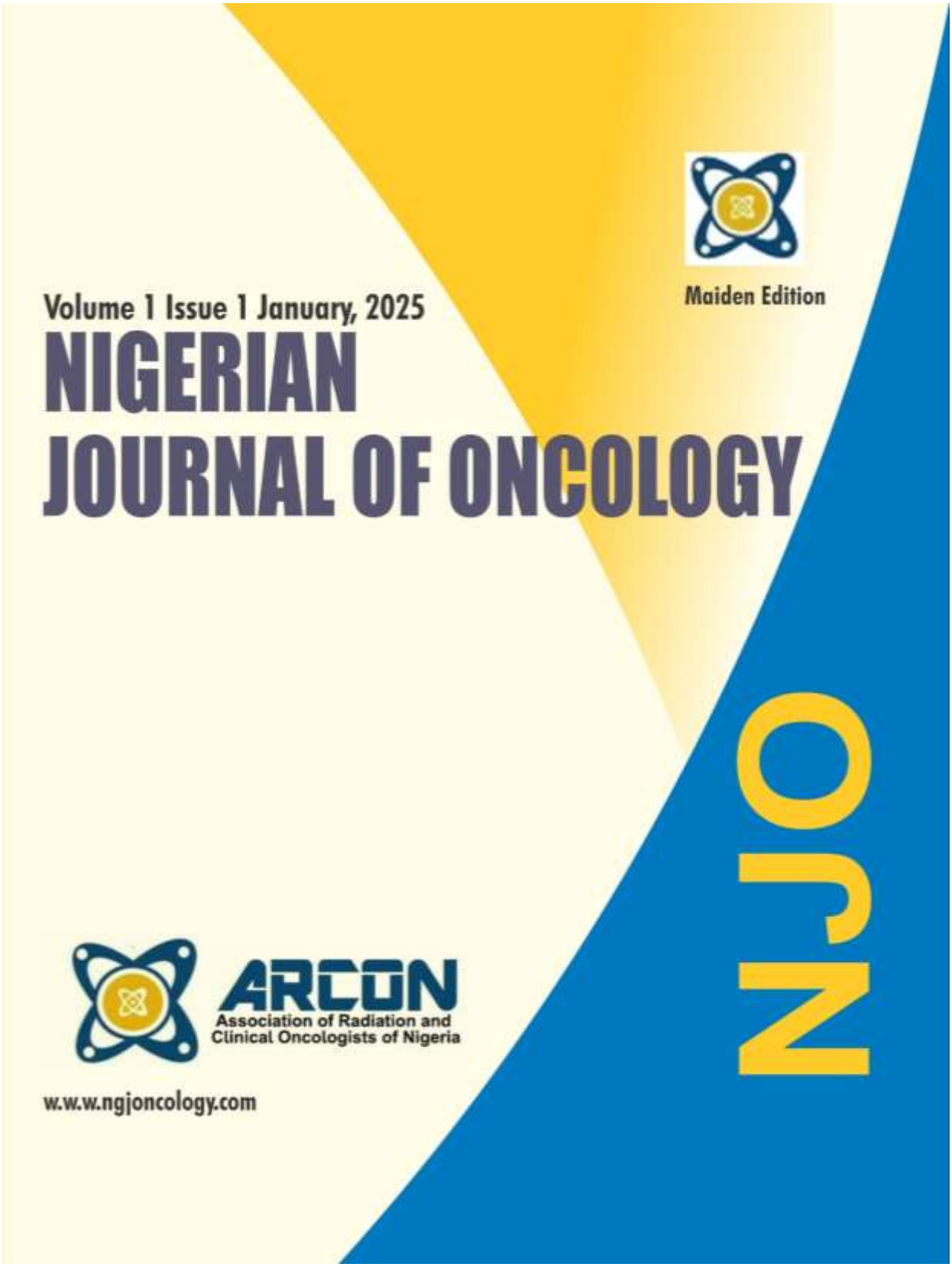
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SCINTIGRAPHIC PATTERN OF SKELETAL METASTASIS BASED ON MOLECULAR SUBTYPES OF BREAST CANCER AT THE DR GEORGE MUKHARI ACADEMIC HOSPITAL GARANKUWA, SOUTH AFRICA

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ABSTRACT

Introduction: The presence of metastasis is the most important factor affecting overall survival of patients with breast cancer. Though tremendous progress has been made in area of treatment, 20-30% of patients will develop metastasis, with the skeleton as one of the major sites of distant spread. There is marked variability among breast cancer patients who develop metastasis including the pattern. The histopathological molecular subtypes of breast cancer have distinct biological features with variability in the metastatic pattern, response to treatment and overall clinical outcome. Bone scintigraphy (bone scan) is the most commonly used imaging modality for the detection of skeletal metastasis and Methylene diphosphonate (MDP) complexed with gamma-emitting radionuclide technetium-99m (99mTc-MDP) is the most commonly used tracer for this imaging.

Objective: To assess the pattern of occurrence and distribution of skeletal metastases detected by 99mTc-MDP bone scintigraphy in the various molecular subtypes of breast cancer at the Dr George Mukhari Academic Hospital Garankuwa, Guateng.

Methods: A retrospective review of all the bone scans of two hundred and two consecutive breast cancer patients irrespective of their clinical details (age, menopausal status, stage, treatment received, presence of other metastatic sites etc.) seen at the Department of Nuclear Medicine of Dr George Mukhari Academic Hospital, Garankuwa South Africa, between 2011 to 2015 was conducted. The patients were classified into four molecular subtypes (Luminal A,

Luminal B, Human epidermal growth factor receptor-2 enriched (HER2-enriched) and Triple-negative) based on the expression of estrogen receptor (ER), progesterone receptor (PgR), Human Epidermal Growth Factor Receptor-2 (HER-2) and Ki-67 determined by immunohistochemistry at the time of diagnosis. All the patients had a minimum of two annual bone scans done between 2011 and 2015. The bone scans were reviewed for the presence of skeletal metastases and those with skeletal metastases were further classified into respective histopathologic molecular subtypes. Relevant data related to demographic information, clinical presentation, metastasis pattern, and histopathological details of the patients were retrieved from the case folders and entered into a proforma.

Results: A total of 202 patients met the study eligibility criteria; out of which 106 (52.5%) had skeletal metastasis (positive bone scans). The mean age at presentation of patients was 57.9 years with 77.4% at stages 3 and 4. The majority (72%) of the patients were ER-positive, about (46.2%) were of the Luminal B molecular subtype while Luminal A, triple-negative, and HER2-enriched subtypes accounted for 27.4%, 17% and 9.4% respectively. The highest frequency (77%) of occurrence of bone metastasis was seen in the HER2-enriched subtype. The multiple metastasis pattern of metastasis were the commonest (77.4%) pattern of distribution noted followed by solitary pattern, while super scan pattern was the least common (2.8%). Thoracolumbar vertebrae were the most commonly affected site while bones of the lower extremities had the least affectation. The sternum was the most common site of affectation noted with the solitary pattern of distribution. The multiple metastases pattern of distribution remained the most frequent in all molecular subtypes, the solitary was noted more (71.4%) with the luminal subtypes while super scan was found only in the luminal subtypes.

Conclusion: This study has shown that multiple metastasis pattern of distribution of skeletal lesions remains the most frequent form with the thoracolumbar vertebrae and lower extremities being the most and least affected sites respectively. The solitary and super scan patterns are commonly associated with the luminal subtypes. The findings could guide the development of surveillance protocol to predict bone metastases in breast cancer patients based on molecular subtypes.

KEYWORDS: Breast cancer; skeletal metastasis; bone scan; immunohistochemistry; molecular subtypes.

INTRODUCTION

Breast cancer remains a major health burden worldwide with a high rate of morbidity and mortality, particularly in developing countries.[1] It is the most commonly diagnosed cancer and the leading cause of cancer death amongst females, second to lung cancer for both sexes.[2-4] The occurrences of distant metastases are not uncommon in breast cancer, and it is associated with low survival in most patients worldwide with the median survival of 12 months without treatment, and 2-3 years with great variability in treated patients.[4-6]

Metastatic breast cancer (MBC) is believed to be incurable and about 90% of deaths from breast cancer have been attributed to metastatic dissemination.[6] The skeleton is the most common site of metastasis and it has been reported to be the first site of distant spread in 26-50% of the MBC patients and 30-85% of breast cancer patients would develop bone metastasis in the course of the disease.[7,8] Majority of breast cancer patients will have evidence of skeletal metastasis at death.[4] Skeletal metastases are clinically significant because of the associated symptoms, complications including pathological fractures and their profound significance for staging, treatment and prognosis.[4,7,9]

Tumor molecular subtypes have been associated with survival and pattern of metastasis in patients with breast cancer. Understanding this association is useful in determining choices for surveillance and therapy for individual patients.[8,10,11] The molecular subtypes of breast cancer differ in

their preferred sites of metastatic relapse which may serve as a biomarker for prediction of future metastatic sites and useful to direct disease surveillance after treatment.[12-15]

Skeletal scintigraphy (Bone scan) is the most commonly used modality for the detection of skeletal metastases in developed countries.[16, 17] However it is not widely available in Africa and it provides an entire skeletal survey. Technetium 99 methylene diphosphonate (^{99m}Tc-MDP) is the most commonly used tracer for radionuclide skeletal imaging, it is a marker of bone turnover. Bone scan detects abnormality with as little as 5-10% change in the ratio of lesion to normal bone, making it highly sensitive in the detection of skeletal metastasis. [16, 18] Bone scan is still the most commonly used modality for investigating bone metastasis. Single photon emission tomography (SPECT) may be added to improve accuracy for lesions in certain sites like the vertebrae while a positron emission tomography/computed tomography (PET/CT) is recommended when further evaluation is required.[18, 19]

The aim of this study was to evaluate the pattern of distribution of skeletal metastasis as detected by bone scan in the various molecular subtypes of breast cancer.

METHODS

Two hundred and two (202) consecutive breast cancer patients seen at the Department of Nuclear Medicine of Dr George Mukhari Academic Hospital, Garankuwa South Africa between January 2011 and December 2015 were retrospectively studied. The details from bone scans results, histopathology report and other clinical records of the patients were reviewed.

Bone scans were performed for all patients using a large field of view dual-head gamma camera (E.CAM; Siemens Medical Solutions USA, Inc.) equipped with a low-energy, high-resolution parallel hole collimator with a 10% energy window (± 5%) centered over 140KeV photo peak of ^{99m}Tc Pertechnetate. Images were acquired 3 hours after intravenous administration of 740-1110 Mega Becquerel (MBq) of ^{99m}Tc-MDP. Whole body scans in anterior and posterior projections were acquired and SPECT/CT performed when necessary. The images were accessed from the computer where they were stored.

The histopathology records of the patients were retrospectively evaluated for details including histological type, tumor grade, hormone receptor status (ER and PgR), Human Epidermal Growth Factor Receptor 2 Status (HER-2) and the proliferation index (Ki-67). The patients were then classified into the various molecular receptor subtypes of breast cancer. The review of the images was conducted by two independent certified Nuclear Medicine physicians while the interpretation of the immunohistochemistry assay of the patients was carried out by qualified anatomical pathologists at diagnosis.

RESULTS

The results were presented in the form of tables and graphs. Patient and tumor characteristics, showing the demographic and clinicopathologic features of the patients are represented in Table 1. The frequency of positive bone scan indicating the presence of bone metastasis and their distribution according to the molecular subtypes is shown in Table 2 while the distribution of the pattern of metastases is shown in Table 3. Tables 4 and 5 show the frequency of affectation of the

various bones in the multiple and solitary group of distribution patterns respectively.

Table 1. Patient and Tumor Characteristics (N= 106)

Characteristics	Frequency (n)	Percentages (%)
Age (Years)		
20-29	8	7.5
30-39	16	15.1
40-49	15	14.2
50-59	33	31.1
60-69	16	15.1
70-79	13	12.3
80-89	5	4.7
Menopausal Status		
Premenopausal	33	31.1
Post-Menopausal	73	68.9
Stage of Disease at Diagnosis		
Stage 1	2	6.8
Stage 2	21	19.9
Stage 3	76	71.4
Stage 4	7	1.9
Histological Subtypes		
Invasive Ductal Carcinoma	89	84.0
Invasive Lobular Carcinoma	13	12.3
Others	4	3.7
Histological Grade		
Grade 1	3	2.8
Grade 2	38	35.8
Grade 3	65	61.3
Receptor Status*		
ER Positive	85	80.2
PR Positive	62	58.5
HER-2 Positive	22	20.8
Molecular Subtypes		
Luminal A	29	27.4
Luminal B	49	46.2
HER2-Enriched	10	9.4
Triple Negative	18	17.0

*Values are not mutually exclusive; therefore, the sum of their percentages exceeds 100

Table 2. Distribution of Bone Metastases according to Molecular Subtypes (N= 106)

Molecular Subtypes	Positive Bone Scan (n)	% Of Subtype
Luminal A	29	27.4
Luminal B	49	46.2
HER2 Enriched	10	9.4
Triple Negative	18	17.0

Table 3. Distribution of Pattern of Skeletal Metastases by Molecular Subtypes (N= 106)

Pattern/Molecular Subtypes	**Frequency (%)**		
	Multiple	**Solitary**	**Super Scan**
Luminal A	22 (20.8)	6 (5.7)	1 (0.9)
Luminal B	38 (35.8)	9 (8.5)	2 (1.9)
HER2-Enriched	7 (6.6)	3 (2.8)	Nil (0)
Triple Negative	15 (14.2)	3 (2.8)	Nil (0)

Table 4. Distribution of Multiple Metastases by Anatomical Sites (N=82)

Site	**Frequency**	**% Patients***	**% Sites**
Spine	73	89.0	26.0
Pelvic Bone	58	70.7	20.8
Skull, Ribs, Sternum, Clavicle	62	75.6	22.3
Upper Extremities	38	46.3	13.7
Lower Extremities	47	57.3	17.0

*The sum of percentages exceeds 100 because values are not mutually exclusive

Table 5. Distribution of Solitary Metastases by Anatomical Sites (N=21)

Site	Frequency	% Patient
Skull	1	4.8
Sternum	10	47.7
Spine	3	14.2
Ribs	3	14.2
Scapular	1	4.8
Clavicle	1	4.8
Pelvic Bone	2	9.5

DISCUSSION

Bone scan is the widely accepted study of choice for the initial evaluation of skeletal metastasis in patients with breast cancer. This is because of its high sensitivity, the early detection of lesions and ability for a whole-body survey when compared to conventional radiology.[6,7,16,20-24] A host of risk factors including clinicopathological, genetic and metabolic factors have been studied in the

development of bone metastasis in breast cancer patients.[8,25] Intrinsic subtype has been implicated in several studies[1,5,8,10-15,25,26] as a major risk factor. Results of several studies on molecular subtypes have had useful impact on clinical decision-making and offered new insights into the management of metastatic breast cancer leading to an optimal personalized approach and appropriate follow-up.[13,15,26-30]

In this study, we investigated the pattern of bone metastases as detected by bone scan in the various molecular subtypes of breast cancer. The patients were grouped into age groups with a mean age of 57.9 years; over half of the patients were postmenopausal (68.9%) with locally advanced stage 3 disease (71.4%) at initial diagnosis. The tumors were mainly invasive ductal carcinoma (84%) and of high grade (61.3%). Most (80.2%) of the tumors were estrogen receptor positive, 58.5% had progesterone receptor positivity and 20.8% were human epidermal receptor- 2 positive tumors. The molecular subtypes comprised of 46.2% Luminal B, 27.4% Luminal A, 17% Triple Negative and 9.4% HER2-enriched.

Of the 202 breast cancer patients studied, over half (52.5%) of the patients had bone metastases as evidenced by a positive bone scan, while the remaining 96 (47.5%) had a normal scan showing no evidence of metastases or features of benign bone disease. Studies by Hosen et al[7] and Kim J et al[31] showed that 33.47% and 53.6% of patients had positive bone metastases respectively. Our results showed that the frequency of bone metastasis in patients with HR-positive subtypes (Luminal subtypes) was significantly higher than that for patients with HR-negative subtypes (HER2-enriched and triple negative). Eighty percent of the patients with positive bone scan had ER-positive tumors with the luminal subtypes of breast cancer having the highest frequency of bone metastases (luminal B subtype 46.2% and luminal A 27.4%). This is similar to several studies which observed that luminal molecular subtypes form the majority of bone metastases.[1,10,32-36,37]

Only one-third of the patients with triple-negative disease had a positive bone scan. This is in keeping with several studies that showed more of visceral rather than bone metastasis in this group of patients.[1,10,32,35-37] In this study, it is of note that although only about 10% of the patients who developed bone metastases were from the HER2-enriched subtype, the prevalence of bone metastasis was high within the HER2-enriched group with 10 patients out of 13 (77%) having a positive bone scan. Similarly, the study[31] recorded bone metastases in 57.9% of HER2-enriched tumors.

This study showed that the multiple pattern of distribution was the most frequent form of distribution of bone metastases. Of the 106 patients with positive bone scan, eighty-two patients accounting for 77.4% had multiple wide spread pattern, twenty one patients (19.8%) had the solitary pattern, while three patients (2.8%) had the super scan pattern. These patients (multiple pattern) present classically as widespread, multifocal, asymmetrical, intense uptake involving two or more bones. This is similar to several other studies.[7,18,20,22, 24, 26, 31] A study involving 703 patients showed 41% solitary and 59% multiple patterns of distribution. [37] The multiple pattern of metastases was the most frequently observed pattern of distribution in all the molecular subtypes, the solitary pattern was most frequently observed in the luminal

subtypes while the super scan pattern was exclusive to these subtypes.[37]

In patients with multiple metastases, the spine was the most frequently affected bone (26%) followed by the pelvis (20.8%), flat bones (skull, ribs, sternum and clavicle) and the extremities. In another study of the pattern of skeletal metastases in breast cancer patients,[7] the spine accounted for 80.89%, ribs, sternum and clavicle (57.35%) and the pelvis (47.06%).

Among patients with solitary metastasis, the sternum was the most frequently affected bone (47.7%), followed by spine and ribs (14.2% each), pelvic bone (9.5%), skull, clavicle and scapular (4.8% each). A study[37] recorded the sternum as the most (34%) frequent site of solitary metastases while several other studies have shown the spine as the most frequently affected solitary bone.[7,20,22,32] Metastasis to the sternum occurred most frequently in patients with a solitary metastatic bone lesion, while metastasis to other skeletal sites occurred more frequently in patients with multiple metastatic bone lesions. This is also similar to the pattern seen in the study by Koizumi et al.[37]

CONCLUSION

Several factors are known to increase the risk for breast cancer metastasis to the bone with the intrinsic molecular subtype being widely accepted as a major risk factor. The present study found that the hormone receptor positive breast cancer (Luminal subtypes) has the highest incidence of bone metastasis and elicit predominance in all the patterns of distribution studied.

The high prevalence of skeletal metastasis in the HER2-enriched subtype and low prevalence in the Triple-negative subtype in this study supports the need for further studies to assess the molecular mechanisms driving these differences.

The follow-up protocol of patients with early breast cancer may likely change over time if imaging for bone metastasis is based on the combined power of disease staging, presence of symptomatic bone pain and molecular subtype classification of all patients.

It is recommended that molecular subtype classification of breast cancer be included in the routine investigation of breast cancer patients. Management guidelines should include molecular subtyping as part of the criteria when requesting, scheduling for and/or reporting a bone scan considering its importance in influencing bone metastases prediction.

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