

RESEARCH ARTICLE

Lower Incidence but More Aggressive Behavior of Right Sided Breast Cancer in Pakistani Women: Does Right Deserve More Respect?

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Abstract

Background: The aim of this epidemiological study was to establish the laterality of breast cancer (BC) and its association with size, receptor status of the primary tumor and bone metastasis (BM) in a local population. **Materials and Methods:** This retrospective study included cases of BC from Jan-2009 to Dec-2011 who were referred for metastatic work up or follow up survey with Technetium-99m MDP bone scan (BS) to the Nuclear Medicine Department of Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN). A total of 384 patients out of 521 were included and all reviewed for age, primary tumor size (PTS), laterality, receptor status like estrogen receptor (ER) progesterone receptor (PR) and Her-2-Neu receptor, presence or absence of BM with sites of involvement and time interval between diagnosis of BC and appearance of BM. **Results:** The left to right sided BC proportion was significantly higher than unity (59%:41%; $p < 0.001$). The right sided BC was observed in younger age group (46:52 years; $p < 0.0001$) and with a smaller PTS than the left sided (3.43:4.15 cm; $p < 0.0001$). The patients with BM had relatively higher negative receptor status with a significant predominance of right sided BC. The overall incidence of BM on BS was 28% and relatively higher in right than left breast (33%:24% $p = 0.068$). The average number of BM sites was also significantly greater for the right side (6:4, $P < 0.0001$). The % cumulative risk of BM in right breast was noted at significantly smaller PTS than left side with log rank value of 5.579; $p < 0.05$. The Kaplan Meier survival plot for event free survival of BM in left sided BC was significantly higher than for the right side (log rank value=4.155, $p < 0.05$), with an earlier appearance of BM in right BC. **Conclusions:** 1) A left sided predominance of BC was seen in local population; 2) right sided BC had a more aggressive behavior with extensive and earlier appearance of BM at relatively younger age, smaller PTS and receptor (s) negativity.

Keywords: Breast cancer - laterality - bone metastasis - receptor negativity - primary tumor size

Asian Pacific J Cancer Prev, 14 (1), 43-45

Introduction

Among Pakistani women the breast cancer is considered as the most frequently diagnosed cancer and reported incidence is 17% over 2006-2009 (Fatima et al., 2010). The paired organ in human body may exhibit asymmetry in their anatomy and physiology which may influence in laterality of cancer in paired organs (Roychoudhuri et al., 2006). Various studies have shown higher incidence of diagnosed breast cancer on left side (Garfinkel et al., 1959; Weiss et al., 1996; Perkins et al., 2004) however, no valid reason for left sided excess or lateralization has been elucidated (Weiss et al., 1996). It was studied in large epidemiological trial on cancer laterality in paired organs that incidence of right sided BC started at a relatively younger age than left sided breast cancer (Roychoudhuri et al., 2006) with higher

incidence of nodal metastasis as well (Dane et al., 2008). However in Japanese population there is no significant left sided predominance has been observed presumably due to different sleeping habits (Fields, 2011). Bone is the most frequent site of metastatic spread in BC (Coleman, 2006) and is the reason for significant morbidity as associated with skeletal related events (SRE) like bone pain, pathological fracture or spinal cord compression (Coleman and Rubens, 1987). The aim of this study was to find out the laterality of BC and its association with size, receptor status of primary tumor and bony metastasis in local population.

Materials and Methods

This is a retrospective study included cases of BC from January 2009 to December 2011 who were referred for

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metastatic work up or follow up survey with Technetium-99m Methylene Diphosphonate (Tc-99m MDP) bone scan to Nuclear Medicine Department of Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN), Karachi, Pakistan. Total 384 patients out of 521 hospital record files were included while patients with bilateral BC (15 cases), unknown laterality (due to incomplete information on available records in 34 cases), male gender (2 cases), Hodgkin disease of breast (1 case) or with incomplete histopathology details of primary tumor (85 cases) were excluded. The records of included women were reviewed for age, primary tumor size, laterality, receptor status like estrogen receptor (ER) progesterone receptor (PR) and Her-2-Neu receptor, presence or absence of bone metastasis with sites of involvement and time interval between diagnosis of breast cancer and presence of bone metastasis. The studied population was broadly divided into two groups based on laterality; 225 subjects with left sided and remaining 159 were with right sided breast cancer.

Data were analyzed by using commercially available packages the Medcalc® statistical software version 11.3.10 and statistical package for social sciences (SPSS version 17®). Comparisons between two groups were performed using Student's t test for continuous variables and the Chi-square (χ^2) test for categorical variables. Continuous variables were described by mean±standard deviation (SD). Comparison of cumulative risk of bone metastasis with primary tumor size and time of appearance of bone metastasis in relation with lateralization of breast cancer were analyzed by Kaplan Meier survival plots and log rank value was analyzed for comparison of survival curves. For all P-values <0.05 were selected as significant.

Results

The demographic distribution of studied women is demonstrated in Table 1. The proportion of left to right sided breast cancer is significantly higher (59%:41%; p<0.001). The women with right sided breast cancer were significantly in younger age group and with smaller

Table 1. Demographic Distribution of Studied Population

Variables	Total Ca Breast (384)	Ca Left Breast (225; 59%)	Ca right Breast (159; 41%)	p value
Age (Mean±SD) years	49±13.00	52±12.00	46.00±13	<0.0001*
Size of primary tumor (Mean±SD) (cm)	3.85±1.49	4.15±1.59	3.43±1.24	<0.0001*
Bone Metastasis	108 (28%)	55 (24%)	53 (33%)	0.068
Sites of bone involvement (Mean±SD)	5±3.00	4±3.00	6.00±2	<0.0001*
Skull	24 (22%)	9 (16%)	15 (29%)	0.003*
Sternum	39 (36%)	18 (32%)	21 (40%)	0.0132*
Ribs	69 (64%)	24 (42%)	45 (87%)	<0.0001*
Scapula	7 (6%)	6 (11%)	1 (2%)	0.0021*
Dorsal spine	60 (56%)	27 (48%)	33 (63%)	0.0051*
Lumbar spine	70 (65%)	33 (59%)	37 (71%)	0.0212*
Pelvis	60 (56%)	24 (43%)	36 (69%)	<0.0001*
Appendicular (Humerus/femur/tibia)	52 (47%)	24 (43%)	28 (54%)	0.0431*

*SD=Standard Deviation; ER=Estrogen Receptor; PR=Progesterone Receptor; Her-2 N=Her-2 Neu

primary tumor size than the left sided breast cancer (Table 1). The patients with bone metastasis have relatively higher negative receptor status (Figure 1). The right sided breast cancer with bone metastasis was prone to be triple negative as well as individual ER, PR, Her-2-Neu negativity (Figure 1).

The overall incidence of bone metastasis on Tc-99m MDP bone scan was 28% and relatively higher in right breast than left (33%:24% p=0.068). The average number of skeletal sites for metastatic involvement and distribution pattern both in axial and appendicular skeleton was significantly extensive in right side than left sided BC (Table 1).

The cumulative risk (in percentage, %) of bone metastasis in right breast was noted at significantly smaller primary tumor size than left side with log rank value of 5.579; p=0.0182 (Figure 2). The Kaplan Meier survival plot for event free survival of bone metastasis in left sided breast cancer was significantly higher than right side (log rank value=4.155, p=0.042) and also revealed earlier bony metastasis in patients with right BC (Figure 3).

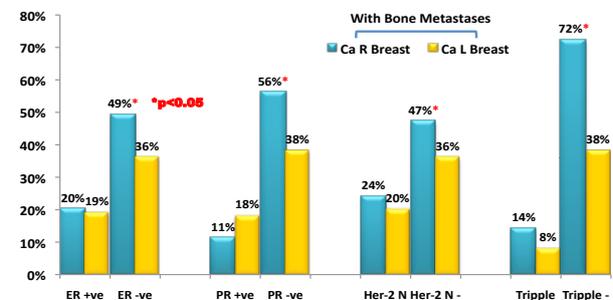


Figure 1. Comparison of Receptor Status with Bone Metastases in Relation with Lateralization of Breast Cancer

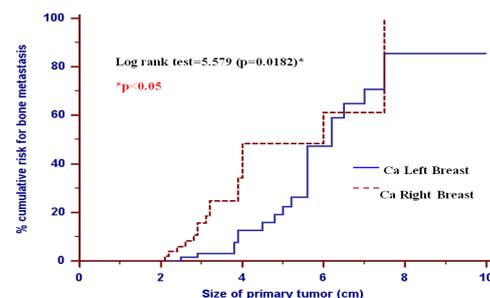


Figure 2. Comparison of % Cumulative Risk of Bone Metastasis with Primary Tumor Size in Relation of Lateralization of Breast Cancer

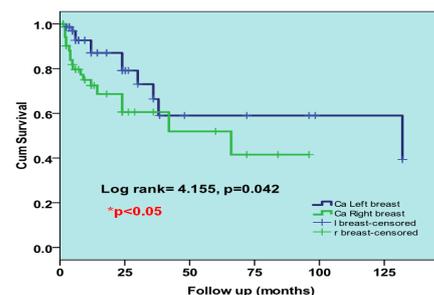


Figure 3. Kaplan Meier Survival Plot for Bone Metastatic Free Survival in Relation with Lateralization of Breast Cancer

Discussion

Breast cancer is the most common female malignancy and a major female killer after lung cancer in USA. However, over the last few years a decline in death rate from BC has been observed due to increased awareness, stringent screening and better treatment options. All these are indeed fueled by continuous and multidimensional research about breast cancer.

In this study incidence of left sided breast cancer was significantly higher than the right and this is in accordance with established and well documented facts published from western world (Ekbom et al., 1994; Wilting and Hagedorn, 2011). The reason of increased risk in left breast is unclear (Weiss et al., 1996) but few studies have shown a possible correlation with relatively larger left breast size (Ing et al., 1997), unilateral lactation (Ing et al., 1997), detection biased due to predominant right handedness (Perkins et al., 2004) or more denser left breast (American Cancer Society, 2011-12). This study also revealed that women having right breast cancer were younger than those having left sided disease and this concurs with various published studies showing left sided laterality is more pronounced at higher ages (Busk, 1947; Garfinkel et al., 1959; Senie et al., 1980).

Interestingly in this study, patients with right sided disease had smaller primary tumor size and were more prone to have triple negative as well as isolated ER, PR and Her2-Neu negativity. These data draw our attention towards more aggressive behavior of right sided breast tumor which needs to be elucidated as we don't have any plausible explanation for this observation. Overall incidence of bone metastasis in our study is lower as compared to locally published data (Afzal et al., 2009) and this low incidence may be due to biased sampling or relatively low specificity of radionuclide bone scan. However, incidence of bone metastasis was relatively higher with right sided than left sided disease (albeit non-significant) but significantly more extensive (more metastatic lesions) with right sided disease. We could not find any other study supporting this observation although studies have shown higher incidence of nodal metastasis in right sided breast which is indeed an established factor for recurrence (Coleman, 2006). On the same note, the cumulative risk for developing bone metastasis with a smaller size right sided primary tumors and lower event free survival in patients with right sided disease. Unfortunately we did not have nodal status in this retrospectively studied cohort which is a limitation of this study.

The data of this retrospective study revealed right sided breast cancer is prevalent at a relatively younger age, more receptor negativity, extensive and earlier appearance of bone metastasis with smaller primary tumor size and lower event free survival as compared with left sided disease. We are not sure whether these findings put a caution-note to surgeons and oncologists to be very vigilant with right sided breast cancer. But we strongly believe that laterality biased aggressiveness of breast cancer must be explored with well designed larger clinical trials.

We conclude that right sided BC has a lower incidence

than left sided disease but had an aggressive behavior with extensive and earlier appearance of BM at relatively younger age, smaller PTS and receptor (s) negativity.

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