

Pattern of Spread of Breast Cancer among Patients attending Cancer Unit of Lagos State University Teaching Hospital

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Abstract: Breast cancer spread usually result in high tumor burden with poor outcome. We aimed to determine the pattern of metastasis, relationship between characteristic of primary breast cancer and extent of subsequent metastasis. Background information and histological type were obtained from the patients records. Clinical, Radiological, Staging (Manchester) and site of metastasis information were obtained during pre-treatment examination and follow-up periods. Data analysis was done using descriptive statistics. The mean age of the respondents was 48.7 years and the peak age was 30-39 years. Evidence of metastatic involvement at presentation for care was lymph node 41.7%, lungs 20.2%, liver 5.4% and spine 4.2%. Site of metastasis after 2 years of follow up revealed that out of stage III patients, distant metastatic involvement observed were: Lymph node 85% (59), 22.2% (2), lungs 11.8% (4), spine 16.7% (1) and anterior chest wall 50% (3). For stage II, 5.9% had metastasis to the lung, 16.7% had spread to the spine and 16.7% had anterior chest wall recurrence. Distant recurrence remains common and incurable. Early recognition of metastatic breast disease will allow rapid institution of effective palliative treatment.

Keywords: Breast cancer, lagos state, metastasis, recurrence, spread, stage

INTRODUCTION

Breast Cancer is a global health problem. It is the most frequently diagnosed cancer in women living in Western countries accounting for approximately 30% of all cancer diagnosed and about 16% of all cancer death (Sotiriou and Piccart, 2007). In Nigeria, the peak-age of breast cancer in women is about a decade earlier than in Caucasian women (Okobia *et al.*, 2006).

It has unfavorable prognosis in women aged forty years or younger. Studies from various ethnic populations in Nigeria have reported the demographic profile of breast cancer. A review of breast biopsies in the Lagos State University Teaching Hospital identified 34% of all breast biopsies done over a 10 year period to be malignant. A report from Zaria another location in Nigeria described the mean age at presentation of breast cancer as 42 years with 30% occurring in women less than 25 years of age. A ten year review of breast cancer in Eastern Nigeria revealed that patients with breast cancer constituted 30% of all patients with breast disease and that 69% of these patients were pre-menopausal (Salaudeen *et al.*, 2009).

A comparison of the rate of breast cancer at risk population of a typical Africa country shows that whereas the size of at risk population remain largely stable in France it is increasingly steeply increasing in Nigeria (Akarolo-Anthony *et al.*, 2010).

Approximately 10-15% of patients with breast cancer has aggressive disease and develops distant metastasis within 3 years after the initial detection of the primary tumor. However the manifestation of metastases at distant site 10 years or more after initial diagnosis is also not unusual (Journal citation reports Thompson, 2006).

Metastasis is the leading cause of mortality in patient diagnosed with breast cancer (Schoppmann *et al.*, 2002). Most breast cancer deaths are due to advanced cancer, diagnosed when metastases have already disseminated to lymph nodes or distant organs (Autier *et al.*, 2009).

Despite many advances in diagnosis and screening, the disease is frequently discovered after spread to regional lymph node or ever after dissemination of distant metastasis (Maki and Grossman, 2000). About 20 to 30% of patients with breast cancers will experience relapse with distant metastatic disease (Anonymous, 2005).

The peculiar characteristics' of breast cancer among black are increasingly being appreciated by research worldwide. Blacks often have aggressive unpredictable disease, some patients come with relatively early stage disease and die of widespread metastasis within 6 month to 1 year, while others present with advanced disease and yet survive longer (Gakwaya *et al.*, 2008).

Majority of patients in Nigeria present at advanced stage, the factors responsible for late presentation with advanced disease include low social economic level, fear

of mastectomy (Elumelu *et al.*, 2011; Ajekigbe, 1991) and poverty (which does not only impede access to health care system, but is associated with other co-factors that can relatively affect outcomes such as co-morbidity and lack of breast health awareness) (Oluwole *et al.*, 2003).

Tumor size is one of the most important factors in describing tumor biology. This is emphasized as observed by a 1% increase in mortality with every millimeter increase in tumor diameter. As the tumor size increase so the probability of finding positive lymph node increase (Engela *et al.*, 2003). Another study group also found this linear correlation, up to 5 cm (Michaelson *et al.*, 2002).

The treatment of metastatic disease is generally palliative and early diagnosis may only improve survival to a limited extent." These patients can benefit from the judicious use of systemic therapy, local radiotherapy or surgery. The t

The aims of this study is to determine the pattern of metastasis in patients with breast cancer and to search for any relationship between characteristic of primary breast cancer, extent of subsequent metastasis and the site of metastasis.

MATERIALS AND METHODS

The Study was carried out at the Oncology Clinic of the Lagos State University Teaching Hospital, Ikeja, Lagos between 2005 and 2010.

Data collection: The study began in 2005 and 176 patients who were diagnosed histologically with breast cancer at the oncology clinic of Lagos State University Teaching Hospital, Ikeja, Lagos were recruited into the study. These patients were followed up for a period of 5 years. The records of the patients which contain their background characteristics were kept and information on health outcomes was recorded once they were noticed. The information were based on; histological variety, clinical examination, radiological examination, clinical staging during pre-treatment examination and follow-up periods. Clinical staging was determined using Manchester staging, Tumor grade I, II, III, Other information obtained were; site of metastasis, modality of treatment received for example surgery, chemotherapy, hormonal therapy and radiotherapy.

Treatment policy: Breast Cancer patients were referred by surgeons to oncology clinic after histological confirmation and pretreatment investigation using FBC, CXR, Abdominal USS for either neoadjuvant for locally advanced breast cancer to downsize the tumour or adjuvant treatment. Surgical treatment was breast conserving surgery, mastectomy and axillary clearance for early disease. Toilet mastectomy was performed in late disease.

Combination chemotherapeutic agents using Intravenous Adriamycin, Cyclophosphamide (AC), 6 cycles, Intravenous Epirubicin, cyclophosphamide X 4 courses followed by Intravenous Paclitaxel every 3 weeks X 4 courses. Radiotherapy was given to the anterior chest wall and lymphatic drainage at a dose of 45 Gy in 18 fractions and for patients with breast conserving surgery 15 Gy boost was given to the scar. 30 Gy in 10 fractions was given for palliative. Hormonal therapy was given using Tamoxifen for all patients as assay of estrogen receptor ER and progesterone receptor assay has recently become available and accessible to patients.

Data management: Data entry and analysis were done using SPSS version 19.0 Descriptive statistics was used to describe the data. Continuous variables were expressed as means (standard deviation) and categorical variables expressed as proportions.

Ethical consideration: Ethical clearance to conduct the study was sought from the Ethical Review Committee of the Lagos State University College of Medicine, Ikeja.

Study limitations: Histology reports of many of our patients does not contain grade.

RESULTS

Background characteristics of the respondents: A large proportion of respondents were aged 30-39 years. All the participants in the study were females. The mean age of the respondents was 48.7 and the peak age group was 30-39 years at presentation for care 46% of our study patients had stage III breast disease; 35% had stage IV disease, 16.6% had stage II disease and 2.4% had stage I disease (Table 2). Histologically, at presentation for care 95.9% had invasive ductal Carcinoma, 3.1% had lobular carcinoma and 1.2% had papillary carcinoma (Table 1).

Only 37 (21%) out of 176 patients' tumor grade were documented, 5.4%, well differentiated, 64.9% moderately differentiated while 29.7% were poorly differentiated

Table 1: Frequency distribution of respondents based on stage at presentation

Stage	Frequency	(%)
1	4	2.4
2	28	16.6
3	77	45.6
4	60	35.5
Total	169	100.0

Table 2: Frequency distribution of respondents based on disease histological type

Variables	Frequency	(%)
Ductal carcinoma	162	95.8
Papillary carcinoma	2	1.2
Lobular carcinoma	5	3.0
Total	169	100.0

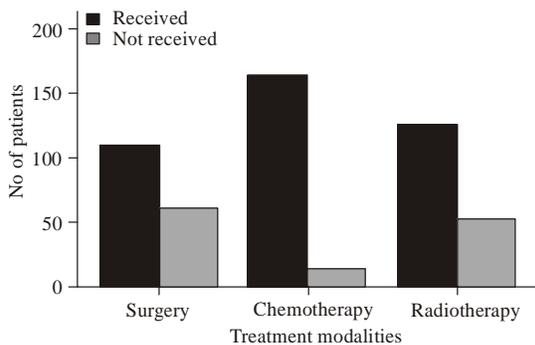


Fig. 1: Distribution of respondents based on treatment modalities

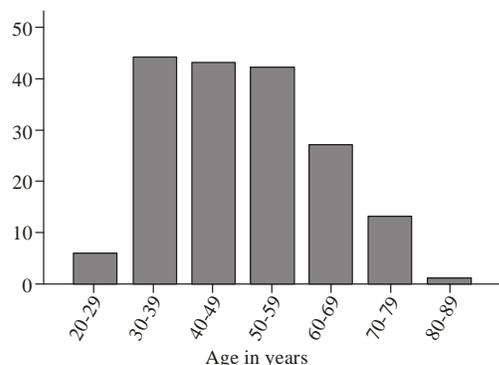


Fig. 2: Bar chart showing the age distribution of respondents

The treatment modalities for all the respondents in the study are shown in Fig. 1. Highest number of the patients received chemotherapy (176), followed by radiotherapy (124), while the least had surgical operation (115).

Age: The peak age at presentation was 30-39 years. The mean age at presentation was 48.73 years. The youngest

Table 3: Frequency distribution of patient's site of metastasis

Site of metastasis	Frequency	(%)
None	25	14.9
Lymph node	70	41.7
Lung	34	20.2
Liver	9	5.4
Spine	7	4.2
Recurrence ant chest wall	7	4.2
Lung and liver	7	4.2
Lung, liver and brain	1	0.6
Lung and spine	2	1.2
Lung and ant chest wall	2	1.2
LN and ant chest wall	1	0.6
Liver and ant chest wall	1	0.6
Lymph node and spine	1	0.6
Spine and liver	1	0.6
Total	168	100.0

age was 23 and oldest 80 years. The age distribution of the studied patients is shown in Fig. 2. Majority of the patients clustered around age 30-59 years.

Histological grade: Thirty seven (21%) out of 176 patients' grade were documented and (64.9%) were moderately differentiated while 29.7% were poorly differentiated.

Staging:

Axillary involvement at presentation: One hundred and seventy patients (96.6%) out of 176 patient status of axillary lymph node metastasis were recorded.

(87.6%) presented with axillary lymph node involvement while 12.4% had no axillary involvement (Table 3)

Site of metastasis after 2 years of follow up as depicts in Table 4 revealed that out of stage III patients, distant metastatic involvement observed were: Lymph node 85% (59), 22.2% (2), lungs 11.8% (4), spine 16.7% (1) and anterior chest wall 50% (3). For stage II, 5.9% had metastasis to the lung, 16.7% had spread to the spine and 16.7% had anterior chest wall recurrence (Table 4).

Table 4: Frequency distribution of stage according to site of metastasis

Site of metastasis	Staging				Total
	1	2	3	4	
None	12.0 (3)	72.0 (18)	16.0 (4)	0.0 (0)	100.0 (25)
Lymph node	0.0 (0)	5.8 (4)	85.5 (59)	8.7 (6)	100.0 (69)
Lung	0.0 (0)	5.9 (2)	11.8 (4)	82.4 (28)	100.0 (34)
Liver	0.0 (0)	0.0 (0)	22.2 (2)	77.8 (7)	100.0 (9)
Spine	0.0 (0)	16.7 (1)	16.7 (1)	66.7 (4)	100.0 (6)
Recurrence ant chest wall	0.0 (0)	16.7 (1)	50.0 (3)	33.3 (2)	100.0 (6)
Lung and liver	0.0 (0)	0.0 (0)	28.6 (2)	71.4 (5)	100.0 (7)
Lung, liver and brain	0.0 (0)	0.0 (0)	0.0 (0)	100.0 (1)	100.0 (1)
Lung and spine	0.0 (0)	0.0 (0)	0.0 (0)	100.0 (2)	100.0 (2)
Lung and ant chest wall	0.0 (0)	0.0 (0)	0.0 (0)	100.0 (2)	100.0 (2)
LN and ant chest wall	0.0 (0)	0.0 (1)	0.0 (0)	0.0 (0)	100.0 (1)
Liver and ant chest wall	0.0 (0)	0.0 (0)	0.0 (0)	100.0 (1)	100.0 (1)
Lymph node and spine	0.0 (0)	0.0 (1)	0.0 (0)	0.0 (0)	100.0 (1)
Spine, lymph node and spine	0.0 (0)	0.0 (0)	100.0 (1)	0.0 (0)	100.0 (1)
Total	1.8 (3)	17.0 (28)	46.1 (76)	35.2 (58)	100.0 (165)

Table 5: Frequency distribution of stage according to the occurrence of metastasis

Staging	Metastasis		Total
	yes	no	
1	0.0 (0)	100.0 (4)	100.0 (4)
2	35.7 (10)	64.3 (18)	100.0 (28)
3	97.4 (75)	2.6 (2)	100.0 (77)
4	100.0 (58)	0.0 (0)	100.0 (58)
Total	85.6 (143)	14.4 (24)	100.0 (157)

Table 6: Frequency distribution of grade according to the occurrence of metastasis

Grade	Metastasis		Total
	yes	no	
1	100.0 (2)	0.0 (0)	100.0 (2)
2	83.3 (20)	16.7 (4)	100.0 (24)
3	100.0 (11)	0.0 (0)	100.0 (11)
Total	89.2 (33)	10.8 (4)	100.0 (37)

Table 5 depicts the frequency distribution of the patients' metastasis status and staging. The data revealed that significant association existed between staging and occurrence of metastasis ($p < 0.001$). In the Table, it would be observed that 10 (35.7%) Lymphnode involvement occurred in stage II. In stage III, (75) 97.4% of the women in this category present with locoregional metastasis. Stage IV is metastatic disease (Table 5).

Table 6 depicts the association between grade and metastasis. Among those 24 patients with histological grade 2, 83.3% (20) had metastasis, it is striking that all patients with grade III (11) had metastasis. However the data show there was no significant association between metastasis and grade ($p > 0.05$).

DISCUSSION

Breast cancer is a clinically heterogeneous disease. Approximately 10-15% of patients with breast cancer have an aggressive disease and develop distant metastasis within 3 years after the initial detection of the primary tumour (Journal citation reports Thompson, 2006).

In the result of this study, the mean age at presentation was 48 years; peak age at presentation was 30-39 years with about 87% between the ages of 30 and 50. Elumelu *et al.* (2011) in their study on pattern of breast cancer metastasis at the radiotherapy clinic in Ibadan reported similar mean age of 48.15 in Ibadan. These are young women. Many authors have suggested that breast cancer in young women is biologically different from that of older women, specifically, the tumours progresses faster, present with higher grade and are more often estrogen receptor negative than tumours in older patients (Albain *et al.*, 1994; Althuis *et al.*, 2003; Chung *et al.*, 1996; Colleoni *et al.*, 2002; Maggard *et al.*, 2003)

Delayed diagnosis is probably partly due to the fact that the breast tissue of younger women is denser and therefore difficult to examine clinically and by mammography (Rapiti *et al.*, 2005).

The current study also revealed that greater percentage of our patients present at an advanced stage. This pattern of presentation is similar to studies carried out by Anyanwu (2000) in South-East and by Kene *et al.* (2010) in North Western part of Nigeria. Most of these people present late because of fear of mastectomy (Ajekigbe, 1991).

The incidence of axillary metastasis was high (87%). The high incidence of axillary metastasis could be attributed to advanced disease and the fact that frequently, the initial sites of metastasis are regional lymph nodes (Ketiku, 1986).

Clinical and experimental data suggest that migration of tumour cells into the lymph node is greatly facilitated by lymphangiogenesis. This process is dynamic during embryogenesis but is relatively rare in adulthood. Enhanced lymph node lymphangiogenesis and lymph flow in tumour-draining lymphatic vessels have also been reported to contribute to metastatic spread (Ran *et al.*, 2010).

The most common sites of distant metastasis in this study were lungs, liver, bone and brain. Lung was found to be the most common visceral organ with metastasis with incidence of 20%. This is similar to Adesun *et al.* (2006) from Ile-Ife who reported an incidence of 20.3%. Elumelu *et al.* (2011) reported an incidence of 9.1% among Caucasian with breast cancer. This lower figures in Caucasian could be due to early presentation and less aggressiveness of their disease. Also, our study found that the incidence of liver metastasis was 5.4% which is comparable with 7.7% figure reported by Elumelu *et al.* (2011) in Ibadan. The disparity in their figure and ours could be a larger sample size (518) used in their study (Elumelu *et al.*, 2011)

Bone metastasis was 4.2% in our study, a figure which is low compared to studies in our environment, Elumelu *et al.* (2011) (24.1%) in Ibadan, (Ketiku, 1986) in Lagos (19.6%), 61% reported by Catty *et al.* (1995). This may be because our study utilized conventional imaging tools and it has been noted that conventional imaging would not necessarily detect all metastatic disease, with subclinical metastasis being missed simply because no or inappropriate imaging was performed (Kennecke *et al.*, 2010).

Table 5 shows that direct relationship ($p < 0.05$) existed between the stages and the incidence of metastasis. This means that as the stage advanced, the incidence of metastasis increases. This pattern is consistent with the result from previous studies. For

instance, it has been found that increasing tumour size is associated with an increase in the extent of regional lymph node metastases (Kambyj *et al.*, 1991). Inconsistently however, the series carried out by Kennecke *et al.* (2010) (metastatic behavior of breast cancer subtypes) it was found that large tumour size (T3/4) was associated with significant lower rate of brain and liver metastasis, a finding with no obvious explanation (Kennecke *et al.*, 2010).

However, in models of metastatic spread and tumour self-seeding put forward by Norton and Massague (2006), it was pointed out that angiogenesis may relocate early from the primary site, allowing the disease to establish distant sites without ever demonstrating a large primary mass. Thus, there may be overlapping mediator between early dissemination and establishment of disease in the brain and liver.

CONCLUSION

Despite improving breast cancer outcomes, distant recurrence remains common and incurable and hence a major challenge. Early recognition through diagnosis of metastatic disease will allow rapid institution of effective palliative treatment. This will improve the quality of life of patients after treatment and increase their life-span.

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