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SURVIVAL AND QUALITY OF LIFE IN PATIENTS WITH BRAIN METASTASIS AFTER PALLIATIVE RADIOTHERAPY TO THE BRAIN IN LAGOS STATE, NIGERIA

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ABSTRACT

Background: Brain metastases are a devastating complication of cancer affecting 20-40% of patients with systemic disease. Patients with brain metastasis have limited survival; therefore, improving the quality of life of the patient is the primary goal of treatment by employing treatment with minimal complications.
Objective: To assess median survival and the quality of life of patients who received whole brain radiotherapy for brain metastases.
Methods: Patients with radiologically confirmed brain metastasis who had whole brain radiotherapy between March 2021 and February 2022 at Lagos University Teaching Hospital and Eko Hospital in Nigeria were recruited. Overall survival at 6 months was estimated using Kaplan-Meier survival curve and compared using log-rank test. Cox regression analysis was used to identify independent predictors of mortality (sex, stage of primary disease at diagnosis, number of metastases and size of metastasis). Quality of life was assessed using FACT-Br questionnaire at baseline and monthly for 6 months.
Results: A total of 25 patients were recruited. The mean age was 48.12±12.9 years, and the vast majority of the participants were females (92.0%). Common clinical features of brain metastasis were headaches (68.0%), motor deficits (52.0%), seizures (32.0%), speech abnormalities (32.0%), irrational behaviour (30.0%) and loss of consciousness (30.0%). Breast cancer was the most common primary malignancy (88.0%), and just over half of the patients (56.0%) presented with locally advanced or metastatic disease. Most of the brain metastases were located in the cerebrum (76.0%) and cerebellum (48.0%). Over half of the patients had more than 2 brain metastases (56.0%), and the size of the brain metastasis was > 5cm in 36.0% of the participants. The Kaplan-Meier estimated overall survival at 6 months post diagnosis of brain metastasis was 30.0%, and the median time to death post diagnosis of brain metastasis was 2 months. The overall quality of life score was better at 6 months compared to baseline (132.5 vs 105.0).
Conclusion: The overall survival of patients with brain metastasis at 6 months post diagnosis was 30.0%, with a median overall survival of 2 months. Whole-brain radiotherapy was beneficial to the patients who were alive at 6 months, as indicated by improved quality of life.

Keywords: Brain metastasis, survival, outcome, radiotherapy, quality of life.

INTRODUCTION

About 20%–40% of cancer patients will develop brain metastasis during their illness; this is associated with significant morbidity and confers a poor prognosis on the patients involved.[1–3] The incidence of brain metastasis varies from country to country, ranging from 2-14.3/100,000 population, and a prevalence of about 9.6%.[4–6] Common cancers that spread to the brain arise from the lung, melanoma, kidney, breast and colorectal cancers.[4] Brain metastasis accounts for 20% of all cancer deaths annually in the United States.[7,8] About 60% of patients with brain metastases have subacute symptoms. These symptoms include headaches, seizures, nausea, vomiting, nuchal rigidity, photophobia, cognitive dysfunction, and motor dysfunction. Headache was the most common symptom associated with brain metastasis.[9,10,11]

Treatment options include surgical resection, whole-brain radiotherapy (WBRT), and radiosurgery (CyberKnife or gamma knife). Supportive treatment includes corticosteroids, antiepileptic medications, psychosocial, family and spiritual support.[10] Radiation therapy is a primary treatment modality for unresectable brain metastasis; the treatment techniques considered are stereotactic radiosurgery (SRS) and whole-brain radiotherapy. Stereotactic radiosurgery is strongly recommended for 1-4 brain metastases <2cm, while whole-brain radiotherapy (WBRT) is the standard treatment for patients with extensive brain metastases.[12] Radiotherapy aims at delivering a palliative dose of radiation to reduce symptoms by reducing the size of the tumour and surrounding oedema. Whole-brain radiotherapy could be added to either SRS or surgical resection, and it is associated with improved outcomes.[13] This modality helps to reduce neurologic symptoms arising from the metastatic disease and reverse morbidity in the brain.[9]

Treatment outcome and survival depend on several prognostic factors, which include: performance status, age, and primary tumour control.[11,14] Other factors, such as histology of the primary tumour, number and size of metastases, are also crucial in the initial evaluation of the patient.[14] For patients with breast cancer, after a diagnosis of brain metastasis, the median survival can be as short as five months in triple-negative breast cancer and 10–18 months in the other subtypes.[15] In a retrospective study conducted at Ahmadu Bello University Teaching Hospital, Zaria, Nigeria, 30 patients who had radiotherapy to address metastatic brain disease were evaluated; the median survival was three months.[9] In a systematic review carried out by Solange et al., among patients with non-small cell lung cancer, it was observed that treatment with whole-brain radiotherapy was associated with worse overall survival and did not improve the quality of life.[16]

Quality of life aims to focus on the patient's general well-being, improving survival as well as minimising treatment risks and maximising benefits. It is also associated with physical and psychological support.[17] Patients with brain metastases have limited survival; therefore, treatment options that have fewer side effects and maximise the quality of life are considered.[2] According to the systematic review of the quality of life of brain metastasis radiation trials carried out by Wong et al., the

quality of life worsened in patients with more unsatisfactory prognostic characteristics such as advanced age, poor performance status, presence of extracranial metastasis and uncontrolled primary tumour. At the same time, there was an improvement in the quality of life in patients with better prognosis.[2]

In Nigeria, data on the survival and quality of life of patients with brain metastases who received palliative radiotherapy are limited. This study aims to assess the survival and quality of life in patients with brain metastasis treated with whole brain radiotherapy.

MATERIALS AND METHODS

This was a prospective study carried out in the leading referral tertiary hospitals in Lagos: Radiotherapy and Oncology Department of the Lagos University Teaching Hospital (LUTH), and the Radiotherapy unit, Eko Hospital, Lagos, from March 2021 to February 2022. All patients ≥18 years, with histopathologically confirmed primary malignancies and radiologically confirmed brain metastasis, within the study duration, were recruited. They subsequently had whole-brain radiotherapy (30Gy in 10#). None of the patients had SRS or metastasectomy. Patients with previous whole-brain radiotherapy were excluded.

Data Collection

All the participants were interviewed using a semi-structured questionnaire to gather data on patients' sociodemographic data, and clinical information was retrieved from the participants' medical records. The variables studied were classified into four domains: biodata, clinical information, treatment received and the quality of life. Quality of life was assessed using the Functional Assessment of Cancer Therapy–Brain (FACT-Br), a validated disease-specific instrument for patients with brain tumours and brain metastases, which measures physical, social/family, emotional, and functional well-being, as well as additional brain-tumour–specific concerns. Participants completed the FACT-Br at baseline before radiotherapy and at scheduled follow-up intervals after treatment. Each item was rated on a 5-point Likert scale ranging from 0 ("not at all") to 4 ("very much"), reflecting the patient's experiences over the preceding seven days. Item scores within each domain were summed to generate domain-specific scores, with negatively worded items reverse-scored according to FACT-Br scoring guidelines. The overall FACT-Br score was then derived by summing the scores of all domains, with higher scores indicating better perceived quality of life. These scores were used to evaluate changes in quality of life over time and to assess the impact of palliative whole-brain radiotherapy on patient-reported outcomes. FACT-Br was administered by a trained research assistant every month to assess the quality of life and symptoms that may suggest improvement or relapse/recurrence, as well as to offer necessary supportive treatment when needed.

Statistical Analysis

Data was analysed using SPSS version 24. Frequencies, proportions, means and medians were used to summarise data. Overall survival was defined as the time interval between the date of radiological diagnosis of brain metastasis and the date of death. Patients lost to follow-up were censored. Kaplan Meier was used to estimate survival at 6 months and was

compared using the log-rank test. Cox regression analysis was used to identify independent predictors of mortality.

Ethical Consideration

Ethical clearance to conduct this was obtained before commencement of the study from the Health Research Ethics Committee of the Lagos University Teaching Hospital, Lagos. Written informed consent was obtained from the study participants, and there was strict maintenance of the privacy of participants' data. For patients who could not give informed consent due to the effect of brain metastasis, assent was obtained from the patients, while informed consent was obtained from a legally authorised representative. The study was conducted in accordance with the ethical standards of the Institutional Research Committee and the 1964 Helsinki Declaration.

RESULTS

A total of 25 patients (out of 35 patients) who presented with brain metastasis within the study period were recruited. The mean age was 48.1±12.9 years. The majority of the participants were females (92.0%), married (68.0%), and had tertiary level of education (64.0%). Hypertension and diabetes mellitus were present in 7 (28.0%) and 3 (12.0%) patients, respectively. Common clinical features of brain metastasis were headaches (68.0%), motor deficits (52.0%), seizures (32.0%), speech abnormality (32.0%), irrational behaviour (30.0%) and loss of consciousness (30.0%). Breast cancer was the most common primary malignancy (88.0%), carcinoma was the most common histologic type of primary malignancy (92.0%) and just over half of the patients (56.0%) presented with locally advanced or metastatic disease. (Table 1A)

Surgery (80.0%) and chemotherapy (80.0%) were the most common treatment options received for the primary malignancy, from initial diagnosis to presentation with brain metastasis. Most of the brain metastases were located in the cerebrum (76.0%) and cerebellum (48.0%). 24.0% and 20.0% of the study participants presented with solitary brain metastatic lesions and two brain metastatic lesions, respectively, while over half of the patients had more than 2 brain metastases (56.0%). The size of the brain metastasis was ≤ 5cm in 64.0% of the participants. (Table 1B)

At 6 months post diagnosis of brain metastasis, 16 (64,0%) were deceased, and 9 (36.0%) were censored (5 (20.0%) and 4 (16.0%) participants were lost to follow-up and alive, respectively). The Kaplan-Meier estimated overall survival at 6 months post diagnosis of brain metastasis was 30.0%, and the mean and median time to death post diagnosis of brain metastasis were 3.46±0.45 months and 2 months, respectively. [Figure 1] Sex, stage at presentation, number and size of brain metastasis had no statistically significant impact on survival; however, a trend was observed between the size of brain metastasis and survival. The median survival of patients with brain metastasis ≤ 5cm was longer compared to those with brain metastasis >5cm (6months vs 2months, p=0.239). However, this finding was not statistically significant. (Figure 2, Table 2)

There was a drop in the overall quality of life score at 2 months post-treatment compared to baseline (99.0 vs 105.0). For those who were

alive at 6 months, the quality-of-life score improved thereafter, and the overall quality of life score was better at 6 months compared to baseline (132.5 vs 105.0). [Table 3 and Figure 3] For the subscale domains, the physical well-being, emotional well-being, functional well-being and brain cancer symptoms subscales at 6 months were better compared to the baseline, while the social subscale was better at baseline compared to 6 months. (Table 3 and Figure 3).

Table 1A: Sociodemographic and Clinicopathologic Characteristics

Variable	Frequency (n=25)	Percentage
Mean Age at diagnosis (Years)	48.12±12.9	
Age range	25-75	
Sex		
Male	2	8.0%
Female	23	92.0%
Marital status		
Single	2	8.0
Married	17	68.0
Widow	6	24.0
Educational level		
Primary	2	8.0
Secondary	7	28.0
Tertiary	16	64.0
Comorbidity (Multiple response)		
Hypertension	7	28.0
Diabetes	3	12.0
Rheumatoid arthritis	1	4.0
Stroke	1	4.0
Clinical features at presentation		
Headache	17	68.0
Motor deficit	13	52.0
Seizure	8	32.0
Nausea/ vomiting	8	32.0
Irrational talk	7	28.0
Irrational behavior	5	20.0
Loss of consciousness	5	20.0
Cognitive dysfunction	3	12.0
Photophobia	2	8.0
Primary site of disease		
Breast cancer	22	88.0
Lung	1	4.0
Parotid	1	4.0
Gynecologic	1	4.0
Histological type		
Carcinoma	23	92.0
Sarcoma	1	4.0

Melanoma	1	4.0
Stage of Primary cancer at diagnosis		
I	5	20.0
II	6	24.0
III	8	32.0
IV	6	24.0

Table 1B: Sociodemographic and Clinicopathologic Characteristics

Variable	**Frequency**	**Percentage**
Treatment before brain metastasis		
Surgery	20	80.0
Chemotherapy	20	80.0
Radiotherapy	6	24.0
Targeted therapy	6	24.0
Hormone therapy	5	20.0
Location of metastasis in the brain		
Cerebrum	19	76.0
Cerebellum	12	48.0
Meninges	2	8.0
Brain stem	1	4.0
Grey/white matter junction	1	4.0
Number of brain metastases		
1	6	24.0
2	5	20.0
>2	14	56.0
Size of metastatic lesion		
≤5cm	16	64.0
>5cm	9	36.0
Mode of diagnosis		
CT	13	52.0
MRI	12	48.0
Other metastatic site apart from the brain (Multiple response)		
Lungs	7	28.0
Liver	4	16.0
Bone	5	20.0
Status at 6 months		
Censored	9	36.0
Dead	16	64.0

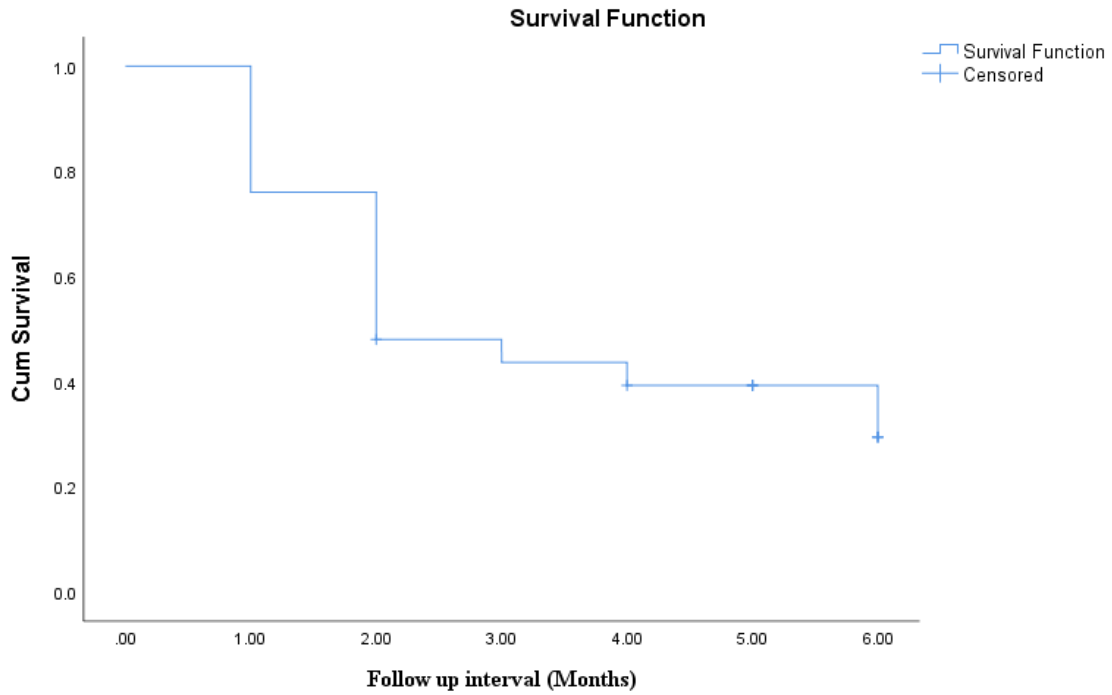


Figure 1: Kaplan-Meier estimated survival post brain metastasis diagnosis

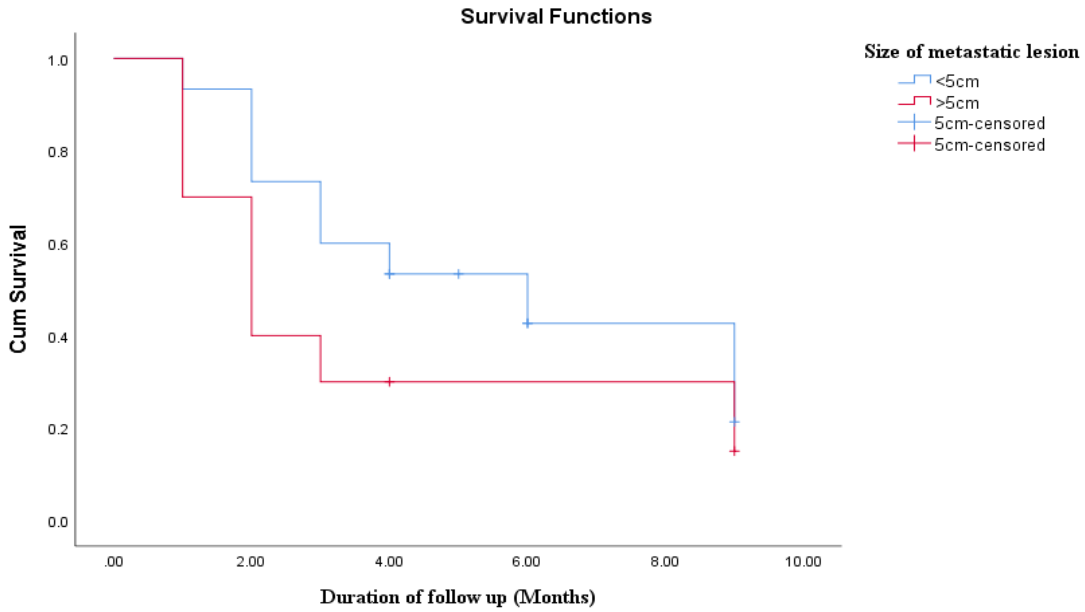


Figure 2: Kaplan-Meier estimated survival post brain metastasis diagnosis by the size of the metastatic brain lesion.

Table 2: Cox Regression Analysis for Potential Prognostic Factors.

	RR	95% CI	p-value
Sex			
Male	1		
Female	0.327	0.066-1.629	0.172
Stage of Primary cancer at diagnosis			
I	1		
II	0.978	0.132-7.265	0.982
III	2.826	0.349-22.903	0.322
IV	3.738	0.275-59.754	0.331
Number of metastatic deposits			
1	1		
2	0.847	0.167-4.312	0.842
>2	1.052	0.226-4.896	0.948
Size of metastatic lesion			
<5cm	1		
>5cm	2.903	0.619-13.624	0.177

Table 3: Mean quality of life scores at different intervals.

Time	**N**	Physical	Social	Emotional	Function	BR	Overall
Baseline	25	17.0	18.0	15.0	5.0	48.0	105.0
1 month	25	18.0	15.0	17.0	6.0	50.0	107.0
2 months	20	16.5	14.5	16.0	6.0	54.0	99.0
3 months	11	19.0	12.0	16.0	11.0	55.0	118.0
4 months	11	22.0	12.0	19.0	10.0	56.0	117.0
5 months	8	23.0	12.0	15.5	11.5	68.0	128.0
6 months	4	23.0	14.5	17.5	14.0	63.0	132.5

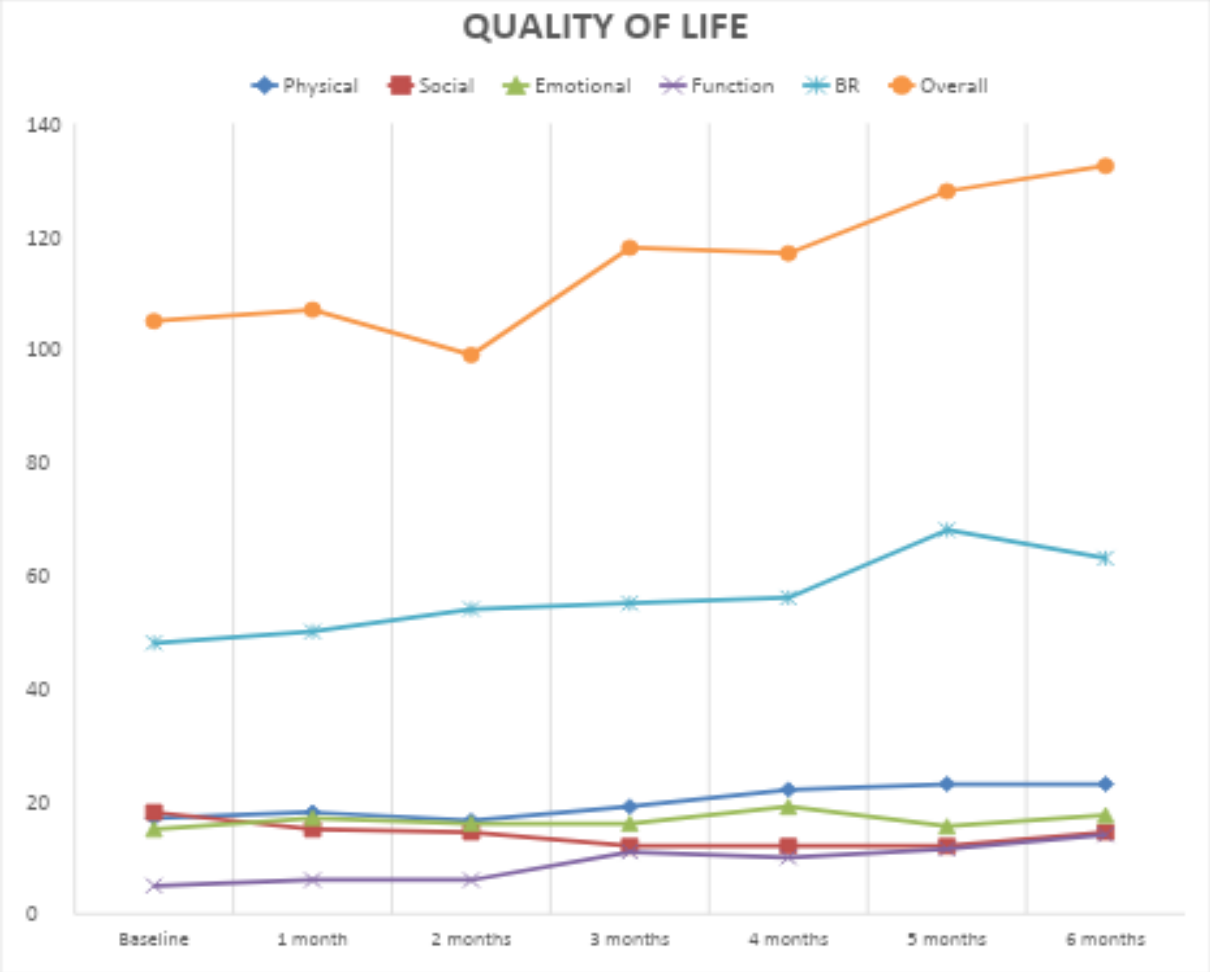


Figure 3: Trend of mean quality of life scores

DISCUSSION

In this study, the mean age of the study participants was 48.12±12.9 years, and the majority (92.0%) were females. These findings are in tandem with results from other studies, which revealed that the mean age of patients with brain metastasis ranged from 51 years to 53 years[18,19,20] and the median age ranged from 54 years to 63 years.[21,22,23] However, the sex distribution in our study, though similar to findings from a study conducted in Nigeria, which showed female preponderance (82.7%),[19] differed from studies done in Romania and Switzerland, which reported slight female preponderance (54.3% and 56.0% respectively),[22,23] as well as studies done in China and Seoul, which reported male preponderance (56.5% and 72.0% respectively).[12,21] This difference could be because breast cancer is the most predominant cancer in Nigeria, and it has a high probability of metastasis to the brain compared to prostate cancer, which is the most common cancer

among males but is less likely to spread to the brain.

Common clinical features in our study were also reported by Chikani et al and Gao et al in studies done in Nigeria and China.[18,20] Patients, caregivers and physicians need to be aware of the clinical features for early recognition and prompt management.

The most common primary malignancy of brain metastasis in our study was breast cancer (88.0%), and this is in tandem with findings from other studies done in Enugu and Lagos (both in Nigeria), which revealed breast cancer as the most common primary malignancy with brain metastasis (29.0% and 65.4%, respectively).[18,19] The lungs were the most common site of primary malignancy for brain metastasis in studies done in Romania, Switzerland, Seoul and China (42.9%, 54.0%,68.0% and 69.6% respectively).[20,21,22,23] This is not unrelated to the fact that breast cancer is the most common malignancy in Nigeria, accounting for about a quarter of all new cancer cases in Nigeria in 2022.[24] Carcinoma was the most frequent histological type of primary malignancy, accounting for 92.0% of cases in our study. This is not unexpected, as it is the most common histological type of breast cancer,[25] which was the most common primary of brain metastasis in our study.

Over half of the participants in our study presented with locally advanced or metastatic primary disease, and most of them had surgery and chemotherapy for the primary disease. Suteu et al demonstrated similar findings as they reported that 74.3% of their study participants with brain metastasis presented with stage 3 or 4 disease.[22] Higher stage of primary disease can be associated with early brain metastasis[26] and reduced survival.

This study revealed that the common sites of brain metastasis were the cerebrum (76.0%), cerebellum (48.0%) and meninges (8.0%). Similar findings were demonstrated by the study done in Enugu State, Nigeria, which showed that metastatic brain lesions were commonly present in the cerebrum [frontal lobe (80.6%), parietal lobe (71.0%) and temporal lobe (54.8%)], cerebellum (41.9%) and leptomeninges (9.7%).[18] The site of brain metastatic lesion could determine the clinical presentation, and the clinical manifestation can provide clues to the location of the brain metastasis. Most of our study participants (76.0%) had two or more brain metastatic lesions, while 36.0% had lesions greater than 5cm. Studies done in Romania, China and South East Nigeria corroborated these findings as they demonstrated that the proportion of patients with two or more brain metastasis ranged from 54.3% to 74.2%,[18,20,22] while another study done in Nigeria by Ayandipo et al revealed 42% of the patients with brain metastasis had metastatic lesions greater than 4cm.[27] These findings corroborate those from our study. The number of metastatic brain lesions, as well as their dimension, which may be related to the clinical stage of the disease, could influence the choice of treatment modality[28] as well as the treatment outcome.[29]

Sixteen percent of the participants in this study were alive at six months after diagnosis of brain metastasis, and the Kaplan-Meier estimated survival at 6 months post-diagnosis of brain metastasis was 30.0%, while the mean and median overall survival were 3.46 months

and 2 months post-diagnosis of brain metastasis, respectively. The study done in South East, Nigeria demonstrated similar findings, as it reported that 16.1% of patients with brain metastasis were alive at 6 months,[18] while another study done in The Netherlands reported that the 6 months Kaplan-Meier estimated survival of patients with brain metastasis from breast and lung cancer were 36.0% and 26.0% respectively[30] and these findings are similar to those in our study. Findings from some studies reported that the median overall survival of patients with brain metastasis who had whole brain radiotherapy ranged from 3.6 months to 6 months[6,19,23,31,32] and these differed slightly from that in our study, which revealed a median overall survival of 2 months. This slight difference could be due to the late stage of presentation as well as the number and size of brain metastasis seen among our study participants, as over half of the patients had locally advanced/metastatic disease at presentation and 76% of the patients had multiple brain metastasis, however, Log rank test and Cox regression analysis showed that these factors had no statistically significant impact on the survival of patients with brain metastasis in our study. This could be due to the small sample size, resulting in reduced power in our study. Worthy of note is that patients with brain metastasis >5cm had worse survival and a higher relative risk of death compared to those with brain metastasis ≤5cm (median survival: 2 months vs 6 months, p=0.239, RR=2.9, CI: 0.619-13.624, p=0.177). This finding was, however, not statistically significant. In contrast to our findings, Suteu et al demonstrated that patients with brain metastasis <5cm^3 and patients with solitary brain metastasis had better survival compared to patients with brain metastasis >5cm^3 and patients with more than one brain metastasis (p=0.04 and p<0.04, respectively).[22] This difference could be due to the smaller sample size in our study, reducing the power of the study.

In this study, an improvement in the mean overall quality of life score was noted at 6 months (for patients who were alive at 6 months) compared to baseline after whole brain radiotherapy (132.5 vs 105.0). There was also improvement at 6 months compared to baseline in the mean score of the following subscale domains: physical wellbeing (17.0 vs 23.0), emotional wellbeing (15.0 vs 17.5), functional wellbeing (5.0 vs 14.0) and brain cancer symptoms subscale domains (48.0 vs 63.0). However, the mean score for the social well-being domain was worse at 6 months compared to baseline (18.0 vs 14.5). These findings are in tandem with those from a Romanian study, which reported significantly higher scores for quality of life/functional domains after whole-brain radiotherapy for patients with brain metastasis compared to baseline.[21] Another study done in Nigeria also corroborated these findings, as it reported statistically significant improvement in physical and emotional functioning in patients with brain metastasis at 6 months post whole brain radiotherapy compared to baseline. The study also reported symptom alleviation at 6 months post whole brain radiotherapy, compared to baseline, though not statistically significant.[18] The improvement in quality of life, which is an important goal of management for patients with brain metastasis, could be attributed to the alleviation of symptoms following whole brain radiotherapy[18,21] as shown by the improvement in mean scores of the brain cancer symptoms subscale domains

at 6 months, compared to baseline, in our study. On the other hand, the improvement in quality of life could be due to the mortality of patients with lower quality of life, resulting in an illusory improvement in quality of life.

Limitations

A major limitation of this study was the small sample size, which reduced the power of the study and limited further statistical analysis. In addition, there is the possibility of under/over reporting by the study participants. Despite these limitations, the study was able to describe the treatment outcomes (overall survival and quality of life) of patients with brain metastasis treated with whole-brain radiotherapy. Further studies, using a larger sample size for better representation and a longer follow-up period, are recommended.

CONCLUSION

The overall survival of patients with brain metastasis at 6 months post diagnosis was 30.0%, with a median overall survival of 2 months. Whole-brain radiotherapy was beneficial to the patients as indicated by improved overall quality of life.

Declarations

Conflict of interest

The authors have no conflicts of interest to declare.

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