conducted at ORCI by reviewing 61 medical records of patients with primary brain tumors over the age of 15 from January 2017 to December 2020. A structured questionnaire was used to retrieve information on sociodemographic, clinical-pathological characteristics, and treatment modalities. The 2007 WHO classification system and the International Classification of Cancer Diseases (ICD-0-3) were used for classification and diagnosis. The X² test and Fisher's exact test were used to compare the proportions and an independent t-test was used to compare the means. A P-value less than 0.05 was deemed statistically significant. The Results: The mean age of the females was 41.8 years and the mean age of males was 42.9 years. Overall M: F ratio was 1:1.2. Meningioma was the only tumor that was more commonly found in women with M:F of 1:2.1. The most prevalent symptom was headache (57.4%). Glioblastoma (GBM) was the most common tumor among adults (38%), followed by astrocytomas (23%) and meningioma (18%). Approximately 91.8% of all tumors occurred in the supratentorial region. The Frontal lobe was the most common site (29.5%). Approximately 81.9% of patients received surgery. The gross tumor resection (GTR) rate was 26.2%, and the subtotal tumor resection (STR) rate was 55.7%. Roughly 18% of the tumors were inoperable. An estimated 80.3% of respondents received radiation therapy. The radiotherapy technique was 3DCRT in two-thirds of the patients and the rest received conventional 2D radiotherapy. The mean equivalent dose in the 2 Gy fractions (EQD2) was 43.9 Gy. Respondents with low-grade intracranial tumors were treated with a mean EQD2 of 47.3 Gy, while those with high-grade intracranial tumors were treated with a mean EQD2 of 44.3 Gy and the difference was statistically significant. Only half of the patients who received adjuvant radiotherapy received it concurrently with chemotherapy. Temozolomide was the most widely used cytotoxic medication. **Conclusion**: Mean age of the patients was 41 years old. Most tumors were in the supratentorial area and GBM was the most common tumor. Only meningioma was a bit more common amongst females. Overall, radiotherapy doses and the gross tumor resection rates were low. Concurrent chemotherapy with radiotherapy was given to a few patients.

Keywords

Primary Brain Tumor, Clinical Profile, Treatment Modalities, Tanzania

1. Background

Primary brain tumors are a heterogeneous group of malignant and benign brain parenchymal tumors and the structures around them. Tanzania is ranked as a low human development index (HDI) country in the UN Development Program's four-level system. There were 330,000 cases of CNS cancer and 227,000 deaths worldwide in 2016, with an increase in age-standardized incidence rates of CNS cancer from 17.3% to 26.9% globally between 1990 and 2016. The top three countries with the highest number of incident cases were China, the USA, and India [1]. These tumors can be classified as grades 1 to 4 (WHO), while grades 1 and 2 are defined as benign tumors, while grades 3 and 4 are defined as malignant tumors [2]. According to Globocan 2018 estimates, the worldwide incidence of age-standardized rates (ASR) of the brain and nervous system cancer in high/very-high HDI (Human Development Index) regions versus low/medium HDI regions was 5.0 and 2.4 for men and 4.0 and 1.7 for women respectively. These incidence rates were about twice as high in high/very high HDI countries as in low/average HDI countries and slightly higher for men than for women [3].

In Tanzania, primary brain tumors are rare, accounting for around 3% of all cancer cases per year (hospital data). They are associated with significant morbidity and mortality due to the disease itself and treatment modalities, placing a greater burden on patients and caregivers [4]. Neuroepithelial tissue tumors are the most common primary intra-axial brain tumors. Gliomas are the most common and are further subdivided into oligodendrogliomas, astrocytomas, ependymomas, and mixed oligoastrocytomas [5].

The treatment of brain cancer is multidisciplinary and patients navigate between the neurosurgeon, radiologist, and oncologist [6]. Ocean Road Cancer Institute (ORCI) specializes in radiotherapy and chemotherapy for cancer patients while surgery is carried out in other centers. There is a paucity of data concerning clinic-pathological profiles of the patients with primary brain tumors in Tanzania and the treatment modalities used. The purpose of the study was to establish a baseline profile of patients with primary brain tumors in Tanzania.

2. Materials and Methods

2.1. Ethical Statement

Ethical clearance and permission to conduct the study were sought from the Ethical Clearance Board (IRB) of the ORCI. All methods were performed per the ORCI guidelines and regulations. A waiver of informed consent was requested and approved by ORCI Ethical Clearance Board because of the retrospective nature of the study design.

2.2. Study Design and Population

This was a retrospective descriptive study conducted at ORCI.ORCI is the largest cancer hospital in Tanzania. ORCI has specialized in providing radiotherapy and chemotherapy. It has two LINAC teletherapy units, two Cobalt-60 teletherapy units and two high dose rate (HDR) Cobalt-60 brachytherapy units. Approximately 6000 new cancer patients are seen at ORCI annually, out of which approximately less than 3% have a primary brain tumor. Approximately 95% of patients with primary brain tumors in Tanzania who need adjuvant treatment after surgery are usually referred to ORCI. We reviewed medical charts of patients having primary brain tumors who presented at ORCI from January 2017 to December 2020.

2.3. Inclusion and Exclusion Criteria

Patients who were above 14 years of age with histologically or radiologically confirmed primary brain and meninges tumors were included in the study. Patients who had metastatic brain malignancy, primary CNS lymphomas, hematopoietic malignancies, cranial nerve tumors, and primary bone tumors with intracranial extension were excluded from the study.

2.4. Treatment Protocol

All patients had brain MRI. Radiation treatment comprised external beam radiotherapy (EBRT). The radiotherapy technique was either two-dimensional radiotherapy (2DRT) using Cobalt 60 teletherapy units or three-dimensional conformal radiotherapy (3DCRT) using LINAC. Patients who were treated using 3DCRT were immobilized by using thermoplastic masks. Patients who were treated with 2DRT were treated with whole-brain radiotherapy without the thermoplastic masks. We mostly used 2DRT before we acquired LINAC in 2018. Clinical markup was used for 2DCRT planning and a CT simulator was used for 3DCRT. Target volumes and organs at risk were contoured when 3DCRT was used. The prescribed dose was 30 Gy/10 fractions when 2DRT was used and it was higher, according to the nature of the tumor when 3DCRT was used. Concurrent chemotherapy with radiotherapy and adjuvant chemotherapy was given according to the histology of the tumor.

2.5. Data Collection and Variables

We extracted data from medical charts by using a self-designed structured questionnaire. The covariates were age, gender, histology, tumor grade, tumor site, symptoms, surgery extent, radiotherapy dose, radiotherapy technique, and the use of concurrent chemo-radiotherapy. A pilot study was conducted to test the validity of the questionnaire and inter-rater reliability was used to assess the reliability of the questionnaire.

2.6. Statistical Methods

SPSS version 21 (SPSS Inc., Chicago, IL) was used for statistical analysis. Continuous variables were summarized and presented as frequency and mean, and we summarized categorical variables as proportions. X^2 test and Fisher's exact test were used to compare proportions and an independent sample t-test was used to compare means. A P-value of less than 0.05 was considered statistically significant.

3. Results

The study recruited 61 patients.

The most commonly affected age group was 15 - 39 years. The mean and median age of the respondents was 42.4 years and 41.4 respectively, with a range of 15 - 73 years. The ratio of females to males was 1:1.2. The mean age of the females was 41.8 years and the mean age of males was 42.9 years, although the difference was not statistically significant by t-test (P = 0.08) (**Table 1**).

The most common histology was Glioblastoma (GBM) (37.7%) and most respondents had a high-grade tumor (66%). About two-thirds of the respondents presented with headaches. The most commonly affected lobe was the frontal lobe (29.5%). About 91.8% of all tumors were supratentorial and 8.2% were infratentorial (Table 2).

GBM was the most common tumor (39.3%) (Figure 1).

Headache was the most common symptom, followed by motor weakness in all affected lobes (Figure 2).

Variable		Frequency	(%)
	15 - 39	28	45.9
Age (Years)	40 - 59	22	36.1
	60 - 79	11	18.0
Gender	Female	28	45.9
Gender	Male	33	54.1
	1	11	18.0
ECOG	2	26	42.6
ECOG	3	13	21.3
	4	11	15.0

Table 1. Characteristics of respondents (N = 61).

ECOG-Eastern Cooperative Oncology Group.

Variable		Frequency	(%)
	Low	17	34.0
Grade (n = 50)	High	33	66.0
	Headache	34	64.8
	Dizziness	10	18.9
	Weakness	18	34.0
	Seizures	9	17.0
Symptoms	Blindness	12	26.6
	Loss of balance	5	9.4
	Amnesia	5	9.4
	Loss of consciousness	6	11.3
	Incontinence	1	1.9
	Parietal	17	27.9
	Frontal	18	29.5
	Occipital	3	4.9
	Posterior fossa	5	8.2
Affected site	Temporal	9	14.8
	Meninges	1	1.6
	Thalamus	3	4.9
	Corpus callosum	1	1.6
	Cerebellum	4	6.6

Table 2. Clinical-pathological characteristics of the study population (N = 61).

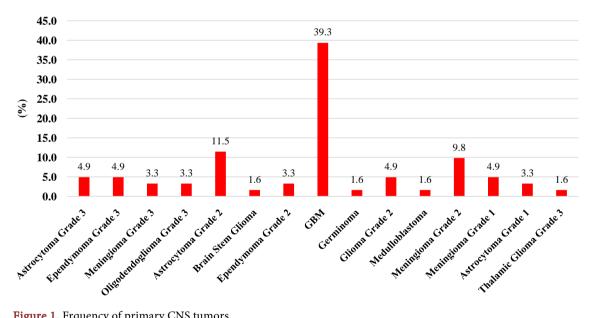


Figure 1. Frquency of primary CNS tumors.

In this series, most of the respondents had subtotal-tumor excision (STR) (55.7%). Respondents with Ependymoma had the highest gross tumor resection (GTR) rate (25%) followed by Astrocytoma (35%). The GTR rate for GBM was about 26%. About 80% of the respondents were given radiotherapy, and for about two-thirds of the respondents who were given adjuvant radiotherapy the

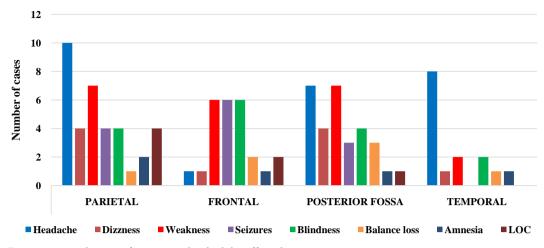


Figure 2. Distribution of symptoms by the lobe affected.

technique used was 3DCRT. The mean overall EQD2 was 45.8 Gy. About 28.6% of the respondents who were given adjuvant radiotherapy were also given concurrent chemo-radiotherapy and the most common cytotoxic drug used was Temozolamide (87.5%). About 60% of the patients with GBM were given concurrent temozolomide (**Table 3**).

Respondents with GBM had the highest mean age, and respondents with germinoma had the lowest mean age. Meningioma was more common in females (M:F = 1:2.7). Respondents with meningioma and medulloblastoma were treated with the overall highest mean EQD2 (53 Gy) and respondents with germinoma were treated with the overall lowest mean EQD2 (30 Gy). Among the respondents who were treated with 3DCRT, those who had meningioma were treated with the highest EQD2 (55.9 Gy) (**Table 4**).

About 82% of the patients had reports of histologic grades. Two-thirds of the tumors had high-grade histology. All GBM and Oligodendroglioma were of high grade. Tumors that had the highest proportions of low-grade histology were astrocytoma (75%), meningioma (71.4%), and brainstem glioma (66.7%) (Table 5).

Patients with high-grade intracranial tumors were treated with a lower dose (EQD2) in comparison to those with high-grade tumors and the difference was statistically significant by t-test (Table 6).

The 3-year OS rate was 18% and the median survival time was 24 months.

4. Discussion

The overall mean age in this study at diagnosis was 42.4 years and the age range was between 15 and 73 years, which is similar to a study by Lapointe *et al.* [7] but differs from a study done in Ghana by Ekpene *et al.* [8] showed a small mean age of 32 years (range 2 - 73 years) in patients with primary brain tumors. The higher mean age in our study could be because of the exclusion of pediatric patients.

The female to male ratio was 1:1.2 in the index study. It's consistent with an

Variable		Frequency	Percentage
	Gross Tumor resection	16	26.2
Surgery	Subtotal tumor resection	34	55.7
	No surgery	11	18
	Yes	49	80.3
Radiotherapy	No	12	19.7
Radiotherapy technique	2DRT	14	28.6
(n = 49)	3DCRT	35	71.4
Construct the second	Temozolomide	14	83.3
Concurrent chemotherapy $(n - 16)$	Vincristine	1	5.6
(n = 16)	Bevacizumab	1	5.6
Radiotherapy dose in	Less than 50 Gy	29	55.2
2 Gy fractions (Gy) $(n = 49)$	Over 50 Gy	20	40.8

Table 3. Treatment profile of study population (N = 61).

2DRT—Two-dimensional radiotherapy; 3DCRT—Three-dimensional conformal radio-therapy.

Histology	Mean age (Years)	M:F	Location (ST/IT)	Mean EQD2 (Gy) Overall (n)	Mean EQD2 (Gy) 2D (n)	Mean EQD2 (Gy) 3DCRT (n)
GBM	52.2	1:1.1	22/1	43.2 (20)	32.5 (7)	49.5 (13)
Astrocytoma	34.4	1:0.6	13/1	48.1 (11)	32.5 (2)	51.6 (9)
Oligodendroglioma	49.5	1:0	2/0	32.5 (2)	32.5 (2)	-
Germinoma	17.0	1:0	1/0	30.0 (1)	30.0 (1)	-
Ependymoma	29.5	1:0.3	4/0	50.8 (3)	-	50.8 (3)
Meningioma	42.3	1:2.7	10/1	52.9 (8)	32.5 (1)	55.9 (7)
Glioma	30.8	1:0.3	4/1	41.6 (3)	31.2 (1)	46.8 (2)
Medulloblastoma	51.0	0:1	0/1	53.0 (3)	-	53.0 (1)

ST—Supratentorial; IT—Infratentorial; GBM—Glioblastoma; EQD2—Equivalent dose in 2 Gy fractions.

Table 5. Distribution of histology by grade and GTR rate.

Histology	Low grade (%)	High Grade (%)	GTR rate (%)	Total (%)
GBM	0 (0)	22 (100.0)	26.1	22 (100.0)
Astrocytoma	9 (75.0)	3 (25.0)	35.7	14 (100.0)
Oligodendroglioma	0 (0)	2 (100.0)	0	2 (100.0)
Ependymoma	1 (25.0)	3 (75.0)	50	4 (100.0)
Meningioma	5 (71.4)	2 (28.6)	18	7 (100.0)
Brainstem Glioma	2 (66.7))	1 (33.3)	20	3 (100.0)
Total (%)	17 (34.0)	33 (66.0)	26.2	50 (100.0)

GBM—Glioblastoma.

Table 6. Association between mean radio	herapy dose (EQD2) and	grade of tumors.
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	Grade	N	Mean	Std. Deviation	Std. Error Mean
Mean radiotherapy	Low	12	47.42	10.389	2.999
dose	High	27	44.32	13.007	2.503

P = 0.02.

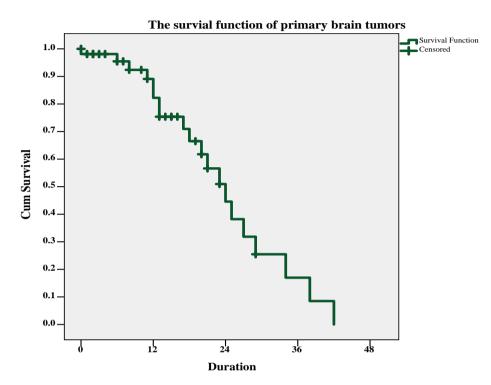


Figure 3. Overall survial rate.

Ekpene *et al.* study in Ghana [8]. In this study, meningioma was more common in females with M:F ratio of 1:2.7. Other studies have also shown a higher preponderance of women developing meningioma and they linked this preponderance with reproductive and hormonal factors, which predisposes women to be more at risk compared to males [8].

Most of the tumors were of high grade (66.7%) and the most common histology was glioblastoma (GBM) accounting for 39.3%. Similar findings were observed in England by Wanis *et al.* [9]. Some other studies reported meningioma to be the most common primary brain tumor, which is not in keeping with findings from the index study, possibly because of ethnic, geographical, and environmental differences [10]. The finding that most of the tumors were of high grade could be attributed to the type of patients that are referred to ORCI. ORCI is a tertiary hospital specializing in providing radiotherapy and chemotherapy as adjuvant treatment, while surgery is done in other centers. Patients with high-grade tumors and subtotal resection (STR) are usually referred for adjuvant treatment. That being said, Wanis *et al.* also found that the majority (two-thirds) of primary brain tumors in England are malignant (high grade) by using a population-based cancer registry [9].

The most affected site was the frontal lobe. This is consistent with other studies that have also shown frontal lobe dominance, especially in malignant tumors [11]. The most common symptoms were headaches (64.8%), weakness (34%), vision impairment (26.6%), and seizures (17%). Weakness and blindness could be because of the direct effect of tumor or post-surgery sequelae [6]. The headache was also the most common symptom in other studies [11] although other studies showed seizures as the most common presenting symptom [12]. Seizures have been reported to be more frequent in low-grade gliomas and GBM, developing from low-grade astrocytomas as compared to "primary" GBM. A lower incidence of epilepsy in high-grade gliomas may be because of their preferentially white matter location and the incessant tumoral growth that might prevent the development of the "epileptogenic focus". We might relate a low frequency of epilepsy in these patients to shorter survival from high-grade tumors compared with low-grade tumors [13]. However, in this study, there was no statistically significant association between grade and the occurrence of seizures, perhaps because of the inclusion of meningiomas.

Treatment decisions are based on tumor type, tumor site, malignant potential, the patient's age, and physical condition. Treatment may require only surveillance, but commonly includes surgery, radiotherapy, chemotherapy, or a combination. The preferred treatment of primary brain tumors is the maximal safe surgical removal of the tumor, followed by radiotherapy and chemotherapy. Benefits of maximal resection include relief of mass effect, decreased tumor burden, improved diagnosis, and a trend toward prolonged survival [14].

In this series, the overall gross tumor resection (GTR) rate for all intracranial tumors was 26.2%, but it ranged from 0% in oligodendrogliomas to 50% in ependymomas. The GTR rate for GBM was 26.1%. In a retrospective study done in Turkey to assess the extent of resection among gliomas, they showed GTR rate was 62.2% [15]. This difference could be because of a difference in the definition of the extent of surgery and variation in resource availability. In the index of study, the extent of resection was determined by using the surgical notes after resection and not the post-operative brain MRI. Post-operative brain MRI is a gold standard in assessing the extent of tumor resection [6]. It will be very interesting to find out how the survival of patients with intracranial tumors at ORCI compares to that in other parts of the world with such low GTR rates.

Radiotherapy can be used as primary treatment or adjuvant treatment following surgical resection. Radiotherapy can improve progression-free survival and overall survival in patients with high-risk low-grade gliomas, defined as patients younger than 40 years with subtotal resection or biopsy, or patients older than 40 years with any type of resection [14]. A total dose of 60 Gy in 30 fractions is usually delivered for GBM, and a dose of 59.4 Gy in 33 fractions is typically given for anaplastic gliomas [16]. A systemic analysis done by Kaur *et al.* Showed that doses below 50 Gy are inadequate for treating atypical meningioma and grade three meningioma [17]. In this study, the mean dose in 2 Gy fractions (EQD2) used to treat high-grade intracranial tumors was only 44.5 Gy, while that for low-grade intracranial tumors was 47.3 Gy. Doses of radiation therapy were low, possibly due to advanced disease at the time of presentation, unavailability of 3DCRT in the years before 2018, and poor patient performance status.

Temozolomide was administered to only two-thirds of patients with GBM who also received adjuvant radiotherapy following surgery, possibly as a result of affordability issues. Concurrent use of temozolomide and radiotherapy in high-grade glioma has been associated with improved survival and better outcomes compared to radiotherapy alone as was shown in a study by Stupp *et al.* which showed temo-zolomide improved median survival in newly diagnosed GBM when given concurrently with radiotherapy and for maintenance after radiotherapy [18].

5. Conclusion

In conclusion, this is the first single institutional study from Tanzania to elaborate on clinical-pathological features and treatment modalities of patients with primary brain tumors. GBM was the most common tumor among adults. The GTR rate was low and radiotherapy doses were low. Few patients were able to afford temozolomide. The limitations of this research include histological classification without molecular profiling. In addition, the study was subject to reference bias since ORCI is the reference cancer center, which provides mainly radiotherapy and chemotherapy without surgical facilities. Consequently, these outcomes may not be generalized to centers with surgical facilities. We couldn't gather some information because of the retrospective nature of the study. A population-specific cancer registry is essential for obtaining the exact incidence of primary brain tumors in Tanzania.

Ethics Approval and Consent to Participate

Permission to carry out the study was sought from Ocean Road Cancer Institute Ethics Committee with reference number 10/VOL.XXI/16B. All methods were performed according to ORCI guidelines and regulations.

Availability of Data and Materials

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

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Authors' Contribution

Concept and design: Alita S. Mrema, Emmanuel Lugina, Salama Iddy;

Collection and assembly of data: Salama Iddy, Alita S. Mrema, Emmanuel Lugina;

Data analysis and interpretation: Emmanuel L. Lugina, Alita S. Mrema;

Financial support: Alita S. Mrema, Emmanuel Lugina;

Manuscript writing: Emmanuel L. Lugina, Alita Mrema;

Final approval of manuscript: Alita S. Mrema, Salama Iddy, Emmanuel L. Lugina;

Agree to be accountable for all aspects of work: Alita S. Mrema, Salama, Mamsau Ngoma, Nanzoke Mvungi, and Emmanuel L. Lugina.

Conflicts of Interest

The authors do not disclose any conflict of interest.

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Appendix

The questionnaire

- 1) Hospital registration number
- 2) Age (Years)
- 3) Gender
 - a) Female
 - b) Male
- 4) Presenting symptoms (Circle all that apply)
 - a) Headache
 - b) Dizziness
 - c) Weakness
 - d) Seizures
 - e) Blindness
 - f) Loss of balance
 - g) Amnesia
 - h) Loss of consciousness
 - i) Incontinence
- 5) What lobe of affected?
 - a) Parietal
 - b) Frontal
 - c) Temporal
 - d) Occipital
- 6) Histology
- 7) Grade
 - a) Low grade
 - b) High Grade
- 8) Year of diagnosis
- 9) Type of surgery
 - a) Gross tumor resection
 - b) Subtotal tumor resection
- 10) Was adjuvant radiotherapy given?
 - a) Yes
 - b) No
- 11) Type of radiotherapy
 - a) 2D radiotherapy
 - b) Conformal radiotherapy
- 12) Dose of radiotherapy in 2Gy fractions
- 13) Was concurrent chemotherapy given?
 - a) Yes
 - b) No
- 14) Type of chemotherapy given
- 15) Date at last contact
- 16) Status at last contact

a) Aliveb) Deadc) Loss to follow up

Abbreviation

GBM: Glioblastoma multiforme; EQD2: Equivalent dose in 2Gy fractions; ASR: Age-standardized rate; HDI: Human development Index; CNS: Central nervous system; GTR: Gross tumor resection; STR: Subtotal tumor resection.