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ORIGINAL RESEARCH

Does the laterality of breast cancer affect disease outcomes on bone scan?

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Abstract

Background: The incidence of breast cancer (BC) continues to rise, with the latest record being 2.08 million globally. It also remains the most common female malignancy worldwide. Increasing awareness and screening have been suggested as contributory factors.
Objective: To determine the relationship between disease laterality in breast cancer and disease outcome in terms of bone metastasis.
Methods: The study is a hospital-based six-year retrospective review of all breast cancer patients who had bone scans done between 2011 and 2016.
Results: A total of 992 bone scans (BS) were analysed for 500 (50.4%) patients with left-sided breast cancer and 492 (49.6%) with right-sided breast cancer. While 638 bone scans were abnormal, 354 were benign and 242 (24.39%) were equivocal. There was no association between primary tumour laterality and BS outcome ($p = 0.544$). Furthermore, Chi-Square for trend assessed the association between patients' age and BC laterality but yielded no significance ($p = 0.67$).
Conclusion: The laterality of breast cancer did not affect the stage of breast cancer as shown by bone scan outcomes in this study.

Keywords: Bone scan; Bone scintigraphy; Breast cancer; Laterality of breast cancer; Nuclear Medicine, Tumour.

Introduction

The incidence of breast cancer (BC) continues to rise in developed nations such as Australia, North America, North, and West Europe; the global figure is 2.09 million for 2018, which is a global close second to lung cancer also with an incidence of 2.09 million for the latter. BC is also the most common cause of female cancer deaths in Nigeria, with an associated mortality of 11,564 deaths. [1] Increased awareness and screening rates have also contributed to its rising incidence.

BC has a multifactorial origin; both genetic and hereditary factors are involved in its development, such as possession of *BRCA1, BRCA2* or *RET* genes, and personal or family history of ovarian cancer. [2] While breastfeeding and physical exercise are protective, risk factors include hormonal exposure from early menarche coupled with late menopause, postmenopausal hormone replacement therapy, nulliparity, use of oral contraceptive pills, as well as obesity. [3] These risk factors account for 90-95% of BC. Primary BC may progress to locoregional spread and distant metastases. Skeletal metastases develop via haematogenous dissemination of tumour, with proffered explanations including Paget's postulate of the seed and soil theory. [4,5]

The practice of Nuclear Medicine (NM) involves the diagnosis and treatment of disease conditions using radioisotopes. The bone scan (BS), also known as bone scintigraphy, is an established nuclear imaging modality that stages, monitors and restages skeletal involvement of breast cancer after

patients have been treated. It has the advantage of providing whole-body images of the skeleton without additional radiation to the patient. The most common indication for BS is the detection of skeletal metastases. BS involves the intravenous injection of patients with an appropriate radioactive bone-seeking compound (a diphosphonate), which then allows imaging of the skeleton.

Technetium-99m is the most widely used radioisotope for BS; it has a physical half-life of six hours. The radioactive compound (a radiotracer or radiopharmaceutical) localizes in bone in proportion to bone perfusion and the degree of osteoblastic activity. Peak skeletal uptake subsequently occurs by one-hour post-injection and remains steady for three hours post-injection. [6] Half of the administered radiopharmaceutical is taken up by the skeleton; of this, approximately 67% is chemi-adsorbed to hydroxyapatite and the remaining third to calcium phosphate. [6]

As the bone radiopharmaceuticals are incorporated into the growing phase of bone, BS portrays osteoblastic lesions more often than osteolytic lesions. Skeletal metastases usually have irregular uptake and are asymmetrical, with a haphazard alignment. Metastases may appear as solitary, multiple or widespread bony lesions. While osteoblastic lesions appear as areas of abnormally increased uptake, lytic ones have relatively reduced or absent uptake on the scan; as such it is not recommended as the primary imaging modality for staging tumours with purely osteolytic metastases. [6]

Breast cancer laterality has been investigated in connection with patient age, handedness, gender, tumour size, and disease outcome. [7, 9] Similarly, it was suggested that from clinical practice and from previous assertions in the literature, that laterality of BC could affect disease outcome on the BS. In this study, we investigated the influence of BC laterality on findings in BS in our practice. While previous local studies on breast laterality have been conducted, none has involved the BS as a measure of disease outcome.

This study determined the relationship between disease laterality in BC and disease outcome in terms of bone metastasis on the BS. It was hypothesized that laterality of BC may influence the outcome of BS in the patients; the latter reflecting as the presence or absence of skeletal metastases on BS. To our knowledge, no other studies from this region have studied the outcome of BC in terms of BS finding and in relation to laterality of disease.

Methods

A retrospective six-year review of all BS carried out from January 2011 to December 2016 to stage BC at the Department of Nuclear Medicine, University College Hospital, Ibadan was done. Males were excluded from the study due to their small numbers. Other exclusion criteria included bilateral breast cancer, non-documentation of the location of primary BC, missing bone scan results as well as missing/insufficient records.

Radiopharmaceuticals were made by adding radioactive Technetium-99m pertechnetate to the diphosphonate [hydroxymethylene diphosphonate (HMDP) and methylene diphosphonate (MDP)]. Following an intravenous injection of the radiopharmaceutical, a minimal uptake period of two hours was observed to allow for adequate skeletal uptake of the radiotracer. In this study, a single-head Siemens eCam camera and a dual-head Mediso camera, acquired images using low-energy high-resolution collimators. Anterior and posterior whole-body sweeps of the entire skeleton were acquired along with additional spot views of areas of interest where necessary.

Patients were referred for BS for the initial staging of BC patients, for the assessment of unexplained bone pain in these patients, disease surveillance and assessment of the efficacy of therapy. Follow-up scans were also performed for patients whose bone scans had previously displayed indeterminate lesions. A normal BS was defined as one which showed normal skeletal uptake along with excretion through the kidneys and the urinary bladder. An abnormal BS had lesion(s) with increased uptake exceeding that of the surrounding skeleton; metastases and equivocal lesions were areas of atypical uptake on BS as previously described above. BS findings were categorized as normal (1) or abnormal (2). Findings in abnormal scans were further

classified as skeletal metastases (1), suspicious lesions (2) or a mixture of metastases and suspicious lesions (3). Primary breast tumour sites were grouped as left or right according to patients' health records. BC laterality ratio was computed as the ratio of left-to-right breast cancer.

The body mass index (BMI) was calculated as: weight (kg) ÷ height^2 (m^2)
The normal range of BMI values is 18.5-24 kg/m^2; patients with BMI less than 18.5 were classified as underweight, those with BMI 25-30 kg/m^2 were classified as overweight, and those with BMI above 30 kg/m^2 were regarded obese.

The study was carried out in accordance with the ethical standards of the responsible committee on Human Experimentation (Institutional and National) and with the provisions in the Helsinki Declaration of 1975, as revised in the year 2000.

Data were analysed using SPSS software version 23 and Epi-Info software version 7.2. Prior to data analysis, patients' records were anonymised. The variables assessed included age at presentation, BMI, BC laterality, disease duration, the quantity of radioactivity administered, as well as bone scan findings. The Chi-Square test was used to determine the effect of BC laterality on scan outcome

Results

A total of 1044 bone scans had been carried out for 998 patients aged 24-93 years. Excluded from the study were 31 (2.97) BS performed on patients with bilateral BC, 9 (0.86%) BS for males, as well as 12 (1.15%) patients with missing bone scan results.

Therefore, the sex ratio for BC in this study was 0.87 while the male to female sex ratio was 1:115. Of the remaining 992 BS (95.02%), left-sided BC was present in 499 BS (47.8%), while 493 (47.22%) BS was performed for right-sided BC. The laterality left to -right ratio for BC was 1.01. The overall average age of the patients studied was 49±11.3 years, while patients with right BC had an average age of 49±10.7 years compared to 50 ± 11.9 years for left-sided BC (t = 0.876; 95% CI = -0.78 – 2.05; p = 0.381). The modal decade age group at presentation was 41-50 years.

The overall mean BMI was 29±5.8 kg/m^2; 29.1±6.1 kg/m^2 for left BC and 28.9±5.44 kg/m^2 for right BC; details were missing for 66 patients (6.7%) who were too ill to have their weight or height taken. BMI did not have a correlation with disease outcome on BS (t = 0.334; 95% CI = -0.622 - 0.877; p = 0.738).

Table I shows parity in relation to BC laterality; women with right BC had the highest parity with 11 children, slightly higher than nine for left BC. The records of parity were not available for 13 (1.31%) women. Of the available details, 135 women (13.79%) were grandmultiparous. Parity was not a significant predictor of disease outcome on BS (t = -1.336; 95% CI = -0.10 - 0.19; p = 0.182).

Six hundred and thirty-nine (64.41%) of the 992 BS were abnormal. There was evidence of advanced disease in 397/992 (40.02%) with BS evidence of skeletal metastases while 242/992 (24.40%) had equivocal findings. Only 353/992 (35.58%) had benign BS. Of the BS with evidence of metastases, 255 (64.23%) had multiple osseous secondaries, 106 (26.7%) had widespread metastases, 30 (7.56%) BS had solitary metastases, while the nature of metastases was not known for six (1.51%) cases. Equivocal bone scan results were most common in the modal age group 41-50 years (75, 31.1%), followed by the older age group of 51-60 years (72, 29.9%) and then 31-40 years (46, 19.1%). No bone scans in the ninth and tenth decades were deemed equivocal.
In patients with disease duration ≤1 year (408, 41.13%), BS outcome was no bony metastases in 170 (41.67%), metastases in 147 (36.03%), and had ambiguous results in 91 (22.30%).

Tables II and III show patients' bone scan findings by age and laterality. However, there was no association between primary tumour laterality and BS outcome (p = 0.544). Furthermore, Chi-Square for trend to assess the association of patients' age and BC laterality yielded no statistical significance (p = 0.67).

Table I: Parity distributed according to the laterality of breast cancer

	LEFT BREAST CANCER		RIGHT BREAST CANCER		TOTAL	
Parity	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
0	48	9.8	46	9.4	94	9.6
1	40	8.1	41	8.4	81	8.3
2	71	14.4	58	11.9	129	13.2
3	94	19.1	119	24.4	213	21.8
4	101	20.5	82	16.8	183	18.7
5	71	14.4	73	15.0	144	14.7
6	41	8.3	40	8.2	81	8.3
7	18	3.7	14	2.9	32	3.3
8	7	1.4	10	2.1	17	1.7
9	1	0.2	2	0.4	3	0.3
11	0	0.0	2	0.4	2	0.2
Total	492	100.0	487	100.0	979	100.0

Table II: Distribution of abnormal scans by laterality of primary breast cancer

	Normal bone scans	Metastatic bone scans	Equivocal bone scans	Total
Left breast cancer	167 (16.8%)	211 (21.3%)	121 (12.3%)	499 (50.3%)
		Subtotal	335 (33.5%)	
Right breast cancer	186 (18.8%)	186 (18.8%)	121 (12.2%)	493 (49.7%)
		Subtotal	307 (30.9%)	
Total	353 (35.6%)	397 (40.0%)	242 (24.4%)	992 (100.0%)

Table III: Distribution of abnormal bone scans by age

Age group	Frequency (%)	Normal bone scans (%)	Metastatic bone scans (%)	Equivocal bone scans (%)
21-30	37 (3.7)	10 (27.03)	17 (45.94)	10 (27.03)
31-40	196 (19.8)	69 (35.20)	81 (41.33)	46 (23.47)
41-50	324 (32.7)	122 (37.65)	133 (41.05)	69 (21.3)
51-60	266 (26.8)	98 (36.84)	97 (36.47)	71 (26.69)
61-70	125 (12.6)	48 (38.40)	49 (39.20)	28 (22.4)
71-80	35 (3.5)	8 (22.86)	15 (42.86)	12 (34.28)
81-90	5 (0.5)	3 (60.0)	2 (40.0)	
91-100	1 (0.1)	1 (100.0)		

Discussion

The women in this study had almost a similar number of left and right BC, debunking the previously held clinical observation in the hospital. Female BC patients presenting for BS at this centre had a slightly higher proportion of right-sided primary tumours. BC patients from an earlier study from this centre also had a similar higher preponderance of right-sided primary tumours (50.5%) than in the left (46.2%), while 3.3% were bilateral. [9]

This study set out to determine the possible influence of laterality on disease outcome of BC but found no association. Furthermore, laterality was not a significant predictor of disease outcome as shown by the presence or absence of skeletal metastases on BS. However, these results differ from the findings in other research performed regarding the laterality of BC. For instance, Nosheen *et al.* studied an Asian population of 384 Pakistani women with BC; left laterality predominated in these patients with a left to right laterality ratio of 1.45. In that report, right BC cases

exhibited greater aggression than the left, as shown by a higher proportion of bony metastases. Whereas there was little disparity in age between both groups of our patients, the Pakistani women with right BC were significantly younger with a mean age of 46 ± 13 years. [7] The latter also had other indicators of tumour aggression: a higher propensity for receptor-negative BC, as well as triple-receptor negative BC.

Patients' handedness has been cited as a factor in the laterality of primary BC; it has been suggested that left BC was more common in right-handed patients who performed self-breast examination with their right hand, would be more thorough in assessing the left breast, and would thus be more likely to discover primary breast tumours on that side. However, this theory has been debunked by other researchers. [10] Moreover, considering that a great majority of the population is typically right-handed than left-handed, this should have translated to an overwhelming prevalence of left BC than is currently the case.

Previous studies had considered the often larger size of the left breast as a reason for the left preponderance of BC. [10] However, this theory was subsequently debunked, as no significant association was found between breast size and laterality of BC. [11,12] Another proposition is that mothers tended to nurse their children more often from the right breast, thus protecting the right breast from developing BC more than the left. [13] Unfortunately, male BC also exhibits asymmetry of location, and so this supposition was debunked. [10] Conflicting reports exist regarding sidedness of BC as an influence on patient survival; while others have reported that sidedness did not affect survival, others purport that left laterality is an indicator of better patient survival. [14,15] In a study of 2,409 Chinese female patients with unilateral BC, Cheng *et al.* discovered a left predominance of five percent. Left BC was more common in patients younger than 40 years, while the right BC was more frequently seen in older patients. Left BC was also more likely to harbour non-invasive tumours than was right BC; it was also more likely to be associated with other histological subtypes except invasive mucinous and invasive medullary. [16] Contrarily, Ekbom *et al.* found that left BC was more dominant in patients older than 45 years. [10] In the population of patients in the present study, there was little difference in the mean ages of patients with left BC (52 years) and those with right BC (49 years). This is suggestive of a homogeneous population, as they also had a tumour laterality ratio of one.

Kharazmi *et al.* had also previously reported a link involving laterality of BC among first-degree relatives. There was a higher risk of BC occurring in patients with older first-degree relatives who are older than 40 years with contralateral BC. Having younger relatives aged less than 40 years with multiple ipsilateral BC foci also resulted in a risk of BC. [17] An Egyptian study of 5,459 male and female patients with BC showed a higher incidence of left BC in both older and younger patients. In contrast, the patients in the present study had a similar ratio of left-to-right BC and a higher frequency or incidence of bone metastases due to late presentation. In this study, the overall survival was lower in left BC than right BC, although without statistical significance. [18]

Although younger ages of onset have been cited in the literature, the subjects in the present study tended to be middle-aged, in the 5th and 6th decades of life, with the average age at presentation being 49 years, and the modal decade being the fifth, consistent with existing literature [19,20] There was also little disparity in age between both groups of BC laterality. However, in a Swedish study, left laterality exceeded right in both male and female BC patients older than 45 years. This comprised an altogether different cohort of Caucasian women and a different research methodology was used. [10]

Nulliparity and older age at first conception/childbirth contribute to the pathogenesis of BC from the prolonged exposure of breast tissue to hormonal stimulation. Parity in itself has been shown to reduce the risk of BC by 25%. [21,22] In this study, 55% of the women had a parity of three to five and 14% were grandmultiparous, while 10% were nulliparous. Thus, nulliparity was not a major risk factor in the development of BC in the present cohort.

Obesity as a risk factor for BC was present in a fifth of our study participants; while a similar number was overweight. These figures reflect the national obesity rate for females which

exceeds the 10% obesity rate of the general population. [23] Despite the advanced stage of disease as seen on BS in 40%, approximately half of our patients had normal BMI. Patients who were underweight might have been cachectic from the advanced status of BC, or this might reflect their pre-morbid nutritional status. In agreement with the findings in the present study, Adebamowo *et al.* did not find an association between obesity and BC. [24] However, other researches have established obesity as a significant risk factor for developing BC, although the mechanism is poorly understood. [25,26]

As shown by the number of patients with abnormal BS with outright metastases or equivocal lesions on BS (64.41%), it can be inferred that the patients in this region of the country still present late to the hospital. One of the reasons for this has been the fear of mastectomy. [27] Of all the patients presenting for BS within the first year of diagnosis, 36% had BS evidence of stage IV disease. As shown in older studies, up to 40% of patients in this environment tend to present with advanced metastatic cancer and a further 25% with equivocal findings. [28] This reflects the attitude of patients seeking alternative curative treatment before being forced to present at orthodox medical facilities as a last resort. [29-31] The patients studied by Nosheen *et al.* had an overall incidence of 28% for bone metastases, which was lower than the findings in the present study, while research by Largillier *et al.* discovered metastases in 40% of cases. [32] The latter group also found that bony metastases conferred better survival than visceral ones.

With advancing age comes the attendant phenomenon of degenerative spinal column disease. These are known variants on the BS. However, in elderly patients with BC, the diagnosis of metastases may not be feasible especially for solitary lesions, and in the absence of three-dimensional single-photon emission computed tomography/computed tomography (SPECT/CT) imaging. SPECT/CT offers hybrid imaging with a fusion of both functional (SPECT) and anatomical (CT) scans. Both sets of images are acquired sequentially, and the CT aspect of the scan improves localization of the indeterminate lesion seen on the simple BS. [33] Unfortunately, this modality was not available for most of these bone scans, with the resultant high number of indeterminate foci on BS. In this study, approximately one-quarter of scan results might have been resolved as being benign or malignant if this modality were available.

The BS has been described as being non-specific; however, adequate clinical information, as well as the typical patterns of multiple or widespread osteoblastic lesions, are sufficient to report metastases in the absence of hybrid SPECT/CT. Indeed, this was adequate to make decisive conclusions in 75% of our patients with normal BS (35.6%) or metastases (40.1%). Moreover, lytic lesions are poorly detected on BS for reasons as stated above. For this reason, the scan may have underestimated disease spread in these patients.

Unlike previously cited research, patients' receptor status and histology were not available for statistical analysis of their effect on BS findings. Long-term patient survival was also not assessed due to the short duration of the period covered; this may be evaluated in future research.

Conclusion

The patients with BC in the present study had an almost symmetrical number of right and left-sided tumours. The laterality of breast cancer did not affect the stage of BC as shown by bone scan outcomes in this study.

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