Pattern of Bone Metastasis in Breast Cancer Patients at a Radiotherapy Facility in Lagos

Popoola A.O.¹, Igwilo A.I¹, Sowunmi A², Ketiku K.K ²&³, Duncan K.J.T³, Hou N.⁴, Huo D.⁴

¹Oncology Unit, Dept of Radiology, Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria; email: pabiodun2001@yahoo.com

¹Oncology Unit, Dept of Radiology, Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria; email: ihuomaigwilo@aol.com

²Dept. of Radiotherapy, Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria; email: toniasow@yahoo.com

²&³Dept. of Radiotherapy, Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria; email: kingsleyketiku@yahoo.com

³Radiotherapy Unit, Eko Hospital, Ikeja, Lagos, Nigeria; email: jtkduncan@gmail.com

⁴Dept. of Health Studies, University of Chicago, Chicago, IL, U.S.A; email: NHou@healthbsd.uchicago.edu

⁴Dept of Health Studies, University of Chicago, Chicago, IL, U.S.A; email: dhuo@healthbsd.uchicago.edu

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

Aim: To determine the pattern of bone metastasis in breast cancer patients.

Study Design: Retrospective case series

Place and Duration of Study: Data were collected at Eko Hospital radiotherapy facility, Lagos, Nigeria, between years 2006 and 2011.

Methodology: A total of 67 patients with a histologically confirmed diagnosis of breast cancer from 2006 to 2011 treated 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 breast cancer 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 patients who received radiotherapy, 58 (87%) have bone metastases. The most common sites of bone metastases are spine (61%), pelvis (22%), and long bones (22%). Among the 32 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. Thirty-one 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
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 distant metastasis in 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 directly stimulate osteoclasts, such as interleukin 8 or tumour necrosis factor (TNF), leading to increased bone resorption and osteolytic lesion. When osteoclast resorbs bone, release of TGF-beta not only promotes RANKL (a member of the TNF family) production and further osteoclast activity but also stimulates angiogenesis and other parts of the metastatic cascade. Binding of RANKL to RANK is endogenously inhibited by osteoprotegrin, another TNF expressed by the osteoblasts. The ratio of RANKL to osteoprotegrin regulates osteoclast formation; 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 binds 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 breast cancer from 2006 to 2011 at radiotherapy unit of the Eko Hospital located at Ikeja, Lagos State, Nigeria, were included in 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 Southwest Region of Nigeria although patients from other parts of Nigeria also come.

2.1 Eligibility Criteria:

Patients who were 18 years old and above, with histological confirmation of breast cancer treated the radiotherapy unit of the Eko Hospital were eligible. Patients with psychiatric illness were excluded.

2.2 Statistical Analysis

Most of the statistical methods in this study are descriptive, including proportion, mean, median, standard deviation and range. Fisher’s exact test was used to examine relationship between site of bone metastasis and tumour stage. Wilcoxon rank-sum test was used to test whether duration from diagnosis to bone metastasis is the same between patients with stage II and III tumours. All analysis was done using the statistical package Stata 12.0 (Statacorp, College Station, TX, USA).

3.0 RESULTS

Between 2006 and 2011, 1784 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 (standard deviation, 11 years old), ranging from 28 to 77 years old. There were 31 (46%) patients who presented with metastatic disease at diagnosis (stage IV). The number of patients with stage III breast cancer was 20 (30%) and stage II, 16 (24%).
Among all 67 breast cancer patients who received radiotherapy, 58 (86.6%) had bone metastasis. The most common sites were the spine (n=41; 61%), pelvis (n=15; 22%) and long bones (n=15; 22%). There were 4 patients (6%) having metastases in the skull, and 1 patient had metastasis in the ribs. There was no association between site of bone metastasis and tumour stage (all p>0.38, see Table 1). The majority of patients had multiple metastases (86%) while others had solitary metastasis.

Among the 57 patients with known types of radiological bone metastases, 31 had osteoblastic lesions, 24 had osteolytic lesions, and 2 had mixed osteolytic and osteoblastic lesions.

Among 32 patients without distant 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. 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, Figure 1).

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), magnetic resonance imaging (MRI), 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 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).

MRI is highly sensitive to the presence of skeletal metastases within the bone marrow. 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 patient series, the majority of breast cancer patients (76%) had advanced diseases (stage III and IV). 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).

In the current study, we found that 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, with 61% spread to the spine, 22% to the pelvis and 22% in the long bones, which corroborate the previous studies. In the study by Elena et al, 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 the study carried out by Muhammad Shahzad et al, axial skeleton was the most frequent site involved, spine being the commonest (8). In our study, 86% of patient have multiple metastasis and 14% have solitary metastasis, 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).

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).
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. This pattern was observed possibly because of 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 administration 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.

6.0 ACKNOWLEDGEMENTS

We, the authors, wish to acknowledge and appreciate all the Record staff and nursing team of Eko Hospital, who provided us with data and all the support much needed for the successful completion of this paper.

This paper is not under review in any other journal.

No conflicts of interests or competing interests. No financial disclosure to be made.
7.0 AUTHORS’ CONTRIBUTIONS:

Popoola designed the study and wrote the protocol and first draft of the study. Igwilo and Sowunmi managed the literature searches. Ketiku and Duncan participated in the data collation and statistical analysis. Huo and Hou conducted the statistical analysis and contributed to the first draft of the study. All authors read and approved the final manuscript.

8.0 ETHICAL APPROVAL:

No human or animal subjects were used in the study and the study was approved by the ethnical research board of the institution.
<table>
<thead>
<tr>
<th></th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any bone metastasis</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>19</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Spine</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>13</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>7</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td><strong>Pelvis</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>15</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td><strong>Lone bone</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12</td>
<td>14</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td><strong>Number of metastasis sites</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>Multiple</td>
<td>12</td>
<td>16</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Solitary</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

*P value from Fisher’s exact test
Figure 1. Box plot of duration from diagnosis to the onset of bone metastasis, by tumour stage

P = 0.0099
REFERENCES:


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


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


