

Pattern of Distribution of Metastatic Lesions within Skeleton in Patients with Breast Carcinoma of Faisalabad and its Vicinity

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ABSTRACT

Objectives: Evaluation of pattern of distribution of skeletal metastases in patients with breast carcinoma. by using ^{99m}Tc MDP Skeletal Scintigraphy

Design: Retrospective Analysis

Place and Duration of Study: Study was conducted at Punjab Institute of Nuclear Medicine (PINUM), Faisalabad Pakistan from January 2006 to June 2009.

Material and Methods: A retrospective study was performed on 465 consecutive patients having CA Breast irrespective of preoperative/postoperative status, presenting for bone scan at Punjab Institute of Nuclear Medicine. Whole body bone scan was performed, along with additional spot views, where needed. The images were interpreted for metastatic deposits by three independent observers. Where needed, plain X-ray was performed to correlate in favor of benign pathology.

Results: Out of 465 patients (453 female & 12 Male), 286 (62%) patients were having either normal bone scan or some benign pathology as correlated with plain x-ray of the suspected area. 179 (38%) patients were positive for metastases within skeleton. Among these, 61.4% patients were having multiple, 14% with two, while 24.6% were diagnosed as having solitary lesions within the skeleton. In patients having multiple skeletal lesions, highest number was noted in spine (84.5%-most common in thoracolumbar), followed by ribs

(55.5%), pelvis (37.3%---most frequent in iliac bone), skull (32%), scapula (27.3%), sternum (26.4%), femur (19.1%), humerus (14.5%), clavicle (3.6%) and tibia (0.9%). In humerus and femur, most lesions were located in their upper ends, followed by shafts. Right side of skeleton was more frequently involved than the left. In patients having lesions in ribs and pelvis, most of the lesions were bilateral. Patients with two lesions showed maximum number of lesions in rib cage (44%), followed by spine (32%-all being in thoracolumbar region), scapula (24%), pelvis & scapula (24% in each), sternum (16%), skull (8%), humerus and femur (4% in each). In patients having solitary focal lesion, highest number was noted in spine (45.5%-most common in thoracolumbar spine), followed by ribs (22.7%), sternum & pelvis (13.6% each), and skull (6.8%). No lesion was noted in appendicular skeleton.

Conclusion: Multiple skeletal metastases are much more common than solitary or two lesions in cases of known breast carcinoma. Axial skeleton including skull is most commonly involved. Spine (especially thoracolumbar) is the most frequent site of involvement followed by rib cage, pelvis and then skull. In peripheral bones, most frequent site is the upper end of femur followed by humerus.

Keywords: Bone Metastases, CA breast, Breast Carcinoma, Methyl Diphosphonate (MDP), Distribution of bone metastases, ^{99m}Tc Pertechnetate (radioisotope).

INTRODUCTION

Breast cancer is the most common malignant tumor of females, the incidence increases of which increase with age [1-3]. Bone metastasis is a common

complication of breast carcinoma. Post-mortem studies indicate that 50%-80% of females dying of breast cancer will have bone metastases. Although bone pain

is a common presenting symptom in these patients, however up to 30 to 50% of these patients may be asymptomatic. Skeletal metastases account for high degree of morbidity from bone pain, impaired mobility, hypercalcemia, pathologic fracture, spinal cord or nerve root compression, and bone marrow infiltration. When these skeletal-related events are considered across all tumor types, patients with breast cancer are found to have the highest incidence of skeletal complications. Approximately 70% of patients with breast cancer treated with placebo experienced at least 1 skeletal complication during a 2-year follow-up period [4-5]. Although literature shows that most of the skeletal metastases from CA breast are osteolytic, more sclerotic lesions are observed now a days probably due to increasing use of zoledronic acid and bisphosphonates [6-8]. Skeletal metastases also herald a poor prognosis with a median survival being 2-3 years [9-10].

Modalities used to investigate include X-rays, CT-scan, MRI, bone scan and PET scan [11-13]. Bone scan is a highly sensitive technique for detection of metastatic disease and staging of tumor. Other potential indications include assessment of response to therapy, and assessment of risk of fracture and its potential sites [11]. Although many radiopharmaceuticals have been tried, T^{99m} MDP is considered the best [2,14]. Prior knowledge of pattern of distribution of metastatic skeletal deposits in cases of CA breast is very important because it help the radiologist & nuclear physician in commenting the nature of lesions within the skeleton. This parameter is also very important for the oncologist in decision regarding management with chemotherapy and radiotherapy. It also assists in finding the involved site of skeleton, having high risk for pathological fracture, and hence adequate management beforehand.

This retrospective study was conducted to find out the pattern of distribution of skeletal metastases by using ^{99m}Tc MDP bone scintigraphy in patients with breast carcinoma.

MATERIAL AND METHODS

A retrospective study was conducted on 465 consecutive breast carcinoma patients irrespective of preoperative/post mastectomy status, referred for bone scan to Punjab Institute of Nuclear Medicine from January 2006 to June 2009. In our study group, 453 were female (97.4%) and 12 were (2.6%) male. Their age ranged from 18 to 85 years, with a mean of $47.6 \pm$

11.1 years. Duration since the diagnosis of breast cancer at time of bone scan ranged from 1 to 156 months with a mean of 21.2 ± 19.3 months. Left breast was the primary site of malignancy in 47.1%, while right in 52.4%. Bilateral breast cancer was present in 0.5% patients.

Detailed clinical history and physical examination of each patient was performed. Twenty mCi of ^{99m}Tc MDP was injected intravenously and patient was advised to drink plenty of water and micturate frequently to achieve better target to background ratio. Frequent micturation also minimized radiation absorbed dose to whole of the body especially to the urinary bladder. Three hours later, patient was positioned supine on the imaging table. Latest SIEMENS ECAM Gamma camera equipped with low energy all purpose collimator was used to perform whole body bone scan. Energy window was centered at 140 KeV with a width of 15%. Both anterior and posterior projections were acquired using a constant speed of 25 cm/min and matrix size of 256x1024. Where needed, additional spot views, each for 600 Kcounts were acquired. All scans were interpreted for metastatic deposits by two independent observers. Where needed, plain X-ray were performed to correlate for possibility of benign pathology.

RESULTS

Out of 465 studied patients, 62% patients (n=286) were having either normal bone scan or some benign pathology as documented with the assistance of clinical history, physical examination, follow up bone scan and radiology. Thirty eight percent subjects (n=179) were positive for metastatic lesions within skeleton. Among patients with skeletal metastases, 61.4% patients (n=110) were having multiple, 24.6% (n=44) two and 14% (n=25) solitary lesion within the skeleton.

Table-1 shows the distribution of metastatic deposits in different parts of skeleton in patients with multiple metastases, two metastases and solitary metastatic deposit. Most commonly involved site in breast carcinoma patients with multiple skeletal metastases was spine followed by ribs, pelvis, skull, scapula, sternum, femur, humerous, clavicle and tibia. In patients with vertebral metastases thoracolumbar region was most frequently affected, while in subjects with metastases to pelvic bone iliac bone was most commonly involved. In humerous and femur, most

lesions were located in their upper ends followed by shafts, and right side was more frequently involved than the left half of skeleton. In patients having lesions in ribs and pelvis, most of the lesions were bilateral.

In patients with two bone metastases, maximum numbers of lesions were observed in rib cage, followed by spine, scapula, pelvis, scapula sternum, skull, femur and humerus. Majority (92%) of the lesions in patients with vertebral metastases were located in thoracolumbar region.

In patients with solitary skeletal metastases, most frequently affected site was spine (most common in thoracolumbar region), followed by ribs, sternum, pelvis, and skull. No lesion was noted in appendicular skeleton.

DISCUSSION

Bone scan is a highly sensitive technique in detecting metastatic deposits within skeleton, 50 to 80% more sensitive than radiographs. The high sensitivity of this technique is based on physiological basis for preferential uptake of methyl diphosphonate, which identifies as little as 5-15% alteration in local bone turnover. Delineation of a lytic lesion by conventional radiology requires a minimum size of 1cm and a focal loss of at least 50% of bone mineral, while at least 30% increase in bone mineral content is essential to appreciate sclerotic lesion. That's why bone scan may pick up bone metastases up to 18 months earlier than conventional radiology, with an average lead of 4 months. Although CT, MRI and PET are considered superior to conventional radiology in the diagnosis of skeletal metastases [11, 15-17], but they cannot survey the whole body skeleton. Nonetheless, given the ease of performing a whole body survey, bone scan is probably the study of choice for the initial evaluation for metastases in patients with cancer. This technique not only helps in staging the breast carcinoma patients, but also assists to identify the potential sites for pathological fractures. High affiliation of the breast carcinoma metastases to bone than other organs is probably related to selective colonization of metastatic tissue to bone. Zetter et. al highlighted the importance of vascular endothelial receptors, adhesion molecules, mitogens, growth factors, cellular growth inhibitors and angiogenic factors in this regard [18]. Although, there is low positive yield for bone scan in patients with stage I breast carcinoma, it is still recommended to have a baseline study [19]. The usual appearance of skeletal

metastases on bone scan is focal hot spot, however, rarely focal cold defects are also noted.

In our study, we included preoperative as well as post radical mastectomy breast cancer patients referred to PINUM as part of staging. Our study showed that most breast carcinoma patients with bone metastases presented with multiple secondary deposits. Classical pattern was that of multiple lesions of varying size, shape and intensity distributed throughout the axial skeleton in an irregular pattern. Axial skeleton was the most frequent site involved, spine being the commonest. Plexus of vertebral veins that form rich anastomotic connections with veins of skull, neck, ribs, shoulder girdles and vertebral column, and allow retrograde blood flow owing to the absence of valves within them, are thought to be responsible for the preferable hematogenous spread of breast cancer to the axial skeleton. [20-23]. An alternate mechanism is via arterial emboli to the abundant bone marrow of the vertebral bodies and subsequently into the anterior or posterior extradural space through venous channels [24]. Prior to extension into the osseous structures, more than 90% of metastatic deposits will lodge to the bone marrow. Red marrow is the vascular active marrow, having abundant blood supply from nutrient vessels. With aging, red marrow is progressively concentrated in the axial skeleton, which also contributes to the preferential metastases to axial skeleton. Appendicular metastases are less frequent in patients with breast carcinoma and has been attributed to rare arterial dissemination. These metastases are thought to be transported to the cortex by the anastomotic branches between nutrient and periosteal arteries. Ends of the long bones are more frequently involved than the shaft. This may be explained by the proximity of the bone ends to the nutrient artery, and confinement of red marrow to the ends of the long bones [25-26].

Nakamoto Y conducted PET studies in patients with skeletal metastases and found that the vertebrae were the most frequently involved bones (74%), followed by pelvic bones (70%), ribs (65%), upper extremities including the scapula (48%), sternum (43%), and lower extremities (43%) [27]. In an other study of patients with CA breast, out of 23 subjects with skeletal metastases, 16 cases were having multiple secondaries; and the rate between right and left breast cancer, for these metastases, was 13:10. From all the 23 cases, the most involved site was the ribs (18 cases), followed by the spine (in 17 cases), the

iliac bone (9 cases), the femur (7 cases), the skull (3 cases). In spine, the more frequently involved vertebrae were dorsal (49.23%), followed by lumbosacral (26.13%) and lastly cervical vertebrae (12.3%). On the dorsal vertebrae, in 91% the metastasis were localized between D8 and D12 [28]. Other studies have also shown that vertebral column is the most common site of skeletal metastases.[29] Spinal metastases are a very frequent manifestation of systemic neoplasia, with up to 70% of cancer patients harboring secondary spinal disease.[30-31]. Our study showed more frequent involvement of thoracolumbar spine than cervical vertebrae. Classic autopsy investigations have demonstrated that the distribution of extradural spinal metastases is related to the size of the vertebrae.[32] Thus, metastatic lesions are most commonly located in the thoracolumbar region, less so in the cervical spine.[6] Symptomatic lesions occur more frequently in the thoracic region (70%) than other vertebrae [33] because of smaller size of the thoracic spinal canal in relation to the thoracic spinal cord [31]. Particular predilection for thoracic levels about T-4 and the thoracolumbar junction has been noted [34].

Our findings are similar to that of other studies, which stated that about 80-90% of patients with skeletal metastases present with more than one lesions and about 80% of all metastatic lesions are in the axial skeleton [35, 27]. Jacobson et al reported that as the number of lesions increases within skeleton, the chances of being a case of metastatic deposits also increases in patients with breast carcinoma. They observed that single skeletal lesion has about 11% probability for being metastases in patients with known underlying breast malignancy. This probability increases to 35% when 2 new lesions were detected, 45% for three, 50% for four new detected lesions and reached 100% when 5 new lesions were identified. In patients having lesions between 1 to 4 new abnormalities, the spine was the most frequent site of involvement (53%), followed by skull (15%), extremities and sternum (12%) [36]. Boxer et al found that out of 160 consecutive studied CA breast cancer patients, 79% were having multiple metastatic lesions. Similar to our results, he observed that spine was the most frequent site for both solitary (52%) and multiple (87%) metastases. He stated that solitary metastases are much more common in cases of CA breast, than they are thought to be [37]. Reported incidence of solitary skeletal metastases in breast cancer patients

having skeletal metastases ranges from 11% to 21% [27, 36-37]. This variation in probability of metastatic bone disease may be due to the different location of the solitary bone abnormality as well as the different types of malignant tumor [38]. In patient with known underlying breast carcinoma, a solitary rib lesion has about 10% probability, a solitary sternal lesion has 76% chance, while solitary lesion in spine has 85% probability of being malignant. Solitary skeletal metastases occur more frequently in sternum than other parts skeleton in subjects with breast cancer [37, 39-41]. Jacobson et al looked at the scintigraphic pattern of metastatic bone disease in breast cancer patients with less than 5 new bone scan abnormalities and reported that 56% of the bone metastases are in the spine and only 6% in the ribs. Interestingly enough, rib lesions were the most common new bone scintigraphic abnormality [36].

CLINICAL IMPLICATIONS

Prior knowledge of pattern of distribution of metastatic deposits in skeleton can guide the oncologist regarding management and prognosis. In patients with symptoms related to different parts of body, physician may think of probability of metastases keeping in view the skeletal parts having higher tendency for metastases.

CONCLUSION

Multiple skeletal metastases are much more common than solitary or two lesions in known cases of breast carcinoma. Axial skeleton including skull is more commonly involved than the appendicular skeleton. Spine (especially thoracolumbar) is the most frequent site of involvement followed by rib cage, pelvis and then skull. In peripheral bones, most frequent site is the upper end of femur followed by humerus.

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