Original Article

Preliminary Findings on Metastatic Brain Tumors in Enugu, Southeast Nigeria

Mark C. Chikani[1], Samuel Okpara[1], Mesi Mathew[1], Augustine Onuh[2], Vitalis Okwor[3], Wilfred Mezue[1]

[1]Department of Surgery, Neurosurgery Unit, University of Nigeria Teaching Hospital, [2]Department of Radiation Medicine, Radiology Unit, University of Nigeria Teaching Hospital, [3]Department of Radiation Medicine, Radio-Oncology Unit, University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu, Nigeria

Abstract

Background: Metastatic brain tumors (MBTs) are the most common brain neoplasms seen clinically and are often associated with poor outcomes. This study highlights the demographic, clinical, and radiological profiles as well as outcomes of MBTs managed in a tertiary hospital in Southeast Nigeria. **Methods:** This was a 1-year prospective observational study of patients with MBT who presented to the neurosurgery unit of the University of Nigeria Teaching Hospital, Enugu, from December 2018 to November 2019. Data on the demography, clinical and radiological features, treatment, and outcomes were collected and analyzed. **Results:** Of the 31 patients with MBTs, 58.1% were female and 41.9% male. The mean age was 51.0 ± 15.2 years. The most common presenting features were limb weakness (77.4%), headache (58.1%), and personality changes (54.8%). About a quarter (26.7%) were fully conscious at presentation. Only 45.2% knew that they had a systemic malignancy (SM) before presentation. The breast (29.0%), lungs (22.6%), and skin (19.3%) were the common sources of metastases. The lesions were solitary in 25.8% and multiple in 74.2%. They were predominantly frontal (80.6%), with bilateral distribution in 64.5% of patients. Radiotherapy was done in 58.1% and surgery in 6.5% of patients. Prior knowledge of the existence of a SM ($P = 0.045$) and unilateral brain involvement ($P = 0.013$) were associated with better 30-day survival. **Conclusion:** The breast is the most common source of brain metastasis. Prior knowledge of the existence of a SM and unilateral brain involvement is associated with better short-term survival.

Keywords: Brain, metastasis, primary, survival

Introduction

Metastatic brain tumors (MBTs) are the most common brain tumors seen clinically, constituting more than 50% of cerebral neoplasms in adults.[1-3] MBT epitomizes the progression of a systemic malignancy (SM), and it is seen in 20%–40% of patients with SM.[3,4] The incidence in the United States is approximately 170,000/year.[3,5]

The first case of MBT was documented in 1853 by Schraut, and since then, there has been a perceptible increase in its frequency in the literature due largely to increasing availability and accessibility of diagnostic neuroimaging facilities and improvement in primary cancer survival with advancement in cancer therapy. Susceptibility of the brain to harboring metastasis has also been shown to increase with alteration of the blood–brain barrier by chemotherapeutic drugs, which permits tumor seeding into the brain and by an aging population.[3,4,6-9]

The clinical features of MBT are usually insidious, progressive and are often indistinguishable from manifestations of primary brain tumors (PBTs).[2,10] Computed tomography (CT) scan is the initial diagnostic tool used in excluding acute emergencies (hemorrhage, hydrocephalus, and apoplexy) in suspected MBT or following acute neurological deterioration. Nevertheless, gadolinium-enhanced magnetic resonance imaging (GE-MRI) remains the gold standard for the diagnosis of MBT. High-resolution MRI can detect lesions 1–2 mm in size and reveal multiple lesions in 20% of patients with single lesions on contrast-enhanced CT scan. Cerebral

Address for correspondence: Dr. Mark C. Chikani, Department of Surgery, Neurosurgery Unit, University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu, Nigeria.
E-mail: markochikani@yahoo.com

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metastatic lesions are roughly spherical, well-delineated and often located in the arterial border zone and the gray-white matter interface. Metastatic brain tumours show exuberant peri-lesional vasogenic edema that is more profound than is noticed in primary brain tumours (PBT). In addition, they may demonstrate a mass effect and varied patterns of contrast enhancement – ring, punctate, solid, or mixed patterns.[2,8,11-14]

Biopsy remains the only viable surgical option for multiple small deep lesions without a known primary or when the diagnosis of a solitary lesion is in doubt.[1,12,14] The optimal treatment plan will depend on patient factors (age, general condition, neurological status and Karnofsky Performance Score), disease characteristics (extent of SM; leptomeningeal involvement; MBT size, site, number; and the histological/molecular profiless), and the wishes of the patient and family members. Treatment can be definitive (surgery, radiotherapy, hormonal therapy, or chemotherapy) or symptomatic (anticonvulsants and steroids). Despite advances in cancer management, the multidisciplinary and multimodal approaches to patients with MBT, the outcome is generally poor. Prognosis depends on the natural history, clinical characteristics, and treatment modality utilized.[2,10,14,15]

Very scanty information on this germane topic exists in Nigeria. There is a changing trend in MBTs that reflect the rapid changes in radiodiagnosis, therapeutic manipulations for primary disease, and neurosurgery practice in Nigeria. Unless the scope of the problem is defined locally, the expected surgical and palliative cares for these patients will remain suboptimal. This pioneering study from Southeast Nigeria aims to highlight the demographic, clinical and radiological profiles as well as investigate factors determining outcomes of treatment modalities in MBTs in our setting.

Methods

We carried out a 1-year prospective study of patients with MBT who presented to the neurosurgery unit of the University of Nigeria Teaching Hospital, Enugu, Southeast Nigeria, from December 2018 to November 2019. The hospital is government owned and one of the few referral centers that offer both neurosurgical and radiotherapy services in the country.

Consecutive patients with histologically diagnosed SM and radiologically diagnosed MBT during the study period were enrolled in the study. Radiological diagnosis was made with cranial GE-MRI, contrast CT, or both. MBT lesions were assessed for site, size, and number of the lesions. Based on the number of lesions, MBTs were classified as solitary (only one brain lesion with a controlled primary tumor in the absence of other metastases), single (only one brain lesion with an active primary tumor and other metastases outside the brain), or multiple (two or more MBTs).

Patients were offered treatment based on recommendations of a multidisciplinary team. Surgical options were considered in patients with Karnofsky Performance Score (KPS) >70, accessible and/or symptomatic lesions <4 in number, and in those with controlled SM (stable for three months or more). Other available treatment options include whole-brain radiotherapy (WBRT) and chemotherapy. Supportive measures such as pain control, antiepileptic medications, and steroids were also used as indicated. Patients were followed up for one year or to death (whichever comes first). A structured proforma was used to assess the clinical status of patients at six weeks, three months, six months, and 12 months post-discharge.

Data obtained were collated and analyzed using the Statistical Package for Social Sciences version 21, Chicago, Illinois, USA. Descriptive and inferential statistics were derived, and statistical significance was inferred at $P < 0.05$.

Results

Demographics and clinical profile

Of the 31 patients with MBTs, 58.1% were female and 41.9% male, giving a female to male ratio of 1.4:1. The age at diagnosis ranged from 7 to 79 years, with a mean age of 51.0 ± 15.2 years. The median interval from diagnosis of SM to detection of MBT was 4.8 months (range of <1–15 months) [Table 1]. The average duration of cranial symptoms at presentation was 7.7 weeks.

Focal motor deficits (77.8%) and headache (58.1%) were the most common presenting features.

Patients' KPSs were 10–40 (45.2%), 50–70 (51.6%), and 80–90 (25.8%).

The sources of metastases were breast (29.0%), lung (22.6%), skin (19.3%), and undetermined site (16.1%) [Figure 1].

Radiological characteristics

MBT diagnosis was made with cranial CT scan in 12 (38.7%) patients. Cranial MRI was the diagnostic modality in 14 (45.2%) patients, while 10 patients (32.3%) performed both CT and MRI scans. All the solitary lesions had an MRI scan. The lesions were solitary in 25.8% and multiple in 74.2%. Lesions were predominantly located in the frontal lobes (80.6%) [Figure 2], with bilateral distribution in 64.5% of patients. The largest lesion measured 8.1 cm in diameter. Peri-lesional edema was seen in 100% of cases, while hemorrhagic lesions were seen in 3 (9.7%) patients. Five patients (16.1%) had hydrocephalus.

Table 1: The median time interval from the diagnosis of a primary tumour to the diagnosis of Metastatic Brain Tumours (MBT)

Primary Tumour Type	Number of Patients	Interval between diagnosis of Primary tumour & MBT	30-day Mortality	
			Frequency	Percentage
Breast	9	6.6 months	3	33.3
Lungs	7	0.9 months	5	71.4
Melanoma	4	8.0 months	2	50.0

Treatment modalities and determinants of short-term outcome

WBRT was the most common treatment modality for MBT [Figure 3]. Of the two patients that had surgery, one had a gross total resection (GTR) while the other had a partial resection.

Fifteen patients (48.4%) died within 30 days of diagnosis of MBT and only five patients (16.1%) survived beyond six months. Prior knowledge of the existence of a SM ($P = 0.045$) and hemispheric involvement ($P = 0.013$) significantly affect 30-day survival [Table 2].

Discussion

Demographics and clinical profiles

MBTs are usually from Stage 4 systemic malignancies that have spread to the brain through the hematogenous route or rarely by direct invasion.[8] In this study, only 31 patients with MBTs were seen. This number was short of expectations, and we believe that it is a reflection of the widespread and unfounded belief even among clinicians who refer these patients with obvious MBT that "radical or palliative" care will not benefit or prolong the survival of such patients.[6] Despite the figures, it represents a significant increase in diagnosis when compared to a previous study by Adeloye and Odeku who found 17 MBT over three years,[6] and Benna *et al*. who recently reported an average of nine patients per year over a 16-year period.[16] The increased number of MBT in this study could be attributed to improved cancer survival, awareness and increased access to neurosurgical and neurodiagnostic services in Nigeria.[17]

We found a slight female predilection among our cohorts accounting for 58.1% of all patients. Adeloye and Odeku had previously reported all patients with MBT as females.[6] Unlike their study which was autopsy based, this study was prospective. Several authors have reported a male preponderance in MBTs.[2,16] This difference could be related to the frequency of primary sites. Whereas breast cancer predominates among our patients; lung cancers were more common in these other studies.[2] This is contrary to findings from the Western world where more males than females have MBT. Adeloye's study overwhelmingly

Table 2: Predictors of 30-Day Mortality of Metastatic Brain Tumour

	Frequency (%)	30-day Mortality	*P*
Prior knowledge of systemic malignancy			0.045
Yes	14 (45.2)	4	
No	17 (54.8)	11	
Total	31 (100)	15	
Karnofsky Score			
10-40	7 (22.6)	6	
50-70	16 (51.6)	9	
80-100	8 (25.8)	0	
Total	31 (100)	15	
Side of brain			0.013
Unilateral	11 (35.5)	2	
Bilateral	20 (64.5)	13	
Total	31 (100)	15	
Number of lesions			
Solitary	3 (9.7)	0	
Single	5 (16.1)	1	
Multiple	23 (74.2)	14	
Total	31 (100)	15	

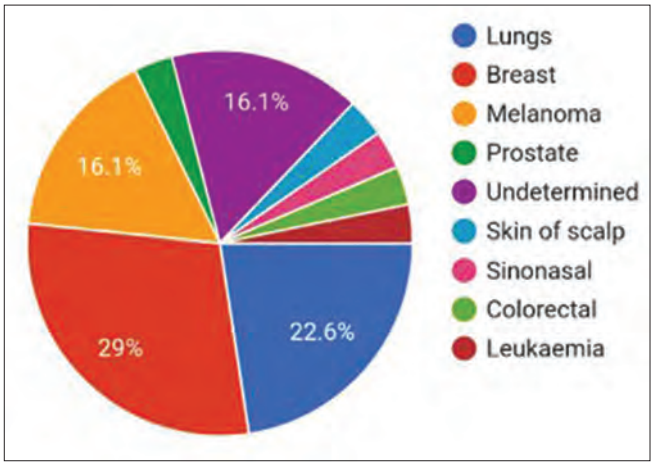

Figure 1: Sources of metastasis to the brain

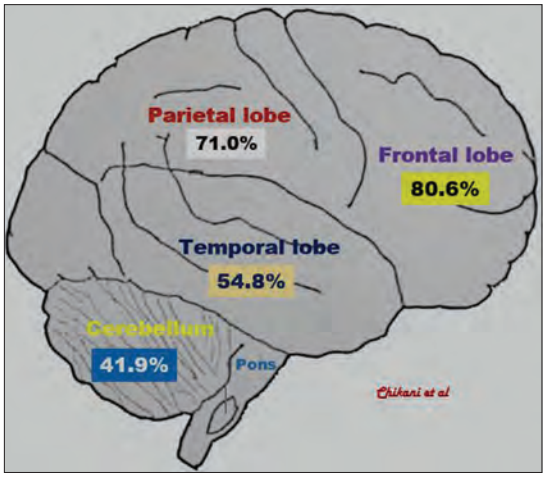

Figure 2: Distribution of lesions in the various parts of the brain

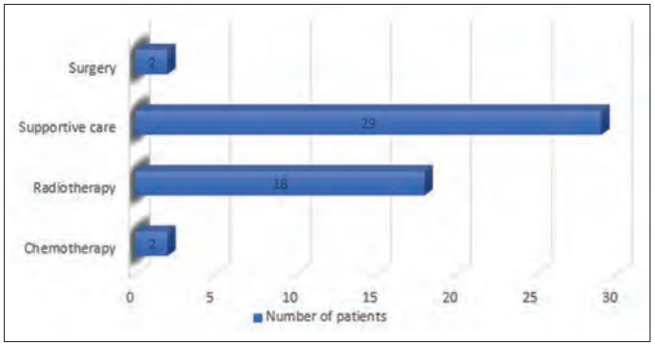

Figure 3: Treatment of metastatic brain tumor

reported uterine choriocarcinoma as the most common source of SBT (70.5%). This reflects a changing trend as choriocarcinomas are now readily treated with chemotherapy with better response compared to breast cancers. Hence, breast cancers are most likely to metastasize in this era than choriocarcinoma.

The lungs (22.6%) and the skin (19.3%) together with the breast accounted for >70% of MBTs [Figure 1]. This is comparable to other studies in the literature except that the lungs were unarguably the most frequent metastatic source in the developed countries. The relatively heavier cigarette smoking among Western nations compared to Nigerians has been proffered as a possible reason for the higher incidence of lung cancers in these countries.[2,12] Moreover, while the diagnosis of breast cancer could be more straightforward, lung cancers could be mimicked by infections such as pulmonary tuberculosis which is prevalent in our setting. These might explain the variation between our most common primary sites and that reported in other parts of the world. Of note in our study is that 100% of the melanoma brain metastases originated from cutaneous melanomas. Others have noted spread from the eye or unidentified sites.[8,18] In five of our patients (16.1%), the primary site was not identified. This is slightly on the high side when compared to the reported range of 2%–14%.[2,16,19] Out-of-the-pocket financing of treatment greatly impedes proper metastasis workup in our patients.

No case of incidental finding of an asymptomatic MBT was recorded in this study, unlike in developed countries, where more MBTs were detected before the occurrence of symptoms, a reflection of the disparity in health-seeking attitude across both populations. Increased awareness campaigns, early screening, and a universal health insurance package will lead to earlier detection of silent MBT.[20]

The most common presenting features among our cohorts were motor deficits (77.4%), headache (58.1%), and personality changes (54.8%). Seizures were seen in <10% of our patients, and a quarter (25.8%) of patients had a good KPS (>70) on presentation.

Radiological characteristics

In the majority of our cases, lesions noticed on brain scan were mainly intraparenchymal, multiple, supratentorial, and frontal in location. Other locations were cerebellum (41.9%), leptomeningeal (9.7%), and pineal region (3.2%) [Figure 2]. Our findings corroborate with Stark *et al*. who reported 68.0% lesions as supratentorial and 32.0% as infratentorial.[19] In a large retrospective review of 309 patients who underwent craniotomy for newly diagnosed brain metastases, 45.6% of patients had solitary brain metastasis, 26.5% had a single brain metastasis, and the rest had two or more brain metastases.[2] We observed a higher proportion of multiple lesions (74.2%) in our series, and this may not be unrelated to late presentation and limited metastasis workup early in the course of SM. Multiple lesions are generally accepted to be relevant in therapeutic considerations.[12] Hemorrhagic lesions were seen in three patients (9.7%), all of whom had melanoma, making it the most cause of hemorrhagic MBT in our series. Metastatic melanomas are known for hemorrhagic lesions that are believed to result from endothelial proliferation and necrosis, which predispose to bleeding with increased venous pressure following raised intracranial pressure.[17,20,21]

Treatment and short-term outcome

Management of MBT is mostly palliative. Yet, this is too great a task to be left for the medical and radiation oncologist alone. A concerted effort is required from a multidisciplinary team including the clinicians (neurosurgeon, oncologist, and pain therapist), patients, and family members.[10] Only two patients (6.5%) of the MBT in our series could benefit from surgery, and both patients survived beyond six months. These constituted 25% of patients presenting with solitary lesions. One of the patients had a GTR. We noted that in selected cases, GTR of a single cerebral metastasis is possible because the lesions have well-circumscribed borders and can be delineated distinctly from normal surrounding brain.[11] Hence, when feasible, surgical interventions should be considered. The fewer cases of surgery in our study are because the patients with solitary lesions were fewer and had inaccessible lesions, poor performance indices, and uncontrolled SM. In a recent 3-year prospective study of cerebral metastasectomy in Ibadan, Nigeria, Ayandipo *et al*. reported better survival in 12 patients managed over the period compared to cohorts who had no surgery.[22]

Whole-brain radiation therapy (WBRT) was utilized in the care of 18 (58.1%) of our patients [Figure 3]. In 17 patients, it was used as a primary modality and in one patient as an adjuvant. Ten other patients scheduled for WBRT did not receive the treatment as they could not afford the services. It is disheartening that despite the key role WBRT plays in palliative care of MBT, it is not readily accessible to end-users. It has been reported that even after overcoming patient-related factors, access to radiotherapy is hampered by equipment malfunctions, power outages, and workers' strikes, among other reasons in Nigeria.[23] Anakwenze *et al*. reported that 80% of patients in Ibadan, Nigeria, could not afford radiotherapy without financial assistance and only 6% of the patients had federal insurance, which did not cover radiotherapy services.[24] It is imperative that government at all levels, corporate bodies, and well-meaning individuals work out funding modalities for cancer patients in such trying moments of their lives.

Nearly half (48.4%) died within 30 days of diagnosis, and only five patients (16.1%) lived beyond six months. We consider survival in this study as poor but not surprising, considering that 74.2% of patients had a KPS <70%, and only two patients were suitable for any form of surgical intervention. Benna *et al*. reported a median survival of four months after a 33-month follow-up of their study.[16] Survival can be improved by screening and collaboration with other managing teams who these patients may present to first.

The prognostic factors for a better 30-day survival were prior knowledge of the existence of a SM ($P = 0.045$) and unilateral

brain involvement ($P = 0.013$) [Table 2]. We postulate that patients who were already on treatment for SM are more likely to have their brain metastasis detected earlier; if the patients receive counseling on possible risk of metastasis, the treating clinicians have a lower threshold for appropriate radiological investigations, and the patients are likely to be referred earlier to Neurosurgery.

Conclusion

The breast is the most common SM source of brain metastasis. Multiple lesions were found in three-quarter of patients. Less than half the patients were aware of a diagnosis of malignancy at the time of presentation. Survival is generally poor. Prior knowledge of the existence of a SM and unilateral brain involvement are associated with a better short-term survival. There is a need to entrench multidisciplinary care on cancer patients to aid early detection of MBT, and a well-structured multicenter study with a larger sample size is needed to properly arrive at practice-reshaping conclusions.

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Conflicts of interest

There are no conflicts of interest.

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