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RESEARCH ARTICLE

Characterizing the Pattern of Metastasis Based on Molecular Subtype in Breast Cancer Among Nigerian Women (Breast Cancer Molecular Subtypes and Metastasis in Nigerian Women)

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ABSTRACT

Background: Breast cancer subtypes are often used as therapeutic and prognostic measures; however, it is unclear whether there is an association between molecular subtypes and site-specific metastasis. Our study aimed to evaluate the relationship between molecular subtypes and developing metastasis in specific sites.

Methods: We selected 118 breast cancer patients with immunohistochemistry confirmed molecular subtype diagnosed in 2020 and 2021 at the Department of Surgery, University College Hospital, Ibadan. We classified the molecular subtypes into four categories, HR+/HER2-, HR-/HER2+, HR+/HER2+, and triple negative (HR-/HER2-). The different sites of metastasis of interest were lungs, liver, brain, and bone. We used the chi-square test to determine the proportions and significance of the subtypes based on the different sites assessed.

Results: According to our study, 45.50%, 18.20%, and 36.40% of patients presented with lungs, liver, and other (multiple organs and contralateral breast) metastasis respectively. Additionally, HR+/HER2- and TNBC patients developed metastasis at a higher rate and account for a combined 90.10% of all metastases (the site-specific distribution was even between both subtypes).

Conclusion: Overall, while there are limitations in our study based on sample size, our data shows that some molecular subtypes are associated with a higher risk of metastasis. Additionally, while not significant in our study, breast cancer subtypes are associated with different metastatic sites.

Keyword: Breast cancer, Immunohistochemistry, Ibadan, Metastasis, pattern

Introduction

Breast cancer is the most common cause of malignant disease in women worldwide and metastases account for most breast cancer deaths¹. Despite advances in cancer research and availability of new therapies, the global burden of breast cancer continues to increase². For many cancers including breast, early detection typically results in favorable prognosis with overall survival rates of approximately 90% in women diagnosed with early breast cancer (Stage I/II)³. However, regional disparities in clinical outcomes exist for both morbidity and mortality of breast cancer in women from different parts of the world². In recent years, incidence and mortality have either remained stable or trended downwards in many developed nations, yet, both measures are on the rise in many African, Asian, and South American countries². According to the World Health Organization (WHO), breast cancer incidence in Nigeria is expected to increase substantially by 2040, with an estimate of 50,921 cases per year, compared to 26,310 cases recorded in 2018⁴. Despite the lower prevalence of cases in Nigeria and the rest of Sub-Saharan Africa (SSA) compared to higher income countries like the United States, the burden of lethal breast cancer is much higher⁵. Nigeria has one of the highest incidence-to-mortality ratio of breast cancer in the world² we can add more ref to this Additionally, breast cancer patients in this population tend to present at an earlier age, have aggressive triple-negative subtype, and in an advanced stage when treatment options are most limited⁶. Therefore, it is imperative that more epidemiology and basic-science research is done to understand the socio-cultural, socio-economic, and biological factors that drive the increasing incidence and worsened prognosis of breast cancer in Nigeria.

Breast Cancer subtype and metastasis

Breast cancer subtypes are often utilized in guiding therapeutic decisions and determining patient prognosis. Some studies have demonstrated an association between subtype and risk of early recurrence and metastasis, response to therapy, and overall survival⁷. It is also known that the site of metastasis may differ based on breast cancer subtype, mainly due to the unique gene signatures

of each subtype that may invade specific organs⁸. While the bone is the most common site for metastasis in breast cancer overall, the rate of (more lethal) brain metastasis is recorded to be much higher in HER2-positive and Triple Negative Breast Cancers (TNBC)^{8,9}. Patients with HR-positive subtypes are also more likely to develop bone metastasis, while HR-negative patients present more frequently with metastasis to the lung and liver⁸. Despite this knowledge, very few studies have evaluated the prevalence of metastasis and in particular, the effect of molecular subtypes on specific metastatic sites.

In many advanced countries, screening measures and early detection programs have led to a significant reduction in the rates of advanced metastatic breast cancers^{10,11}. In the United States for instance, about 5-8% of patients with newly diagnosed breast cancer present with metastasis, whereas in Nigeria where routine screening is not common, a significant percentage of the patients present late stage. As the population of Nigeria continues to increase, the incidence of breast cancer will most likely also follow the same trend. Presently, there are over 27,000 new cases annually, with approximately 70-80% of the patients presenting with advanced or metastatic disease compared to <46% in Europe, and nine of 10 of these women dying within 5 years of diagnosis^{2,12}. These differences are largely attributed to delays in treatment, not particularly delay in treatment alone but late presentation however, characteristics such as a higher prevalence of aggressive breast tumors in younger women also contribute to a worsened age-standardized mortality ratio. Approximately 74% of patients are premenopausal, with a mean age of 43 years, and an estimated 12% are younger than 30 years old¹². TNBC, which is associated with poorer outcomes, also accounts for a significant percentage of breast tumors seen in the Nigerian population¹². Despite the clear evidence on the prevalence of more aggressive tumors and high mortality rates, palliative care is developing but not fully established in some centres in Nigeria. Based on these findings, a population-based approach to understanding breast cancer in Nigerian women is essential. The purpose of this study is to investigate the pattern of metastasis that

commonly occurs in breast cancer among Nigerian women, since they commonly present with untreated advanced stage disease. We need to provide needed information on the most common patterns of metastases based on molecular subtype. Essentially, gaining insight on the association between molecular subtypes and metastatic disease and their effect on survival among Nigerian women with breast cancer might help inform interventions (therapeutic or palliative) and follow-up strategies.

Methods

It is a retrospective study of prospectively collected data of patients with histologically diagnosed breast cancer, who had immunohistochemistry studies performed on the mastectomy specimen and were subsequently followed up in the outpatient's clinic over a two-year period with twice yearly (six monthly) screening for metastases.

Study Population

We obtained data from medical records of patients who were diagnosed and treated for breast cancer at the Department of Surgery, University College Hospital, University of Ibadan with the approval of the Oyo state Ministry of Health Ethical Review Board. Medical records covering a 2-year span from June 1, 2020, to May 31, 2022, were included for review and data extraction based on the following criteria: Patients with histologically confirmed breast carcinoma and hormone receptor status by immunohistochemistry. Patients with unknown metastatic status and molecular subtype were excluded.

The medical records were used to link clinical, pathologic, treatment, and outcome data. Sites of distant metastasis of interest are lung, liver, brain, bone, spine, and other (other organs not classified).

Statistical Analysis

Patients were categorized by molecular subtype: HR+/HER2-, HR-/HER2+, HR+/HER2+, and triple negative (HR-/HER2-). Patients' demographic and clinical characteristics were summarized by Chi-square test and frequency distribution among different metastatic sites was analyzed by odds ratio. The patients were stratified by age at diagnosis which was divided into <40 years, 41-65 years, and >65 years. All tests were two-sided and $P < 0.05$ indicated statistical significance. All statistical analyses were conducted by SPSS (software version 28)

Results

Patient characteristics

Of the patients treated for breast cancer between 2020 and 2021, 118 patients met the inclusion criteria. The general characteristics of these patients are summarized in Table 1. Average age of diagnosis was 52.81 years old (range: 24-81 years), 94 (79.70%) patients were Yoruba, 16 (13.60%) were <40, 48 (40.70%) were premenopausal. Most patients were diagnosed at stage III and IV ($n = 68$, 57.60% and $n = 16$, 13.60% respectively) while 76 (64.40%) had triple negative disease. Of all patients recorded, 22 (18.60%) developed metastasis and the most common site was the lungs ($n = 10$, 45.50%). The stage of the disease and immunohistochemistry status was statistically significant.

Baseline clinical characteristics of breast cancer patients					
Characteristics	No metastasis		Metastasis		P value
	Count	%	Count	%	
Age					
<40	16	13.60%	0	0.00%	0.117
41-65	67	56.80%	18	15.30%	
>65	13	11.00%	4	3.40%	
Subtype					
HR+/HER2-	16	13.60%	10	8.50%	0.013
HR-/HER2+	14	11.90%	2	1.70%	
HR+/HER2+	0	0.00%	0	0.00%	
TNBC	66	55.90%	10	8.50%	
Stage					
I	4	3.40%	0	0.00%	<.001
II	8	6.80%	2	1.70%	
III	64	54.20%	4	3.40%	
IV	2	1.70%	14	11.90%	
Unknown	18	15.30%	2	1.70%	
Ethnicity					
Yoruba	78	66.10%	16	13.60%	0.049
Igbo	8	6.80%	6	5.10%	
Hausa	2	1.70%	0	0.00%	
Other	8	6.80%	0	0.00%	
Parity					
Nullipara	8	6.80%	0	0.00%	0.258
Multipara	84	71.20%	20	16.90%	
Unknown	4	3.40%	2	1.70%	
Menopausal status					
Pre-menopause	42	35.60%	6	5.10%	0.175
Post-menopause	40	33.90%	14	11.90%	
Unknown	14	11.90%	2	1.70%	
Family history					
No	50	42.40%	8	6.80%	0.048
Yes	10	8.50%	0	0.00%	
Unknown	36	30.50%	14	11.90%	

Impact of molecular subtype on metastatic site

The relationship between molecular subtypes and site of distant metastasis was also analyzed. As shown in Table 1, molecular subtype is significantly correlated with the risk of developing metastasis. Although TNBC accounts for 64.40% of all breast cancer cases in the study, only 8.50% developed metastasis compared to HR+/HER2- patients who account for 22.0% of the overall study cases with the same percentage of metastasis (8.50%). Table 2/Figure 1 shows how metastasis is distributed based on molecular subtype. The percentage of patients presenting with lung metastasis was the

highest and evenly split between HR+/HER2- and TNBC subtypes (n=4, 18.20% respectively). Two patients were diagnosed with lung metastasis with a percentage of 9.10%. Additionally, Liver metastasis was the second most common single organ site of distant metastasis. Similarly, to lung metastasis, the distribution was also evenly split between HR+/HER2- and TNBC subtypes (n=2, 9.10% respectively). The site listed as other included patients with multiple organ metastasis which included the brain, bone, and the contralateral breast. Our data also showed an even distribution between HR+/HER2- and TNBC

subtypes (n=4, 18.20% respectively) for the site listed as other. Overall, the differences that we see in site of distant metastasis based on molecular

subtype is not significant and has a p- value of 0.620.

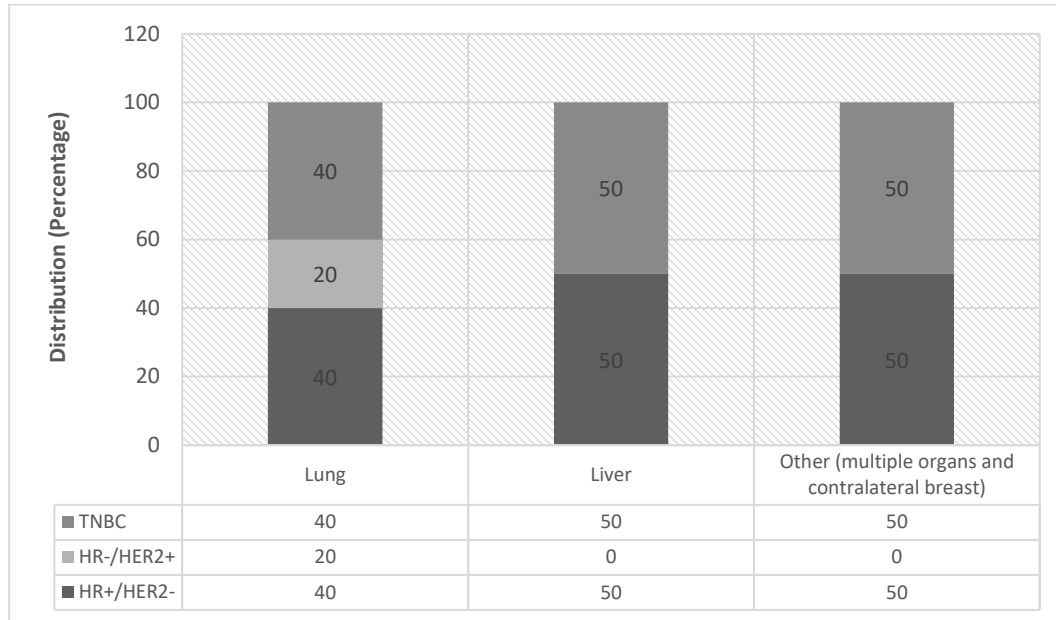


Figure 1. Distribution (percentage) of metastatic sites observed (lung, liver, other) in all molecular subtypes.

	Site of Metastasis						P
	Lung		Liver		Other		
	Count	%	Count	%	Count	%	
HR+/HER2-	4	18.20%	2	9.10%	4	18.20%	0.62
HR-/HER2+	2	9.10%	0	0.00%	0	0.00%	
HR+/HER2+	0	0.00%	0	0.00%	0	0.00%	
TNBC	4	18.20%	2	9.10%	4	18.20%	

Discussion

Breast cancer remains the most frequently diagnosed cancer in women worldwide, with an estimated 2.26 million cases and 685,000 deaths in 2020¹³. Approximately 90% of breast cancer related deaths can be attributed to metastasis, mainly because of resistance to adjuvant therapies^{14, 15}. The bone, liver, lung, and brain represent the most common sites that breast cancer preferentially metastasizes to^{7, 14,15}. Studies have also shown that the site of metastasis is clinically relevant and may contribute to the patients' survival outcome^{14,15}. Additionally, it has also been reported that the molecular subtypes may be differentially

associated with specific metastatic sites^{7, 8, 9, 15}. However, most of these studies that have already identified the bone as the most common site of metastasis were done in advanced countries with mostly Caucasian women enrolled. To our knowledge, very few studies have reported the pattern of metastasis in breast cancer among Nigerian women and none of them have considered the impact of molecular subtypes^{16, 17, 18, 19}. It has been previously reported that characteristics of breast cancer such as incidence-to-mortality rates, demographics, and distribution of molecular subtypes are different in Nigeria and many other developing countries, compared to advanced

countries^{6, 17, 18}. Hence, more studies illustrating the impact of breast cancer molecular subtypes and metastasis pattern among breast cancer patients in Nigeria are needed.

In this study, we aimed to characterize the pattern of distant metastasis based on breast cancer molecular subtypes in a cohort of Nigerian women. We identified 118 patients with immunohistochemistry confirmed breast cancer molecular subtype who were treated in the department of surgery, university college hospital, Ibadan, in 2020 and 2021. In accordance with other studies conducted in different parts of Nigeria, the mean age at diagnosis was 52.81 years, 40.70% were pre-menopausal, 71.20% presented late stage (III and IV), and 64.40% had TNBC^{20, 21, 22, 23, 24}. While these figures are different from what is generally observed in Caucasian women, black women with breast cancer in the United States also tend to be younger and are diagnosed with TNBC at a higher rate²⁵. An analysis of the Surveillance, Epidemiology, and End Results (SEER) data from 1973-2010 show that minority women were 58% more likely to be diagnosed with advanced-stage breast cancer under the age of 50 years²⁶. This further confirms the stark differences in the pattern of presentation of breast cancer in women of different ancestral groups. Although some biological factors may contribute to these disparities, reasons for late-stage presentation of breast cancer in Nigeria can be attributed to poor health-seeking behaviors and delays within the health system²².

The bone is the most common site of metastasis observed in breast cancer patients^{19, 27}. In a study with 584 Nigerian patients with advanced breast cancer seen between 2005 and 2009, *Ibrahim et al.*, reports metastasis in 72.1% with 66.7%, 17.1%, 6.2%, and 2.6% metastases to the bone, lungs, brain, and liver respectively¹⁹. We found that 18.60% of our patient population developed metastasis and the most common site was lung (45.50%), followed by other (45.50%), and liver metastasis (18.20%). Other represents patients with metastasis to the contralateral breast or multiple organs. While we did not see single organ metastasis to the bone and brain, n = 2 patients

developed multiple-organ metastases to the femur and contralateral breast and n = 4 to the brain and lung. This finding is similar to another study conducted in Zaria, Nigeria, by *Abur et al.*, where metastasis occurred in 19.7% of patients and 39.4% patients had metastasis to the lungs¹⁶. None of the studies mentioned above explored the impact of molecular subtype on the site of metastasis or disease outcome. The discrepancy in the observed results may be attributable to differences in sample size but nonetheless, re-affirms the need for large cohort studies that represent Nigerian women, and account for breast cancer staging and IHC.

Recent studies in Nigeria have shown TNBC to be the most common molecular subtype among their patients, with results ranging from 46.6 to 65%^{28, 29, 30}. Our study consistently shows that TNBC is the most common subtype among patients, occurring in 64.4% of all patients in the study, followed by HR+/HER2- (22.10%), and HR-/HER2+ (13.60%). None of the patients in our study were HR+/HER2+, this may be attributed to our small sample size. Based on previous reports, TNBC is often associated with increased risk for early distant metastases, higher incidence of lung and brain metastasis, and overall poorer survival outcomes^{1, 31}. Since a significant percentage of our patients have TNBC, some studies have shown upregulation of (Tumour necrosis factor) TNF in the lungs with TNBC compared to other sites of met this strong relationship between the molecular subtype and lung metastasis may have contributed to why the lung is the most common site reported in our study.

Overall, we reported that molecular subtype was significantly associated with risk of metastasis and the site of distant metastasis differed by molecular subtypes. 8.50%, 8.50%, and 1.70% of patients with metastases had TNBC, HR+/HER2-, and HR-/HER2+ respectively. While our study did not account for survival outcomes or include any patients with single organ metastasis to the brain or bone, our findings show that the TNBC and HR+/HER2- subtypes have similar patterns of metastases. For both subtypes, the lung and other sites were the most common sites (18.20% each), followed by the liver (9.10% each). Metastases occurred the least in HR-/HER2+ and was only seen

in the lung (9.10%). In general, HER2+ subtype, like TNBC, is associated with an increased risk of metastases (brain in particular)^{1,7}. Although absent in our data, HR+/HER2+ subtype confers the best prognosis and an increased likelihood of survival because of available targeted therapies.

Some limitations in our study include a small sample size, which limited the variability in our observed sites of metastasis. However, only cases of metastasis that were diagnosed with imaging were included in our study and analysis.

Additionally, default in follow-up care was common, which also made it difficult to retrieve necessary information on recurrent metastatic diseases status for some patients. Considering the proportion of advanced cases, it is also not unlikely that a reason for the poor follow-up is due to patient mortality.

Conclusion

In conclusion, our study supports the association between breast cancer molecular subtypes, metastasis, and site of distant metastasis. Given the increasing incidence of TNBC and late-stage presentation of breast cancer observed in Nigerian women, and its associated poorer outcome, a focus on early presentation would be beneficial to patients. Although more insight into tumor biology of different molecular subtypes is needed, we illustrated how breast cancer subtypes can confer different clinical and prognostic outcomes especially in our environment where patients present with late -stage disease. Additionally, despite our limitations, results from this study could lay a template for future studies.

Conflict: The authors have no conflict of interest.

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