PATTERN OF BONE METASTASIS IN BREAST CANCER PATIENTS AT A RADIOTHERAPY FACILITY IN LAGOS


1*Oncology Unit, Dept of Radiology, Lagos state university teaching hospital, Ikeja, Lagos, Nigeria; pabiodun2001@yahoo.com

1Oncology unit, Dept of Radiology, Lagos state university teaching hospital, Ikeja, Lagos, Nigeria; ihuomaigwilo@aol.com

2Dept of Radiotherapy, Lagos University Teaching hospital, Idiaraba, Lagos, Nigeria; toniasow@yahoo.com

2&3Ketiku Kingsley, MBBS, FWACS, FNPCS; dept of radiotherapy, Lagos university teaching hospital, Idiaraba, Lagos, Nigeria; kingsleyketiku@yahoo.com

3Radiotherapy unit, Eko hospital, Ikeja, Lagos, Nigeria; jtkduncan@gmail.com

4Dept of health studies & cancer research center, University of Chicago, Chicago, U.S.A; NHou@healthbsd.uchicago.edu

4Dept of health studies & cancer research center, University of Chicago, Chicago, U.S.A; dhuo@healthbsd.uchicago.edu

*Tel: +234-803-302-1434; Email: pabiodun2001@yahoo.com
ABSTRACT

**Aim:** A study to determine the pattern of bone metastasis in Breast cancer patients

**Study Design:** Descriptive study

**Place and Duration of Study:** Data was collated at Eko Hospital Radiotherapy facility, Lagos, between 2006 and 2011.

**Methodology:** A total of 67 patients with histological confirmed diagnosis of breast cancer from 2006 to 2011 at a radiotherapy facility were analysed to describe the pattern of bone metastasis. Radiological imaging included chest X-ray, X-rays of the bone, bone scan, and Computed Tomography scan (CT-Scan).

**Result:** Of the 67 eligible patients, one is male and 66 are female. The average age of the patients was 46 years old, ranging from 28 to 77 year old. Among the 67 breast cancer patients who received radiotherapy, 58 (87%) have bone metastasis. The most common sites of bone metastasis are spine (61%), pelvis (22%), and long bones (22%). Among patients without metastasis at presentation, the median duration from diagnosis to onset of symptoms of bone metastasis was 16.5 months, ranging from 5 to 38 months. 31 patients had osteoblastic lesions, 24 patients had osteolytic lesions, and 2 patients had mixed osteolytic and osteoblastic lesions.

**Conclusion:** Bone metastasis remains common and incurable. Early recognition and better description of bone relapse patterns of metastatic breast disease will allow rapid administration of effective palliative treatment.

**Keywords:** breast cancer, osteoblastic, osteolytic, bone metastasis, radiotherapy, stage

*Tel: +234-803-302-1434; Email: pabiodun2001@yahoo.com*
1.0 INTRODUCTION

Breast cancer is the most common malignant tumour of female (1,2). At breast cancer diagnosis, approximately 5-6% of women present with distant metastasis, with bone representing the most common site of metastatic lesions. (3,4) . It is estimated that 85% of individuals with advanced disease harbour bone metastasis, which is, unfortunately, incurable (5).

In addition, bone represents the first site for release of approximately 50% of patients with breast cancer. (6).

Bone is a common site for metastasis owing to high blood flow in the red marrow, the presence of adhesive molecules on tumour cells that bind them to stroma cells in the bone marrow, and the production of angiogenic factors and bone-resorbing factors that enhance tumour growth, thereby providing access to the resorbed bone matrix for subsequent tumour adhesion and proliferation (7).

High affiliation of the breast carcinoma metastasis to bone has been ascribed to selective colonization of metastatic tissue to bone and the importance of vascular endothelial receptors, adhesion molecules, mitogens, growth factors, cellular growth inhibitors and angiogenic factors has been pointed out in this regard. (8)

Tumour cells produce substance that can’t directly stimulate osteoclasts, such as interleukin 8 or TNF, leading to increased bone resorption and osteolytic lesion. When osteoclast resorb bone, release of TGF-beta not only promotes RANKL (a member of the family of tumour necrosis factor (TNFs)) production and further osteoclast activity by also stimulating angiogenesis and other parts of the metastatic cascade.

Binding of RANKL to RANK is endogeneously inhibited by osteoprotegrin, another TNF expressed by the osteoblasts. The ratio of RANKL to osteoprotegen regulates osteoclast formation, and the higher the ratio, the more osteoclast is formed.
The expression of RANKL on stromal cells and osteoblasts is regulated by osteotrophic substances, including parathyroid hormone, 1,25-dihydroxyvitamin D3, and prostaglandins. RANKL bind to its receptors (RANK) on osteoclast precursors, inducing the differentiation of osteoclasts from myeloid cells through signaling by way of nuclear factor kappa B and Jun N-terminal kinase pathway.

Bone metastasis in breast cancer is characterized by osteolytic bone lesion. These lesions are indicative of marked osteoclast activity. The aggressive resorption of bone osteoclast in breast cancer leads to a feedback loop in which degradation products of bone stimulate both bone loss and growth of metastatic cells. (9)

Skeletal metastasis accounts for many complications such as bone pain, impaired mobility, hypercalcaemia, pathological fracture, spinal cord or nerve root compression, and bone marrow infiltration, and thus it costly demands on healthcare resources (10,11).

Bone scan is a highly sensitive technique for detection of metastatic disease and staging of the tumour; other modalities include X-ray, Computed Tomography scan (CT-Scan), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography Scan (PET scan) (12). Management of bone metastasis is multimodal, which includes radiation therapy, bisphosphonate, and chemotherapy.
2.0 METHOD & MATERIALS

A total of 67 patients with histological confirmed cases of breast cancer from 2006 to 2011 at Eko Hospital radiotherapy Unit located at Ikeja, Lagos State, were analysed for this study. Pretreatment and follow up radiological imaging included chest X-ray, X-rays of the bone, bone scan and CT scan. This radiotherapy facility serves as a referral centre mainly for the whole of South West Region of Nigeria and other parts of Nigeria.

2.1 Inclusion Criteria:

- Patients of 18yrs and above
- Histological confirmation of breast cancer
- Radiological evidence of bone metastasis

2.2 Exclusion Criteria:

- Age below 18yrs
- Patients with psychiatric illness

Descriptive statistics include proportion, mean, median, and range. Fisher’s exact test was used to examine relationship between two categorical variables and Wilcoxon rank-sum test for association between continuous and dichotomous variables. All analysis was done using Statistical software package (Stat 12.0)
3.0 RESULTS

Between 2006 and 2011, 1,784 patients were treated with radiation therapy at the facility. Of these, 67 breast cancer patients were eligible for this study. One patient is a male and the rest are females. The average age at diagnosis was 46 years old, ranging from 28 to 77 year old. There were 31 (46%) patients who presented with metastatic disease at diagnosis (stage IV). Number of patients with stage III breast cancer were 20 (30%) and stage II, 16 (24%). (Figure 1)

FIGURE 1: DISTRIBUTION OF STAGES AT PRESENTATION

Among all 67 breast cancer patients who received radiotherapy, 58 (86.6%) had bone metastasis (Figure 1).

*Tel: +234-803-302-1434; Email: pabiodun2001@yahoo.com
There were no difference in bone metastasis among patients with stage II (n=13), III (n=19), and IV diseases (n=26). The most common sites were the spine (61%), pelvis (22%) and long bones (22%). (Figure 3)
FIGURE 3: DISTRIBUTION OF THE PATTERN OF BONE METASTASIS

The majority of patients had multiple metastases (86%) while others had solitary metastasis. (Figure 4)
FIGURE 4: DISTRIBUTION OF THE MEAN FREQUENCY OF BONE METASTASIS TYPE (SOLITARY VS MULTIPLE)
Among patients without metastasis at presentation, the median duration at presentation and the median duration from diagnosis to onset of symptoms of bone metastasis were 16.5 months and 5-38 months respectively. The duration from diagnosis to bone metastasis was shorter for patients with stage III cancer (median 14 months, range 5-27 months) than patients with stage II cancers (median 25 months, range 10-38 months; \( P=0.0099 \)).

Among these patients, 31 had osteoblastic lesions, 24 had osteolytic lesions, and 2 had mixed osteolytic and osteoblastic lesions. (Table 1)

**TABLE 1: DISTRIBUTION OF TYPES OF RADIOLOGICAL BONE METASTASIS LESION**

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed</td>
<td>1</td>
<td>1.72</td>
<td>1.72</td>
</tr>
<tr>
<td>Osteoblastic</td>
<td>2</td>
<td>3.45</td>
<td>5.17</td>
</tr>
<tr>
<td>Osteolytic</td>
<td>31</td>
<td>53.45</td>
<td>58.62</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>41.38</td>
<td>100.00</td>
</tr>
</tbody>
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*Tel: +234-803-302-1434; Email: pabiodun2001@yahoo.com*
4.0 DISCUSSION

The skeleton, after the lungs and liver is the third most common site of metastatic disease.\(^{(12,13)}\)

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 tumour.\(^{(14)}\)

As post cancer survival has increased with improvements in treatment, the number of patients developing metastatic disease during their lifetime has also increased.\(^{(12)}\) However, the manifestation of metastasis at distant site 10 years or more after initial diagnosis is also not unusual\(^{(14)}\). In addition, bone represents the first site of relapse for approximately 50\% of patients with breast cancer\(^{(6)}\).

Most patients with breast cancer present with a high degree of morbidity from bone pain, which is the most common complaints. The pain of metastatic disease is usually insidious in onset and is present in 75\% of patients at presentation\(^{(15)}\). Painless lesions usually are diagnosed during staging or routine follow up (e.g. technetium bone scan) in patients with a known history of carcinoma\(^{(12)}\). Other symptoms are features of impaired mobility, pathological fracture and spinal cord compression\(^{(13)}\). A predilection for axial skeleton is seen, perhaps owing to the Batson's plexus\(^{(16)}\).

Modalities of evaluating bone metastasis include Radiograph (i.e. X-rays), Bone scan, Computed Tomography scan (CT-scan), MRI (Magnetic resonance Imaging) and Positron Emission Tomography scan (PET scan).

Radiographs of the symptomatic area are the first step in the imaging evaluation of suspected bone metastasis. Up to 40\% of metastatic lesions may be missed on radiographic survey, because 30\% to 50\% of mineral loss or a lesion size of greater than 1.5cm is typically required for consistent detection\(^{(17)}\).

Bone metastasis are typically characterized as lytic (bone destruction), blastic (sclerotic) or mixed according to radiological or pathological appearance of the lesion. Although literature shows that most of the skeletal metastasis from carcinoma of the breast is osteolytic, more sclerotic lesions are observed nowadays probably due to increasing use of zoledronic acid and bisphosphonates\(^{(18)}\). Technetium bone

*Tel: +234-803-302-1434; Email: pabiodun2001@yahoo.com*
scan are very sensitive for detection of metastatic disease and staging of the tumour. Technetium bone scan should be correlated with plain radiographs for confirmation of metastatic disease because Technetium is not specific. CT scan provides excellent osseous detail (11).

MRI is often useful in cases in which bone scan is negative but localised symptoms. In addition, MRI is more sensitive than technetium bone scanning in the detection of bone metastasis because earlier marrow abnormalities may be identified. PET scan is both highly sensitive and specific in detecting metastasis even if CT scan & MRI results are negative (12,19).

Magnetic Resonance Imaging (MRI) is highly sensitive to the presence of skeletal metastases within the bonemarrow. MRI sensitivity is 93%, its specificity is 97% and its overall accuracy is 95%.

Plain X ray films do not have adequate sensitivity and have a false-negative rate of 10-17%. CT Scanning has had a limited impact upon the clinical detection of skeletal metastases (20).

In our study, as shown in figure 1, 46% present with stage IV disease, 30% with stage III and 24% with stage II. This shows that greater percentage of patients 76% (III&IV) are at advanced stage with stage IV already with distant metastasis. Analysis of patients’ characteristics for correlation with bone metastasis showed that nodal status, tumour size and histology were strongly positively correlated with an increase in the incidence of bone metastasis (21).

The median duration of onset of skeletal related event from diagnosis is 16.5 months with 14 months for stage III and 25 months for stage II. Annette et al in their study found that the incidence rate of bone metastasis was highest in the first year after primary diagnosis of breast cancer and higher if the breast cancer patient was diagnosed at a more advanced stage (1). Skeletal metastases also herald a poor prognosis with a median survival being 2-3 years (22). In a study by Yong et al, the 5-year survival was 75.8% for breast cancer patients without bone metastases, 8.3% for patients with bone metastases, and 2.5% for those with both bone metastases and skeletal-related events. The adjusted Mortality rate ratio (MRR) was 10.5 [95% confidence interval (CI) 9.5-11.6] for breast cancer patients with bone metastases,
and 14.4 (95% CI 13.1-15.8) for those with bone metastases and skeletal-related events (SREs),
compared with breast cancer patients with no bone metastases but possibly other sites of metastases (23)

The most common sites of metastasis among 86% of patients that developed bone metastasis are spine, pelvis and long bones as shown in figure 3, with 61% spread to the spine, 22% to the pelvis and 22% in the long bones, 5% in the skull, 1% have metastasis in the ribs which corroborate the study by Elena et al in which spine is the most frequent site for bone metastasis in breast cancer patients, and 17% to 50% of these patients would sustain a vertebral fracture (24). Also in a study carried out by Muhammad Shahzad et al, axial skeleton was the most frequent site involved, spine being the commonest (8).

This is as a result of plexus of vertebral veins that form rich anastomotic connections with veins of skull, neck, ribs, shoulder girdle and vertebral column, and allow retrograde blood flow owing to the absence of valves within them, are thought to be responsible for the preferable hematogeneous spread of breast cancer to axial skeleton.

Early postmortem studies of animals and humans by Batson (25) showed that venous blood from the breasts and pelvic organs, like the prostate, flowed not only into the vena cava, but also into a vertebral-venous (Batson’s) plexus of vessels extending from the pelvis throughout the epidural and perivertebral veins. These direct hematogenous routes may explain in part the high proclivity of breast and prostate cancers for the axial skeleton (25).

In our study, 86% of patient have multiple metastasis and 14% have solitary metastasis( Figure 4) which is the common pattern in breast cancer which typically present with multiple metastasis affecting the axial skeleton, with a concentration of metastasis in the skull, spine, ribs, pelvis and proximal long bones which is similar to that of other studies, which stated that about 80-90% of patients with skeletal metastases present with more than one lesions whereas single metastasis is relatively rare.(12)

Radiological type of bone lesion was determined in 58%, among which 53.5% was osteoblastic, 41% was osteolytic and 3.5% patients has mixed lesion (Table1). This pattern was observed possibly because of

*Tel: +234-803-302-1434; Email: pabiodun2001@yahoo.com
therapy which is similar to the observation of Ukihide Tateishi et al where the morphologic pattern of target lesions on the baseline PET/CT images was classified as lytic 32%, sclerotic 22% and mixed 41%. After treatment, however, the morphology changed to lytic 15%, sclerotic 34% and mixed 50% (26). Mixed lesions are typically due to primary cancers of the breast. (12)

5.0. CONCLUSION

A better description of bone relapse patterns may improve patient outcome by permitting a better understanding of site-specific risk, which will allow rapid institution of effective palliative treatment and a strategy for prevention of bone metastases might be implemented using a specific treatment aimed at reducing clinical progression of disease in this site.

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6.0 AUTHORS’ CONTRIBUTIONS:

Popoola designed the study and wrote the protocol. Igwilo and Sowunmi managed the literature searches. Ketiku and Duncan participated in the data collation and statistical analysis. Huo and Hou wrote the first draft of the study. All authors read and approved the final manuscript.
7.0 CONSENT AND ETHICAL APPROVAL:

No human or animal subjects were used in the study and a written consent was received from the ethical research board of the institution prior to undertaking this research.
REFERENCES:


*Tel: +234-803-302-1434; Email: pabiodun2001@yahoo.com


12. David J.J., Deborah A.F.,Frank J.F.; Metastatic Disease to Bone ,Hospital Physician November 2004


15. Wagnar G.; Frequency of pain in patients with cancer. Recent Results Cancer Res 1984; 89:64-71


*Tel: +234-803-302-1434; Email: pabiodun2001@yahoo.com


*Tel: +234-803-302-1434; Email: pabiodun2001@yahoo.com