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# Metastatic patterns and hormone receptor status among breast cancer patients in Tanzania

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**Abstract**

**Introduction**: Metastatic breast cancer is a common presentation in Tanzania. Estrogen-receptor (ER)-positive tumors are known to metastasize to the bones and require hormonal treatment as first-line therapy. Challenges with accessing immunohistochemistry services can delay information on breast cancer subtypes, further delaying treatment with effective hormonal therapy.

**Objectives:** This study aimed to assess the pattern of distribution of metastatic lesions in patients with metastatic breast cancer and evaluate its association with their hormone and HER-2 status, which could help provide recommendations on the use of front-line hormone therapy in areas where access to immunohistochemistry is a challenge.

**Methods:** A retrospective study covering histologically confirmed breast cancer patients in 2020 with metastatic lesions and complete medical records at Ocean Road Cancer Institute. Clinical information on the number, state and sites of metastasis, presence of symptoms and treatment received, and pathological variables, including histology, ER, PR and HER-2 status, were documented.

**Results:** Forty-nine (96.1%) of 51 patients analysed were female, with a mean age of 49.5 years. 47% presented with up-front metastatic disease. Lung was the most common metastatic site (76.5%) followed by bone/spine (53%). About half the patients had multiple sites involved. ER-positive tumors accounted for 47%, PR positive for 31% and HER-2 positive 39.2%. ER-positive tumors were more likely to present as a recurrence than up-front metastasis. ER-positive tumors were significantly more likely to be associated with bone and spine metastasis (59%) compared to ER-negative tumors (29%)

**Conclusion:** The clinical and pathological features of MBC in Tanzanian women are similar in many ways to those in other African regions. However, the ER positivity rate is lower. This study found a significant association between ER-positive tumours and skeletal metastasis, which has implications for the up-front treatment of these patients, especially where access to immunohistochemistry can be a challenge.

**Keywords:** Breast cancer, metastasis, subtypes, hormone status, HER-2

## Introduction

Breast cancer (BC) is the most frequently diagnosed cancer globally, affecting 2.3 million women and causing 685,000 deaths in 2020. It is also the world's most prevalent cancer, with 7.8 million women alive at the end of 2020 who were diagnosed with cancer in the past five years (World Health Organization, 2021). In Tanzania, breast cancer (BC) is the second most common cancer in women, and the number of new cases of BC diagnosed is expected to increase by 82% by the year 2030 (Ministry of Health, Community Development, Gender, Elderly and Children, 2017). According to Globocan estimates, BC accounted for 9.9% of cancer cases and 7.3% of cancer deaths in 2020 (Globocan, 2020).

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A large proportion of women in Tanzania present with advanced (stage 3 and 4) disease, with a significant number having metastatic breast cancer (MBC) on presentation, i.e. Denovo MBC (dnMBC) or developing the metastatic disease during treatment and follow-up. A meta-analysis of studies done in sub–Saharan Africa shows that between 4% to 70% of patients present with metastatic disease at first presentation. A single-centre study done in north-western Tanzania in 2012 demonstrated that 21.4% of women presented with metastatic disease at first presentation., (Jedy-alba et al., 2016; Nabawanuka et al., 2013; Mabula et al., 2012) Information on the clinical characteristics of women presenting with MBC is scarce, and there has been little documentation of the relationship between the hormonal and HER-2 status of these women with the distribution of metastatic sites.

Metastatic breast cancer (MBC) is defined as a tumor spreading beyond the confines of the breast, chest wall and the ipsilateral regional lymph nodes. Typically, breast tumors spread to the bones, lungs, liver or brain, with bones being the most common site of metastatic site recurrence and the first site of metastasis in the majority of patients. The hormone receptor status of MBC is strongly related to the metastatic pattern. Hormone-receptor-positive (estrogen receptor [ER] and progesterone receptor [PR]) tumors are more likely to spread to bones as their primary site of metastases and have better survival outcomes; whereas hormone receptor-negative or human epidermal growth factor receptor 2 (HER2 - neu) positive tumors tend to develop as visceral metastasis (Pareek et al, 2019; Hou et al, 2021; Tao et al, 2016).

Current recommendations for treating metastatic disease involve the use of first-line hormonal therapy for ER and PR-positive tumors. Hormonal therapy is effective and much better tolerated than chemotherapy, making it a treatment of choice for patients in whom the quality of life is of paramount importance (Kumar et al., 2024). Testing the primary tumour site and the site of metastasis for ER and PR positivity is required but is often a challenge in Tanzania, where immunohistochemistry (IHC) services used to perform these tests are only available in a few large national hospitals, resulting in a long waiting time before patients begin treatment. Sometimes oncologists may begin treating such women with conventional chemotherapy, which is a waste of scarce resources and results in unnecessary side effects. To avoid this, studies have recommended the use of empirical hormonal therapy in patients presenting with clinical features suggestive of hormone-positive disease (Nabawanuka et al., 2013).

Therefore, this study aimed to assess the distribution pattern of metastatic lesions in patients with MBC and evaluate its association with their hormone and HER-2 status. The results of this study may help provide recommendations on the use of front-line hormone therapy in areas where access to immunohistochemistry is a challenge.

## Materials and methods

A retrospective study was conducted at Ocean Road Cancer Institute (ORCI), Tanzania's National Cancer Referral Centre which provides oncology services to patients from around the country. At ORCI patients with breast cancer are treated with chemotherapy and radiotherapy after referral from other treatment centres. Nearly two-thirds of patients present with advanced breast cancer, some of whom are found with metastatic disease at diagnosis, (dnMBC), while others present with recurrence after initial treatment and are found to have developed distant metastasis upon work-up. This study included patients presenting with histologically confirmed BC who have metastatic lesions (confirmed by imaging and/or biopsy) whether newly diagnosed or on follow-up, in the year 2020. Patients who had unconfirmed histology or missing data were excluded. Medical records of breast cancer patients treated in 2020 were

searched to identify patients diagnosed with metastatic disease, including both dnMBC patients and those who developed metastatic lesions as a recurrence.

A data abstraction form was used to document information on sociodemographic, clinical and pathological variables of interest; these included age, sex, education and marital status, age at diagnosis of BC, state of MBC- whether denovo or recurrent, and time between diagnosis of BC and development of metastasis if the initial diagnosis was not MBC. Pathological variables included histopathology and ER, PR and HER-2 status. Number and sites of metastasis, presence of symptoms, and treatment given was documented. Sixty-two records of patients that fit the inclusion criteria were retrieved. After further evaluation, 11 records were excluded:

- 9 did not have complete information on hormonal status.
- 1 had significant missing data on several variables.
- 1 had only lymphnode metastasis and not distant metastasis.
- Eventually 51 patients' records were entered into the analysis.

Data were analyzed using SPSS Version 23 by summarizing demographic and clinical characteristics, distribution, and frequency of metastatic lesions, and exploring the relationship between ER, PR and HER-2 status and distribution of metastatic sites (skeletal, lung or liver) using chi-squared test. We hypothesized that women with ER positive tumors would have lower proportions of dnMBC compared to ER negative tumors, and that the distribution of metastatic sites would be significantly different, with ER positive tumors presenting more with metastasis to the bones and spine, and ER negative and HER-2 positive tumors with greater visceral metastasis. Permission to conduct this study was obtained from ORCIs ethical review committee.

## Results

Of 51 patients whose results were analysed, 49 (96.1%) were female, and two were male. The mean age of patients was 49.5 years (range 26-72 years). For patients who presented with MBC as a recurrence, the median time from diagnosis to development of metastatic disease was 9 months, with a mean time of 16.23 months (SD 24.3, range 1 to 116 months).

Table 1 summarizes the clinical and pathological characteristics. 24 (47%) presented with dnMBC, 26 (51%) with recurrent disease. Lung was the most common metastatic site (76.5%) followed by bone/spine (53%). Nearly half of the patients had more than one metastatic site. The most common documented symptom was dyspnea, with Chest X-rays revealing metastatic lesions in 32 (63%) patients. The remaining 7 patients were diagnosed with lung metastasis through CT scans. Infiltrating ductal carcinoma (IDC) was the most reported histology. 24 (47.1%) of patients were ER positive, 16 (31.4%) were PR positive and 20 (39.2%) were HER-2 positive.

**Table 1: Summary of clinical and pathological characteristics**

| *Characteristic* | | *Frequency* | *Percentage* |
|---|---|---|---|
| ***State of MBC*** | Denovo | 24 | 47.1 |
| | Recurrence | 26 | 51.0 |
| | Missing | 1 | 1.9 |
| ***Metastatic sites*** | | | |
| | Bone/spine | 27 | 52.9 |
| | Lung | 39 | 76.5 |
| | Liver | 10 | 19.6 |
| | Brain | 11 | 21.6 |
| ***No. of metastatic sites*** | | | |

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| | | | |
|---|---|---|---|
| | 1 | 27 | 52.9 |
| | 2 | 18 | 35.3 |
| | 3 | 4 | 7.8 |
| | >3 | 2 | 4.0 |
| ***Presence of significant symptoms*** | | | |
| | Cough | 6 | 11.8 |
| | Pain | 20 | 39.2 |
| | Dyspnea | 29 | 56.9 |
| ***Chest Xray findings*** | | | |
| | Pulmonary Metastasis | 32 | 62.7 |
| | Pleural Effusion | 15 | 29.4 |
| ***Histology*** | | | |
| | IDC | 42 | 82.4 |
| | BC-NST | 4 | 7.8 |
| | Clear Cell | 1 | 2.0 |
| | Missing | 4 | 7.8 |
| ***Hormonal Status*** | | | |
| | ER Positive | 24 | 47.1 |
| | ER Negative | 27 | 52.9 |
| | PR Positive | 16 | 31.4 |
| | PR Negative | 35 | 68.6 |
| ***HER-2 Status*** | | | |
| | HER-2 Positive | 20 | 39.2 |
| | HER-2 Negative | 29 | 56.9 |
| | Missing | 2 | 3.9 |

*IDC = Infiltrating Ductal Carcinoma
*BC-NST = Breast Cancer of No Special Type

A summary of treatment received is presented in Table 2. Information on surgery was available for 47 patients; 41% of these had no surgery done. Modified radical mastectomy (MRM) was the most common surgical procedure. 39 (76.5%) of patients received combination chemotherapy, while only 14 (27.5%) received hormonal therapy. Bisphosphonates (in all cases Zoledronic Acid) was given to 33% of the population, and 86% received analgesics.

**Table 2: Summary of treatment received.**

| *Treatment type* | | *Frequency* | *Percentage* |
|---|---|---|---|
| *Surgery* | | | |
| | Not done | 21 | 41.2 |
| | MRM | 22 | 43.1 |
| | Simple Mastectomy | 3 | 5.9 |
| | Lumpectomy | 1 | 2.0 |
| | Missing | 4 | 7.8 |
| *Treatment Received* | | | |
| | Combination chemotherapy | 39 | 76.5 |
| | Hormonal Treatment | 14 | 27.5 |
| | Trastuzamab | 3 | 5.9 |
| | Bisphosphanates | 17 | 33.3 |
| | Analgesics | 44 | 86.3 |

Table 3 summarizes the bivariate analysis of hormone and HER-2 status against metastatic status. The analysis shows a statistically significant distribution of ER status with state of MBC at presentation, with significantly more patients with ER

positive tumors presenting with metastatic disease as a recurrence rather than denovo (P value 0.049). PR status and HER-2 status were not statistically associated with the state of MBC at presentation.

**Table 3: Bivariate analysis of Hormone and HER-2 status with status of MBC at presentation**

| *Characteristic* | *Status of MBC at presentation* | | *P-value* |
|---|---|---|---|
| | **Denovo MBC** | **Recurrence** | |
| ***ER status*** | | | |
| *Positive* | 9 (35%) | 17 (65%) | **0.049** |
| *Negative* | 15 (62.5%) | 9 (37.5%) | |
| ***PR status*** | | | |
| *Positive* | 7 (43.8%) | 9 (56.2%) | 0.680 |
| *Negative* | 17 (50%) | 17 (50%) | |
| ***HER-2 status*** | | | |
| *Positive* | 10 (50%) | 10 (50%) | 1.000 |
| *Negative* | 14 (50%) | 14 (50%) | |

Table 4 summarizes the bivariate analysis of hormone and HER-2 status against distribution of metastatic sites. From this analysis, ER positive tumors are significantly more likely to be associated with bone and spine metastasis (59%) compared to ER negative tumors (29%), P value 0.031. No other significant association was found between ER, PR and HER-2 status and site of metastasis.

**Table 4: Summary of bivariate analysis of hormone/HER-2 status Vs metastatic site**

| *Characteristic* | *Metastatic site* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Bone/ Spine** | | **Lung** | | **Liver** | | **Brain** | |
| | **N (%)** | **P Value** | **N (%)** | **P Value** | **N (%)** | **P Value** | **N (%)** | **P Value** |
| ***ER status*** | | | | | | | | |
| *Positive* | 16 (59) | | 19 (70) | | 5 (19) | | 5 (19) | |
| *Negative* | 7 (29) | **0.031** | 20 (83) | 0.276 | 5 (21) | 0.835 | 6 (25) | 0.574 |
| ***PR status*** | | | | | | | | |
| *Positive* | 9 (56) | | 11(69) | | 4 (25) | | 4 (25) | |
| *Negative* | 14 (40) | 0.279 | 28 (80) | 0.379 | 6 (17) | 0.512 | 7 (20) | 0.687 |
| ***HER-2 status*** | | | | | | | | |
| *Positive* | 8 (40) | | 16 (80) | | 4 (20) | | 4 (20) | |
| *Negative* | 13 (45) | 0.737 | 23 (79) | 0.953 | 5 (17) | 0.806 | 7 (24) | 0.733 |

*ER = Estrogen Receptor
*PR = Progesterone Receptor
*HER-2 = Human Epidermal Growth Factor 2 Receptor

## Discussion

The mean age of patients at diagnosis in this study was 48.1 years. This is consistent with a study of breast tissue samples analysed at Muhimbili National Hospital in Dar es Salaam in 2013 where the mean age was 48.3 years (Mwakigonja et al, 2017). Although in the West, breast cancer is typically a disease of older women, younger ages at presentation of MBC have been documented in several non-white populations such as in India (47 years) and Uganda (45 years) (Pareek et al, 2019; Nabawanuka et al., 2013).

In this study almost half the patients presented with dnMBC. Late stage at diagnosis is a common occurrence in Sub-Saharan African countries; a systematic review by Jedy-Egba et al documented late

stage presentation at 74.7% (range 30.3-100%) (Jedy-agba et al. 2016). This is in contrast with high income countries where most cases of MBC arise as a recurrence of a previously treated BC (Daily et al., 2021). The distribution of metastatic sites also varies across studies; in our study lung metastasis was the most common (76.5%), followed by bone/spine (53%), with dyspneoa being the predominant symptom, whereas many studies in both low and high-income countries have found spine and bone metastasis to be the most prevalent (Bartmann et al., 2017; Carty et al,1995; Ekpe et al, 2019).

Observed differences could be due to the routine use of scintigraphy/bone scan for MBC patients in high resource settings which would allow early identification of bone metastasis, while at our centre due to cost issues scintigraphy is usually requested only when a physician suspects bone metastasis. On the other hand, chest x-rays are easily available and affordable and routinely used for staging patients, allowing early diagnosis of pulmonary metastasis. Around half of the patients in our study presented with more than one metastatic site. Multiple site involvement is common in MBC. A study in India showed metastasis involving a single organ was present in 188 (50.1%), two organs in 92 (24.5%), and more than two organs in 95 (25.4%) patients, with the most common site of metastasis being visceral metastasis (219 [58.4%] lung, liver, and both [lung plus liver] in 117 [31.2%], 53 [14.13%], and 49 [13.1%], respectively), followed by bone-only metastasis in 100 (26.7%) (Gogia et al, 2019).

In our study, ER positive tumors accounted for 47.1%, There are varying results for hormone receptor status across studies; Sayed et al showed that breast cancer in Kenya had comparable receptor status positivity (72%) to that in the West (Sayed et al., 2014); while more recent Kenyan and Indian studies documented this at 70% and 62% respectively (Gogia et al., 2019; Nabawanuka et al., 2013). It is known that immunohistochemistry (IHC) testing for receptors in breast cancer can be affected by many factors including optimal fixation and type of antibody used (Gown, 2008), however the results may also be a true reflection of receptor positivity in the population and warrant further study. Similarly, 39.2% of this population were HER-2 positive, which is significantly higher than patients in the Kenyan study (19%) but like the Indian study.

Bivariate analysis showed a positive association of ER status with recurrence as compared to ER negative tumours, meaning that patients with ER positive tumours are more likely to present as local disease and then develop metastasis during follow up. There was a statistically significant association between ER positivity and metastasis to the bones and spine, as compared to metastasis to the lung, liver, or brain.

These findings have been discussed previously and shown to be true in many studies, as ER-positive tumors are considered less aggressive than ER- negative tumors (Nabawanuka et al., 2013; Pareek et al, 2019; Hou et al., 2021; Lin et al., 2021). Hence patients with ER positive tumors will typically present with bone metastasis which responds well to palliative treatment. These findings have potential implications for treatment guidelines; when patients present with denovo metastatic disease involving the bones, there may be a role for empirical hormone therapy in previously untreated patients where facilities do not exist for performing hormone receptor tests as is the case in many Sub-Saharan African countries (Vanderpuye, Olopade, & Huo, 2017). A recent study in Northern Tanzania documented that 91% of reviewed cases did not undergo hormone receptor testing, which formed the most frequent reason for failure to treat according to guidelines (Sood et al., 2021)

Our study failed to show association between PR and HER-2 status and MBC state at presentation. It also did not find a statistically significant association between PR and HER-2 status and distribution of metastatic site. These findings would need corroboration with larger studies.

**Limitations**

This was a retrospective study which depended on extraction of medical records. In some cases, information was unavailable or poorly documented which led to the exclusion of the patient or missing data.

**Conclusion**

The clinical and pathological features of MBC in Tanzanian women are similar in many ways to those in other regions, with a mean age of 48 years, and nearly half the patients presenting with denovo disease. The ER positivity of tumors in these patients is however lower than that found elsewhere. This study found a significant association between ER negative tumors and denovo presentation, as well as ER positive tumors and skeletal metastasis, which has implications for treatment. Larger cross-sectional and prospective studies would help to acquire better information on the presentation of these patients, and the use of bone scintigraphy to work up all patients presenting with MBC would help to capture asymptomatic bone disease before it involves other organs.

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