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ORIGINAL ARTICLE

Metastatic Breast Cancer in a Tertiary Hospital in South-Western Nigeria

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OBJECTIVE

Metastatic breast cancer (MBC) is a common presentation among breast cancer patients in Nigeria. Treatment remains mostly palliative. This study aimed to describe the pattern of presentation of MBC, management, and survival outcome in our center.

METHODS

This was a prospective study at Ekiti State University Teaching Hospital, Ado-Ekiti between January 2016 and December 2020. Data were analyzed by SPSS version 23.0. Kaplan–Meier test was used to compare survival with log rank test for statistical significance.

RESULTS

Seventy patients had MBC during the study period. Forty-six (65.7%) presented with metastasis and 24 (34.3%) developed metastasis during their treatment/follow-up. Their ages ranged from 27 to 86 years (mean 49.9±12 years). All patients had breast lump for 3–36 months (mean lump size, 12.0±4.7 cm). The predominant histological variant was invasive ductal carcinoma (97.1%). Fifty-nine (84.3%) tumors were moderately/poorly differentiated. Only six (8.6%) patients had immunochemical studies. Half of the patients (50%) had lungs or pleural metastasis followed by liver secondary's in 11 (15.7%). Chemotherapy (75.7%) and hormonal drugs (71.4%) were the main treatments while only 8 (11.4%) patients had radiotherapy. Survival ranged from 2 to 30 months (median 7.0 months). There was 60% mortality in patients with bone metastasis versus 97% mortality in other metastases over 2 years (log rank test: 0.002). All patients with multiple metastasis died within 1 year while solitary metastasis had 19% mortality within 1 year and 93% mortality in 2 years follow-up (Log rank test: 0.0001).

CONCLUSION

MBC is associated with poorer prognosis and short survival. Improvement in the diagnostic and treatment modalities will most likely result in a better outcome in the near future.

Keywords: Breast cancer; metastasis; survival; treatment.

INTRODUCTION

Breast cancer (BC) is the most common cancer and the leading cause of cancer-related deaths worldwide.[1] According to a review by Jedy-Agba et al.,[2] the proportion of BC patients with late stage (III/IV) disease at diagnosis in sub-Saharan African countries ranges from 30% in South Africa to 98% in Nigeria. Thus, a large

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number of patients still present with advanced BC. In a recent meta-analysis of BC demographics in Africa in the last decade, it was noted that 67% of BCs were advanced: 50% were stage III while 17% were metastatic.[3] Reasons adduced for the advanced stages of the disease at presentation include lack of awareness, poverty, believe in traditional and faith healing, fear of death from mastectomy, inadequate funding of health sector, and lack of organized screening program for BC.[4–7]

Metastatic BC (MBC) is a common presentation among patients with BC in Nigeria and other developing African countries, and this is generally associated with poorer prognosis.[8,9] Despite recent advances, treatment remains mostly palliative: Aiming to control symptoms, improve quality of life, and prolong survival.[10,11]

The length of survival for patients with MBC varies greatly based on inherent tumor biology and patients' response to systemic therapies. In general, the survival rates of patients with MBC have improved over the past few decades with some studies reporting median survival range of 18–30 months once metastasis is detected.[12–14] This will most likely be influenced by the availability of recent medications and more robust treatment facilities and options. It would not be surprising to observe that the chances of survival would be low in the resource-poor settings due to poverty, poor healthcare financing, patients' beliefs and attitude, and other treatment barriers.[15] This study describes the pattern of presentation, management and outcome of management of MBC in our center.

MATERIALS AND METHODS

This was a prospective study carried out at the Ekiti State University Teaching Hospital (EKSUTH), Ado-Ekiti in South Western Nigeria, between January 2016 and December 2020. This study was approved by the Ethics and Research Committee of EKSUTH (EKSUTH/A67/2018/07/008).

All patients who presented at the breast clinic and emergency department of the hospital with MBC (*de novo* stage IV disease) and those who developed distant disease during their treatment and follow-up, after the initial diagnosis of a localized BC, were included in the study.

Information on socio-demographics, clinical presentation, diagnosis, treatments, and outcome were collected using a pre-designed pro forma/data sheet. All patients had histological confirmation of BC at presentation. Abdominal scan and chest X-rays were routinely requested while computerized tomography (CT) and magnetic resonance imaging (MRI) were requested in selected few with symptoms suggestive of distant spread. Bone scan was not routinely done due to non-availability.

Our protocol for the treatment of MBC mainly comprises of systemic therapy using chemotherapy and hormonal agents. Only few patients had palliative mastectomy and radiotherapy to improve their quality of life. None of the patients who initially had mastectomy and were on follow-up treatment received adjuvant radiotherapy before developing metastasis because it was not readily available or accessible.

Follow-up of patients was done at the breast clinic and through phone calls to patients and/or their relatives and records were regularly updated. The data obtained were analyzed for frequencies and simple percentages using the SPSS version 23.0 and results were presented using descriptive statistics: Mean±SD, median and interquartile range (IQR). Using the Kaplan–Meier test, survival analysis was compared based on sites of metastasis, multiplicity of metastasis, and treatment modalities with log rank test used for statistical significance.

RESULTS

A total of 70 patients with MBC were seen during the 5-year study period, 46 (65.7%) presented with metastasis at diagnosis while 24 (34.3%) developed features of metastasis during their treatment and follow-up. Their ages ranged between 27 and 86 years (mean 49.9±12.0, median 47.5 years, IQR=42–56). The socio-demographic variables of the patients are shown in Table 1. Majority (57.1%) of the patients were premenopausal and most (77.1%) had formal education up to secondary and tertiary levels.

All patients presented with breast lump ranging from 5 to 26 cm (mean 12.0±4.7 cm, median 12 cm, IQR=8–15.3) in size with the duration of lump ranging from 3–36 months (mean 12.1±6.7, median 10, IQR=8–15). Only about a fifth (18.6% of patients) presented within 6 months of appearance of the breast lump.

The right breasts were affected in 34 (48.6%), the left breast in 28 (40.0%) and 8 (11.4%) patients had bilateral disease. Twenty-two (31.4%) patients had ulcerated and fungating tumors. The predominant histological variant of BC was invasive ductal carcinoma in 68 (97.1%), while one each (1.4%) was papillary and tubular. In terms of tumor grade, 11 (15.7%), 31 (44.3%), and 28 (40.0%) were well differentiated, moderately differentiated, and poorly differentiated respectively.

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Table 1 Socio-demographic characteristics of the patients

Socio-demographics	Frequency	%
Age group (year)		
21–30	4	5.7
31–40	9	12.9
41–50	27	38.6
51–60	18	25.7
61–70	7	10.0
>70	5	7.1
Sex		
Female	68	97.1
Male	2	2.9
Education		
None	14	20.0
Primary	2	2.9
Secondary	18	25.7
Tertiary	36	51.4
Marital status		
Single	3	4.3
Married	58	82.9
Divorced/separated	4	5.7
Widowed	5	7.1
Menopausal status		
Premenopausal	40	57.1
Postmenopausal	30	42.9
Religion		
Christianity	65	92.9
Islam	5	7.1
Occupation		
Employed	57	81.4
Unemployed	13	18.6

Table 2 Sites of metastasis

Sites	Frequency	%
Lungs	22	31.4
Pleural	13	18.6
Liver	11	15.7
Brain	6	8.6
Bone	5	7.1
Spinal cord	3	4.3
Multiple*	10	14.3
Total	70	100.0

*: Metastasis at two or more sites

Table 3 Treatment modalities

Treatment	Frequency	%
Chemotherapy		
Yes	53	75.7
No	17	24.3
Hormonal		
Yes	50	71.4
No	20	28.6
Surgery		
Simple/toilet mastectomy*	26	37.1
None	44	62.9
Radiotherapy		
Yes	8	11.4
No	62	88.6

*: Twelve patients initially had mastectomy before developing metastasis

Only six (8.6%) of the patients had immunochemical studies, and these were done at some other centers outside our city. The immunohistochemistry results revealed that four patients had tumors that were negative for estrogen receptor (ER)/progesterone receptor (PR) and human epidermal growth factor (HER2/neu)-triple negative; while two other patients had tumors with positive receptors for ER/PR.

The sites of metastasis are as shown in Table 2. Half (50.0%) of the patients had lungs or pleural metastasis, followed by liver secondaries in 11 (15.7%). Multiple metastases were found in 10 (14.3%).

Treatment modalities of the patients are shown in Table 3. The most common treatment options were chemotherapy and hormonal therapies while the least was radiotherapy. Anthracycline-based chemotherapy, using cyclophosphamide, adriamycin/epirubicin and 5-fluorouracil (CAF/CEF) regimen, was employed. Paclitaxel in combination with other agents or as monotherapy was used as second line therapy. Seventeen (24.3%) patients who did not receive chemotherapy were either clinically unfit or lacked the financial capacity to procure medications.

Eight (11.4%) patients received radiotherapy. Tamoxifen was given to 50 (71.4%) based on surgeon's preference. No patient received targeted therapy. Fourteen (24.1%; n=58) patients had surgery after metastasis was diagnosed while the rest initially had a mastectomy and developed metastasis during treatment/follow-up.

Survival after diagnosis of metastasis range from 2 to 30 months (mean 8.7±5.5, median 7.0, IQR=5.0–11.0). The median survival was longer in patients who developed metastasis during treatment/follow-up than those with metastasis at diagnosis (9 months vs. 6 months; IQR=6–14.3 vs. 4.8–9.3). All the patients diagnosed with metastasis at admission (*de novo* stage IV) died within 2 years whereas six (24%) of those who developed metastasis during treatment and follow-up survived 2 years and longer (log rank test 0.026).

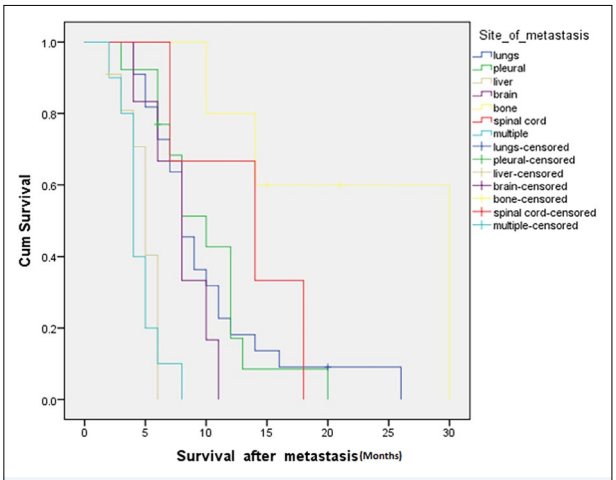

Fig. 1. Graph showing the sites of metastasis and survival.

There was 60% mortality in patients with bone metastasis vs 97% mortality in other metastases over 2 years (log rank test: 0.002) (Fig. 1). Survival among patients with solitary metastasis was significantly longer than those with multiple metastases. All patients with multiple metastasis died within 1 year while solitary metastasis had 19% mortality within 1 year and 93% mortality in 2 years follow-up (Log rank test: 0.0001) (Fig. 2).

The survival based on the treatments received is shown in Figure 3. Patients who received combination of surgery and chemotherapy had significantly longer survival (Log rank test: 0.0001).

Among those who had solitary metastasis, more patients who received the combination of surgery and chemotherapy had extended survival compared to receiving chemotherapy alone. The mean survival among those with solitary metastasis who had combination treatment was 14 months compared to 7 months among those treated with chemotherapy alone (p=0.001). The probability of surviving longer than the average of 9 months among patients with solitary metastasis who received the combination of surgery and chemotherapy was 3.6 (95% CI=1.5–8.3) times the probability among those who had solitary metastasis and received chemotherapy alone.

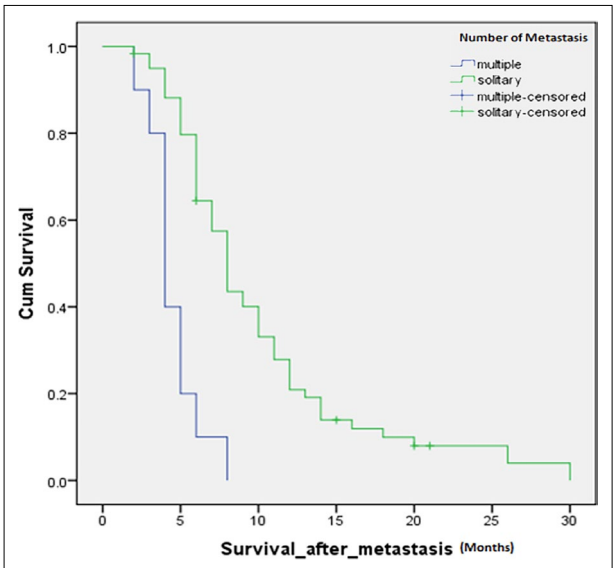

Fig. 2. Graph showing survival in solitary and multiple metastasis.

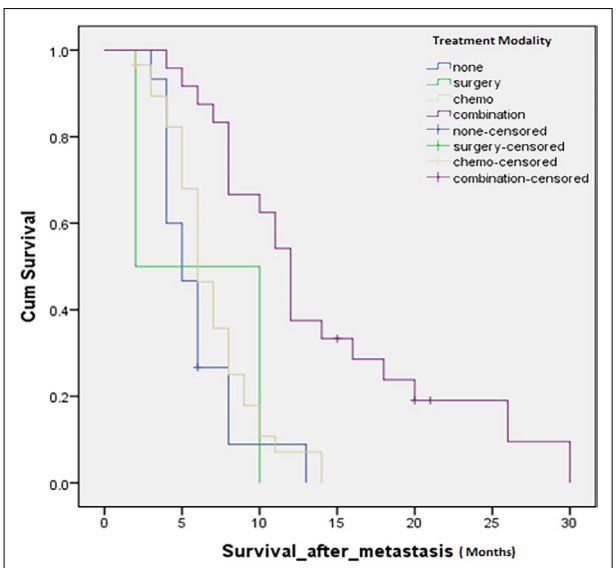

Fig. 3. Graph showing survival based on treatment received.

DISCUSSION

A large proportion of patients with BC still present with advanced stages of the disease in Nigeria. The rates of this late presentation vary from one center/region of the country to another. In the earlier studies by Ntekim and Agbo et al.[15,16] MBC presentation rates were 39% and 44% from South-western and North-western Nigeria, respectively. In a retrospective study carried out at our center, 13.4% presented with MBC.[17] We postulate that lower figures in our studies may be attributable to increasing awareness of BC by the populace over the last decade. Comparatively, in the United States, only about 5–8% to of patients with BC present with stage IV disease.[18] This means that a lot still needs to be done to further reduce the number of patients presenting in advanced stage of BC.

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BC can progress to metastatic disease regardless of the initial stage at diagnosis. However, the more advanced the disease is at presentation, the more likely the chances of progression. Out of the 24 patients who developed metastasis after an initial diagnosis of localized BC in this study, 23 (95.8%) had stage 3 while only one (4.2%) was early disease. Some of these "newly diagnosed" cases might have been at stage IV of the disease *ab initio*: but were missed as a result of inadequate investigations either for financial reasons or lack of facility for that at our hospital. Considering the peculiarities of our setting, the ideal diagnostic imaging techniques (CT, MRI, bone scintigraphy, etc.) which are more sensitive than the routine X-rays and sonography are not available. Thus, patients requiring them would have to access these facilities at private facilities at costs which could be beyond the reach of majority of our clients. Therefore, we had to rely mainly on clinical and basic imaging studies, and for those in whom metastatic lesions are suspected, and who could afford it, we referred for newer imaging protocols where facilities for these exist.

Late presentation is very common among patients with BC in Nigeria. The mean duration of 12 months, coupled with a mean lump size of 12 cm, and about one-third presenting with ulcerated/fungating tumors are indicators of late presentation in this study. Comparing this with a study by Adisa et al.[8] who reported a mean lump duration of 5.8 months and median lump size of 8.5cm over a decade ago, nothing has really changed in terms of late presentation over the years despite seemingly widespread awareness. While efforts should be geared at improving early diagnosis and prognosis of BC patients, acceptance of diagnosis and intentional delay of treatment by patients are serious issues that still need attention among our patients in Nigeria.[19,20]

The majority (77.1%) of our patients had high education and this is similar to the high rates in the studies by Adisa et al.[8] and Ntekim and Nufu,[15] but in contrast to Ali-Gombe et al.[21] that reported a lower rate. Contrary to expectation, the high level of education was found not to have played much role in downstaging BC presentation. Thus, regardless of the patients' level of education, emphasis should still be on BC awareness at every encounter with women in any health facility.

The predominant histologic variant of the tumor in this study was invasive ductal carcinoma (97.1%). This is similar to what has been reported in previous studies.[15,16,21–23] The tumors were poorly differentiated in 40% of the patients and this was similar to 42.7% in Ali-Gombe study. More African women tend to have poorly differentiated and more biologically aggressive form of BC than their western counterparts.[24] This is one of the factors responsible for poor survival outcome in the blacks.

Common sites for breast metastases are the lungs, liver, bones, and brain.[25] The lungs and pleural are the most common sites of metastases in 50% of the patients followed by the liver in this study. This is in consonance with other studies from different centers though with varying rates.[21,23,26,27] In a retrospective study by Adisa et al.,[8] at Ile-Ife, liver metastasis was found to be the most common while another study reported bone metastasis as the most common.[28] The frequency and distribution of metastasis to the viscera and bones also vary in these centers. It is not unlikely that the incidence of bone metastasis might be underreported because most centers lack facility for bone scintigraphy which is more sensitive than X-rays. In general, risk factors for metastases include: Tumor subtypes, receptor status, nodal status, tumor grade, and size.[25,29]

Systemic therapies are the cornerstones of treatment in patients with MBC and they include endocrine therapy, chemotherapy, targeted drugs, and/or biologic agents. The greatest improvement in survival is mostly related to the development and widespread availability of modern systemic therapies.[30] In recent times, new chemotherapeutic agents (taxanes, vinorelbine, eribulin, capecitabine, gemcitabine, liposomal anthracyclines, platinum compounds-carboplatin/cisplatin, etc.), newer hormonal agents, (third-generation aromatase inhibitors and fulvestrant), and biological therapies (trastuzumab, lapatinib, and bevacizumab), have been introduced with resultant improvements in treatment efficacy and outcome in MBC.[31,32] The results of the clinical trials with other agents such as cyclin-dependent kinases (CDK4/6), mTOR, and PI3K Inhibitors have been promising.[32] These agents may be used alone or in combinations based on the patient's BC subtype, receptor status, and sometimes gene mutation.

Chemotherapy and hormonal therapies are the two most commonly used for MBC in our center. The choice of the chemotherapeutic agents is restricted by availability and affordability of the agents. These encouraged the use of the available and seemingly affordable anthracycline/taxane-based regimens as mainstay of BC cytotoxic agent. Other approved second- and third-line agents were not accessible during this study. Tamoxifen was also the preferred agent for the hormonal therapy based on its availability and affordability. However, the majority (91.4%) of patients

did not do immunohistochemical studies which are the main determinants of the usefulness or otherwise of the hormonal and biologic therapies. The major reason for this was the absence of such services in our center and other nearby facilities, and where available the patients could not afford it. It is hoped that with improvement in diagnostic facilities, and government efforts at making the newer drugs available and affordable, there could likely be improvement in the survival of BC patients with metastatic disease.

A few (20%) of our patients had palliative simple mastectomy after neoadjuvant chemotherapy. This was mainly considered to reduce the tumor burden and improve the quality of life. Although the role of surgery is unclear in MBC, several potential advantages have been proposed. By removing the primary tumor, the source of further metastatic spread is eradicated and reduction in the number of cancer cells may increase the efficacy of systemic therapy.[33] Recent studies reported a survival benefit in those who had surgery in addition to systemic therapy especially in ER+, PR+, and HER2+ and those with the most favorable survival.[34,35] A French study by Pons-Tostivint et al.,[36] described a 35% survival benefit with locoregional therapy (LRT). The tumor subtypes/biology, sites of metastasis and overall disease burden were the potential predictors of benefit with LRT, but this was not associated with better survival in triple-negative BC. Some patients who actually required surgery refused it because of the general belief of patients and their relatives that they will die regardless of how rigorous treatment might be and this even affected other treatments. As much as surgery is an option of treatments in our setting where patients still present with fungating tumor, all cases must be individualized and careful patient selection is crucial in the decision-making process.

Survival outcome of MBC is still very poor in Nigeria.[8] The median survival of 7 months (mean 8.7 months) found in this study is far lower than what is obtained in most developed countries in recent times (12–14). In a meta-Analysis and systematic review by Caswell-Jin et al.,[37] the median survival was reported to be slightly over three years, with a range from few months to many years. Some factors which influenced the survival in this study include: Site of metastasis, multiplicity of metastasis and treatment received. Patients who had bony metastasis, solitary organ metastasis and combination of surgery and chemotherapy treatments had extended survival period. Part of the reasons for the poor survival outcome might be lack of newer chemotherapeutic agents, lack of access to palliative radiotherapy, poverty, and patients/relatives' unwillingness to cooperate with the managing physicians or agree to the treatment regimen having lost hope of survival. The high mortality of BC patients in Africa is a clear evidence that there are not yet appropriate treatment strategies in place.[38]

The outcome of patients with MBC still appears gloomy in our setting as nothing seems to have changed as regard its management in recent years. For there to be an improvement, there has to be a strong political will on the part of government to prioritize health, subsidize anticancer drugs and make provisions for diagnostic and treatment facilities. At present, our efforts are geared toward more awareness campaigns and BC information dissemination by working in collaboration with Non-Governmental Organizations to encourage early presentation, prompt diagnosis and treatment. Women presenting at our breast clinic are taught self-breast examination and encouraged to do yearly clinical breast examination. This will definitely reduce the number of patients presenting in advanced stage of BC.

CONCLUSION

MBC has remained a major challenge in our practice and other parts of Nigeria. It is associated with poorer prognosis and short survival in our setting. Despite the broadening of the therapeutic spectrums by introduction of newer agents, availability and affordability of these adjuncts are still serious issues to contend with among our clients. There is a need to make better diagnostic and treatment facilities available and affordable to those who require them. This will most likely improve survival rates in the near future.

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Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Ekiti State University Teaching Hospital Ado Ekiti, Nigeria Research Ethics Committee (no: EKSUTH/A67/2018/07/008, date: 24/07/2018).

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