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Original article

Incremental Value of Single-photon Emission Computed Tomography-computed Tomography for Characterization of Skeletal Lesions in Breast Cancer Patients

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Abstract

The incremental value of single-photon emission computed tomography-computed tomography (SPECT-CT) over planar bone scintigraphy and SPECT in detecting skeletal lesions in breast cancer patients and its effect on patient management is assessed in this study. This is a prospective study which was conducted over 1-year duration. Whole-body planar scintigraphy, SPECT, and SPECT-CT were performed in 85 breast cancer patients with total of 128 lesions. Correlative imaging and clinical follow-up was used as the reference standard. McNemar's multistep analysis was performed for each patient and each lesion. On patient-wise analysis, 47 patients had equivocal diagnosis on planar bone scintigraphy, 28 on SPECT, and eight on SPECT-CT. On lesion-wise analysis, there were 72 equivocal lesions on planar bone scintigraphy, 48 on SPECT, and 15 on SPECT-CT. Overall, SPECT-CT resulted in a significant reduction in the proportion of equivocal diagnosis on both patient-wise ($P < 0.004$) and lesion-wise basis ($P < 0.004$), irrespective of the skeletal region involved. The sensitivity on a per-patient basis was 43%, 58%, and 78% for planar bone scintigraphy, SPECT, and SPECT-CT, respectively. Similarly, the specificity was 85%, 92%, and 94% for planar bone scintigraphy, SPECT, and SPECT-CT, respectively. Patient management was correctly altered in 32% of the patients based on SPECT-CT interpretation. Our data suggest that adding SPECT-CT to whole-body imaging significantly improves sensitivity and specificity in diagnosing bone metastases and significantly reduces the proportion of equivocal diagnosis in all regions of the skeleton. The most important outcome is derived from the accurate alteration in patient management clinically by down- and up-staging of patients and a more precise identification of metastatic extent.

Keywords: Breast cancer, planar scintigraphy, single-photon emission computed tomography-computed tomography, skeletal metastases

Introduction

Bone scintigraphy and single-photon emission computed tomography (SPECT) are known to be very sensitive in detecting bone metastases,[1] but lack the specificity to fully characterize a lesion, making it insufficiently specific for diagnostic purposes.[2] SPECT-computed tomography (SPECT-CT) hybrid imaging system allows combination of the functional specificity of SPECT and lesion characterization by CT.[3] Despite all the supporting data from previous studies,[4-7] its use in the evaluation of possible skeletal metastasis is still evolving. Our aim in conducting this study is to assess the advantages of SPECT-CT as compared to planar

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bone scintigraphy and SPECT alone in a specific group of patients (known breast cancer) and how it effects the overall patient management.

Patients and Methods

Eighty-five patients were prospectively studied between July 2013 and June 2014. The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from all the patients who were included in the study.

Patients with histopathologically confirmed breast cancer who are referred for routine bone scan in our department were consecutively recruited. All patients with skeletal lesions on planar bone scintigraphy (whether definitive or equivocal) were included in the study. Patients with history of known skeletal metastases were excluded from the study.

All patients underwent whole-body planar bone scintigraphy in the anterior and posterior positions 3 h after intravenous injection of Tc-99m MDP (740 MBq). Images were acquired on a hybrid SPECT-CT dual-head camera (GE Infinia Hawkeye, GE Healthcare) equipped with low-energy, high-resolution, parallel-hole collimator, at 140 keV photopeak with 20% symmetrical window, in continuous mode at 12 cm/min. The matrix size used was 256 × 512.

After completion of planar bone scintigraphy, all the patients underwent whole-body SPECT with the same gamma camera used for scintigraphy. SPECT data were collected in step- and shoot-mode with angular range of 180° in 3° increments and duration of 15 s per step. The image acquisition matrix was 128 × 128. Images were acquired on the 140 keV photopeak with a 20% symmetrical window. SPECT images were iteratively reconstructed with three-dimensional ordered-subset expectation maximization with two iterations and 10 subsets on Xeleris workstation. Images were smoothed with Hann and Butterworth filter. Tomographic slices were displayed as transaxial, coronal, and sagittal images.

The CT component of the whole-body SPECT-CT (skull to mid-thigh) acquired on the GE Infinia Hawkeye was done with an X-ray tube mounted within the same gantry on a 512 × 512 matrix, voltage 140 kVp, and current 2.5 mA. Acquisition slice thickness is 5 mm with rotation velocity of 2.6 rpm.

Images were independently interpreted by two readers. In cases of discrepancy, consensus was obtained by joint reading. They were interpreted separately: first the planar bone scintigraphic images, then the SPECT images and finally the fused SPECT-CT images.

Diagnosis for each lesion was visually scored with a three-point scale: (1) definitely benign; (2) equivocal (includes likely benign, likely malignant, and indeterminate lesions); (3) definitely malignant. The criteria for classifying a bone lesion as benign or malignant were determined. For planar and SPECT, the criteria were as follows: (a) radiotracer uptake greater than that in the anterior superior iliac spine located in a anatomic location typical of a metastasis (pedicle and vertebral body) is considered to indicate malignancy, and (b) radiotracer uptake equal to or lower than that in the anterior superior iliac spine and that involved both sides of the joint (e.g. knees, hands, wrists, facet joints, and vertebral endplates) are considered to indicate a benign lesion. The criteria for CT images were as follows: (a) osteolytic lesions with/without sclerosis or osteoblastic lesions and a lesion that showed asymmetric increased density of bone marrow are considered to be malignant, and (b) sclerotic lesions with evidence of degenerative changes (e.g. spondylophytes, disc space narrowing, and subchondral cyst) are considered benign.

A final diagnosis as to the true status of lesions was made after consideration of the clinical information, including a follow-up period of 6–9 months, or when available, additional correlative imagings (plain radiograph, CT, magnetic resonance imaging [MRI], and follow-up bone scan) were used to reach the overall decision. Change in character (lytic or sclerotic) and/or size on imaging studies was considered to indicate malignancy whereas a lesion was considered benign if there is no change. Those which remain unchanged over at least 6 months without therapy were considered benign. A lesion that decreased or increased in size and/or intensity on with treatment (e.g., chemotherapy or radiotherapy) was considered to be malignant.

Assessment of the impact on patient management was done by recording the management of the patient based on diagnosis obtained from planar bone scintigraphy alone as compared to the final management based on SPECT-CT findings.

All the acquired data were expressed as numbers and percentages on lesion-wise basis (benign or malignant/anatomical location/lytic, sclerotic or mixed), patient-wise basis (metastasis or no metastasis), and impact on management. Data comparison (planar and SPECT/planar and SPECT-CT/SPECT and SPECT-CT) was done using McNemar's test. The sensitivity, specificity, and negative predictive value (NPV) and positive predictive value (PPV) of planar bone

scintigraphy, SPECT, and SPECT-CT for diagnosing skeletal metastases were calculated. The Bonferroni test was used for comparison of sensitivity, specificity, and NPV and PPV among the three imaging modalities with a confidence level of 95% ($P < 0.004$ was considered statistically significant).

Results

A total of 104 patients with histologically confirmed breast cancer were included in the study. All the patients are females in the age group of 29–69 years. Eleven patients had a diagnosis of widespread and extensive skeletal metastases based on planar scintigraphy alone. SPECT and SPECT-CT were not done in these patients as no change in management was expected from additional imaging. Another 11 patients were lost to follow-up. Only data from 85 patients were available for further analysis.

The final diagnosis for each of the lesions analyzed was obtained from the reference standard which is either correlative imaging or clinical follow-up for 6–9 months. Forty-three of the patients whose data were analyzed had correlative imaging available. Nine of them had follow-up bone scan, 18 had plain radiography, 13 had CT scan, and three had MRI scan. The other 42 patients with no correlative imaging were followed up clinically for 6–9 months.

Planar bone scintigraphy, single-photon emission computed tomography, and single-photon emission computed tomography-computed tomography

The findings on planar bone scintigraphy, SPECT, and SPECT-CT are detailed in Figure 1. On planar bone scintigraphy, of the 12 patients who were interpreted as having malignant disease, only eight were true positive, and of the 26 patients who were interpreted as having benign disease, 25 were true negative [Figures 2 and 3]. Thirty-seven of the patients who were interpreted as being equivocal were found to be benign and ten were found to be malignant based on reference standard.

SPECT significantly reduced the number of equivocal diagnosis as compared to planar bone scintigraphy alone [$P < 0.004$, Table 1]. The number of patients described as being malignant was similar to planar, of which eight were true positive. The other 45 patients were interpreted as having benign bone disease, of which 44 were true negative.

On SPECT-CT, of the eight patients who had equivocal diagnosis, five were found to have benign bone disease and three were found to have malignant bone disease based on reference standard [Figures 4 and 5]. Twelve patients who were reported to have malignant bone disease were true positive. All the 62 patients who were reported to have benign bone disease on SPECT-CT were also accurately diagnosed based on reference standard. Overall, SPECT-CT resulted in further significant reduction in equivocal lesions as compared to planer and SPECT [Tables 2 and 3].

Sensitivity, specificity, and predictive values were separately calculated for planar bone scintigraphy, SPECT, and SPECT-CT [Table 4].

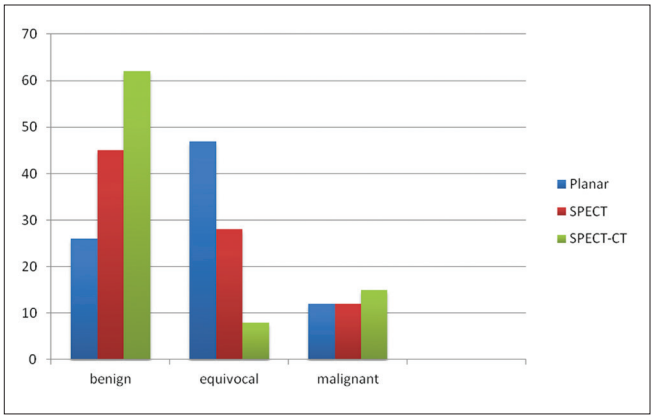

Figure 1: Patient-wise interpretation for planar bone scintigraphy, single-photon emission computed tomography, and single-photon emission computed tomography-computed tomography

Table 1: Patient-wise proportion of equivocal interpretations for planar bone scintigraphy versus single-photon emission computed tomography

Equivocal (%)		Statistical test	*P*
Planar	SPECT		
47 (55)	28 (33)	McNemar χ^2	<0.004

SPECT: Single-photon emission computed tomography

Table 2: Patient-wise proportion of equivocal interpretations for planar bone scintigraphy versus single-photon emission computed tomography-computed tomography

Equivocal (%)		Statistical test	*P*
Planar	SPECT-CT		
47 (55)	8 (9)	McNemar χ^2	<0.004

SPECT: Single-photon emission computed tomography; CT: Computed tomography

Table 3: Patient-wise proportion of equivocal interpretations for single-photon emission computed tomography versus single-photon emission computed tomography-computed tomography

Equivocal (%)		Statistical test	*P*
SPECT	SPECT-CT		
28 (33)	8 (9)	McNemar χ^2	<0.004

SPECT: Single-photon emission computed tomography; CT: Computed tomography

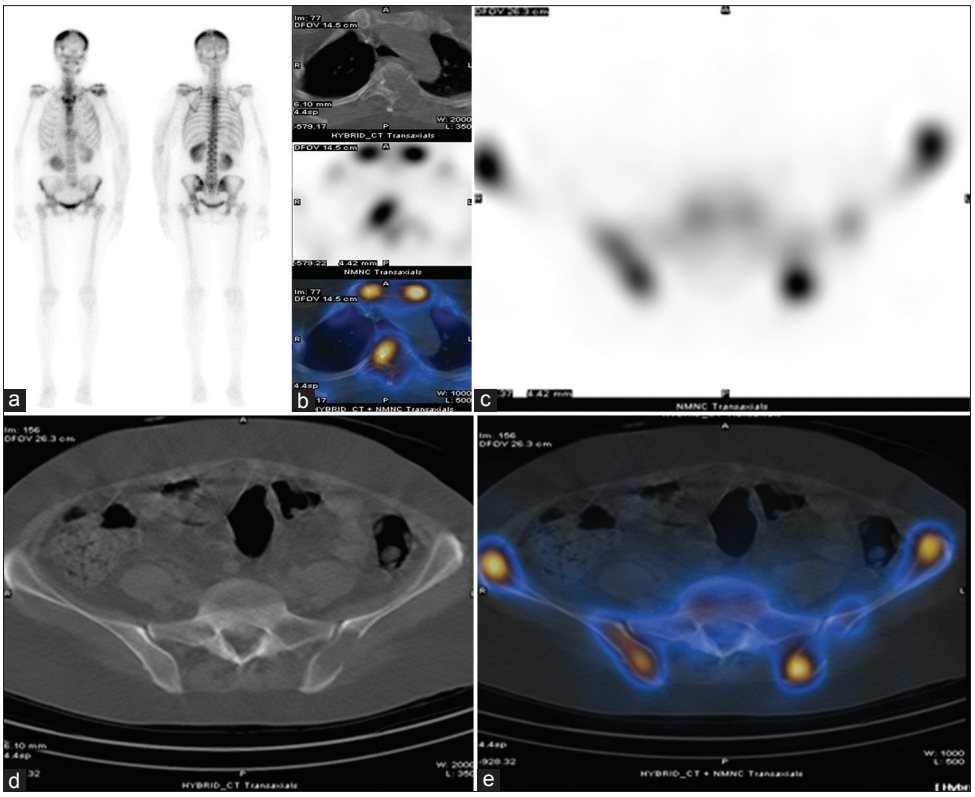

Figure 2: A 58-year-old woman with breast cancer. Anterior and posterior (a) planar bone scintigraphic images with focal increased uptake at upper thoracic spine region (closed arrow) and left ilium (open arrow) which are equivocal for metastases, (b) single-photon emission computed tomography, computed tomography, and single-photon emission computed tomography-computed tomography images showing a lytic lesion at the body and left pedicle of T4 vertebra, (c) axial single-photon emission computed tomography image showing increased uptake at the left ilium, (d) axial computed tomography image showing a lytic lesion with minimal surrounding sclerosis at the left ilium, (e) axial fused single-photon emission computed tomography-computed tomography image showing the focus of increased tracer uptake at the left ilium corresponds to the lytic lesion

Lesion-wise analysis

A total of 128 lesions were identified from the 85 patients whose data were analyzed. On reference standard, 31 lesions were malignant and 97 lesions were benign. SPECT-CT shows a significant reduction in the number of equivocal lesions as compared to planar and SPECT [Table 5]. SPECT-CT interpretation revealed 82 benign lesions, which were all accurately diagnosed based on reference standard. There were 30 lesions which were described as being malignant, of which four were downgraded to benign based on reference standard.

Anatomical location

Interpretation based on location showed that most of the lesions were identified in the spine, with a total of 64 lesions (50%) and within the spine, the lumbar region predominates with 39 lesions (30.4%) [Table 6]. The second most frequent site was the rib cage (17.2%) followed by skull/mandible (11.7%). In all regions of the skeleton, there is a significant reduction in the number of equivocal lesion on SPECT-CT as compared to planar bone scintigraphy and SPECT.

Table 4: Sensitivity, specificity, positive predictive value, and negative predictive value of planar bone scintigraphy, single-photon emission computed tomography, and single-photon emission computed tomography-computed tomography in diagnosing skeletal metastases among the patients evaluated (results with 95% confidence interval)

Parameter	Planar	SPECT	SPECT-CT
Sensitivity	43	58	78
Specificity	85	92	94
PPV	35	54	73
NPV	89	93	95

SPECT: Single-photon emission computed tomography; CT: Computed tomography; NPV: Negative predictive value; PPV: Positive predictive value

Morphology of lesion

Based on the CT morphology of the lesion, 101 were interpreted as sclerotic, 16 were mixed lytic-sclerotic, and 11 were lytic. Of the 16 equivocal lesions on SPECT-CT, ten were sclerotic and six were mixed lytic-sclerotic. Additional lytic lesions were detected in three patients (all malignant) on SPECT-CT, but there was no alteration in overall diagnosis as there were other malignant lesions in all these patients. Additional

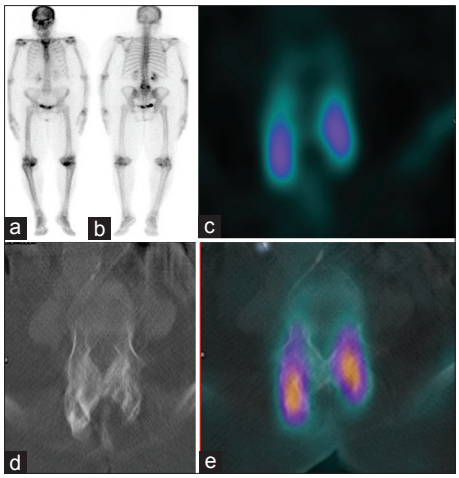

Figure 3: A 63-year-old woman with breast cancer. Anterior (a) planar bone scintigraphic image showing increased uptake at bilateral lateral aspects of L4 vertebra, posterior (b) planar bone scintigraphic image showing increased uptake at bilateral lateral aspects of L4 vertebra, based on planar scintigraphy alone it was difficult to determine whether the uptake is at the pedicles or facet joints. Single-photon emission computed tomography image (c) and single-photon emission computed tomography-computed tomography image (d) showing the activity is localized to bilateral facet joints, (d) computed tomography image showing hyperostosis and osteosclerosis in bilateral facet joints of L4-L5 vertebrae, based on planar scintigraphy alone it was difficult to determine whether the uptake is at the pedicles or facet joints. Single-photon emission computed tomography image (c) and single-photon emission computed tomography-computed tomography fusion image (e) showing the activity is localized to bilateral facet joints

Table 5: Proportion of benign, equivocal, and malignant lesions on planar, single-photon emission computed tomography, and single-photon emission computed tomography-computed tomography

	Planar, *n* (%)	SPECT, *n* (%)	SPECT-CT, *n* (%)
Benign	30 (23.4)	54 (42.2)	82 (64.1)
Equivocal	72 (56.2)	48 (37.5)	16 (12.5)
Malignant	26 (20.3)	26 (20.3)	30 (23.4)
Total		128	

SPECT: Single-photon emission computed tomography; CT: Computed tomography

sclerotic lesions were detected in 13 patients of which nine were benign and six were malignant. However, there was no overall change in diagnosis as there were other lesions to support the diagnosis of benign or malignant disease.

Impact on patient management

Based on SPECT-CT findings, overall diagnosis was altered in 27 (32%) of 85 patients. One patient was upgraded from benign to malignant. Another four patients were downgraded from malignant to benign. All the 27 patients whose diagnosis was altered by SPECT-CT had correct diagnosis based on reference standard (100% accuracy).

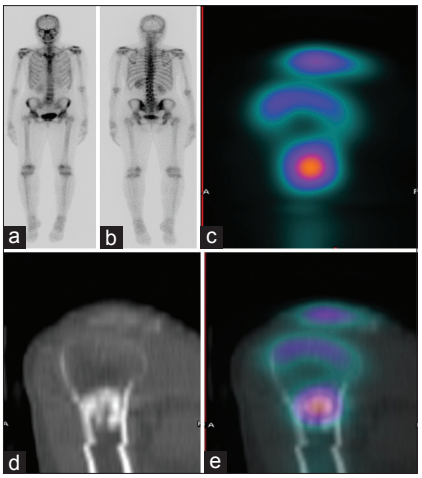

Figure 4: A 48-year-old woman with breast cancer. She had history of fall 2 months prior to this scan. Anterior (a) and posterior (b) planar bone scintigraphic images with increased focal uptake at the neck of right humerus which was equivocal for solitary metastasis, (c) single-photon emission computed tomography image at the level of focal uptake, (d) computed tomography images showing irregular sclerosis, (e) single-photon emission computed tomography-computed tomography fusion image showing the focal uptake corresponds to the sclerotic lesion. This confirmed the diagnosis of solitary metastatic lesion. MRI (not shown) further confirmed this lesion as a metastatic lesion

Discussion

Planar bone scintigraphy is a very sensitive imaging modality to screen for the presence of skeletal metastases in cancer patients. However, it lacks the specificity in accurately diagnosing a skeletal lesion as benign or malignant due to overlap among the skeletal structures and accumulation of the radiopharmaceutical in various other benign conditions, including infection, trauma, and degenerative changes.[8] SPECT is able to minimize the problem of superimposition of overlying activity, which enables more accurate anatomical localization of lesions and easier differentiation between benign and malignant lesions.[4] However, some lesions remain equivocal even after SPECT.

SPECT-CT serves as a method of correlating anatomical information from CT with functional information from SPECT, hence enabling more accurate localization and characterization of SPECT lesions using the CT component. This is of great benefit in complex structures such as vertebrae where the location of a lesion determines whether it is classified as malignant or benign.[9] For example, we noted that most of the benign lesions were within the facet joints or at the end plate of the vertebral bodies whereas the malignant lesions were predominantly within the pedicles and vertebral bodies. In our study, adding SPECT-CT to whole-body planar bone scintigraphy significantly improved both sensitivity

Table 6: Proportion of equivocal lesions based on location

	n	Planar		SPECT		SPECT-CT	
		Equivocal	Percentage	Equivocal	Percentage	Equivocal	Percentage
Skull/mandible	15	11	73.3	7	46.7	3	20
Cervical spine	7	6	85.7	2	28.6	0	0
Thoracic spine	17	11	64.7	8	47.1	4	23.5
Lumbar spine	39	21	53.8	13	33.3	2	5.1
Sacrum	1	0	0	0	0	0	0
Rib cage	22	12	54.5	9	40.9	4	18.2
Scapula	6	3	50.0	3	50.0	1	16.7
Pelvis	7	2	28.6	2	28.6	0	0
Extremities	14	6	42.9	4	28.6	2	14.3
Total	128	72		48		16	

SPECT: Single-photon emission computed tomography; CT: Computed tomography

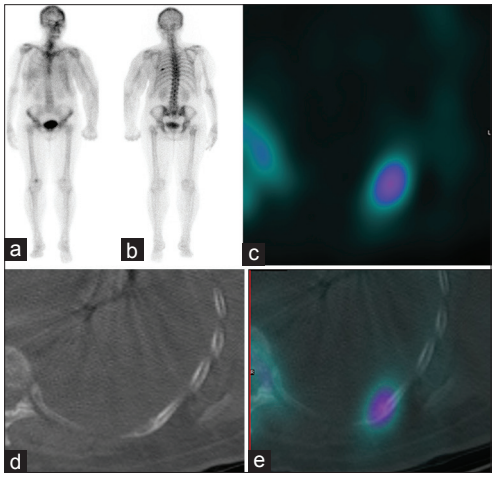

Figure 5: A 64-year-old woman, a case of breast cancer with liver and lung metastases. Anterior (a) and posterior (b) planar bone scintigraphic images showing solitary focal increased uptake at left 8th rib which was equivocal for metastasis or fracture, (c) single-photon emission computed tomography image at the level of uptake, (d) computed tomography images showing a corresponding lytic lesion with minimal sclerosis, (e) single-photon emission computed tomography-computed tomography fusion image showing that the increased area of activity correspond to the lytic lesion, which confirmed solitary skeletal metastasis to the rib

and specificity with fewer equivocal diagnoses as compared to planar bone scintigraphy and SPECT. No patient was upstaged from benign to malignant on SPECT-CT, which shows a high NPV for skeletal metastases. The number of patients being upgraded to malignant based on the number of patients diagnosed as having benign or equivocal bone disease, but which were found to be malignant on reference standard, were also reduced, with three patients on SPECT-CT as opposed to seven patients with SPECT and 11 patients on planar bone scintigraphy. This shows a significant reduction in the number of false negative diagnosis.

The diagnosis of malignant or benign bone disease on bone scintigraphy or other imaging modality may have a significant influence on the management of a patient. The presence of skeletal metastases may indicate a need for additional or intensified treatment such as chemotherapy or radiotherapy. In this study, 27 (32%) of 85 patients had their diagnosis altered based on SPECT-CT, which is consistent with the results of other studies. Ndlovu *et al.*,[5] in their study with a mixed population of patients with cancer recorded an alteration in 40.5% of patients. Roach *et al.*[10] recorded an alteration of diagnosis in 56% of patients in their study. One patient was upstaged from benign to malignant and was given chemotherapy. Four patients were downstaged from malignant to benign and were, therefore, spared from receiving futile treatment. Twenty-three patients had equivocal diagnosis, of which 17 were found to be benign. However, only 15 patients had their management altered as the other two patients had liver and lung metastases, respectively. Six of the patients had malignant bone disease on SPECT-CT, but the treatment plan was altered in only four of the patients, as the other two patients had liver metastases. All the patients were correctly diagnosed on SPECT-CT when compared to reference standard, which gives an accuracy of 100%.

In the lesion-wise analysis, we observed how SPECT-CT influenced the interpretation of each skeletal lesion. SPECT-CT resulted in fewer equivocal lesions than SPECT, with a definitive diagnosis being reached in 87% of lesions. Furthermore, SPECT-CT was correct 96% of the time when a definitive diagnosis was made. This is higher compared to a study by Horger *et al.*, in which SPECT-CT correctly classified 85% of the lesions,[11] but comparable to the study by Zhao *et al.* which documented accuracy of 95.7%.[12] Consequently, SPECT-CT resulted not only in fewer equivocal lesions but also in increased accuracy in the interpretation of these lesions, further supporting its use.

Our study corroborates with the pattern of bone metastases which commonly affects the spine and rib cage.[13] In agreement with other studies, the use of SPECT-CT in our study significantly reduced the proportion of equivocal lesions at all regions, and the

reduction in the proportion of equivocal lesions in the lumbar spine (site with most lesions) was statistically significant ($P < 0.004$).[5,6] This suggests that the addition of SPECT-CT improves the diagnostic confidence in investigation of equivocal lesions at almost all the sites. In particular, addition of SPECT-CT at the region of the spine will be most beneficial as degenerative changes frequently occur at this region. Differentiating this benign process from metastasis is usually difficult on planar scintigraphy and SPECT alone.

In general, breast cancer patients can present with lytic, sclerotic, or mixed bone metastases,[14] with predominantly lytic lesions. In the present study, we analyzed the performance of planar bone scintigraphy, SPECT, and SPECT-CT for lytic, sclerotic, and mixed lesions. However, no statistically significant difference was found between the accuracy of planar bone scintigraphy, SPECT, and SPECT-CT based on morphology of the lesion. Even though additional lesions were identified on the CT component of the SPECT-CT that were not seen on planar bone scintigraphy and SPECT, it did not alter the final diagnosis of the patients. All these patients had other lesions to classify them as having benign or malignant bone disease. Most of the additional sclerotic lesions detected were benign (mostly bone islands). The additional lytic lesions were all malignant which supports the presence of rapidly growing pure lytic lesions with minimal osteoblastic reaction.

Many of previously done studies performed only a single-region SPECT-CT in an area with equivocal lesions detected on planar bone scintigraphy.[4,10,15] We performed SPECT-CT from the skull to the mid-thigh (whole-body SPECT-CT) in all the patients including those with definite benign and malignant lesions on planar scintigraphy. Even though we detected additional 36 lesions on SPECT-CT as compared to planar bone scintigraphy, these findings did not alter the overall diagnosis of the patient as all these patients had other lesions to support the diagnosis of benign or malignant bone disease, but it allowed us to define the true extent of metastatic disease. Therefore, performing whole-body SPECT-CT allows assessment of not only the equivocal lesions but also the other definitive benign and malignant lesions on planar bone scintigraphy. This is of great importance as our study showed that SPECT-CT accurately upstaged one patient (1%) with definitive benign bone disease on planar bone scintigraphy to metastasis and downstaged six patients (7%) with definite metastases on planar bone scintigraphy to benign bone disease. This outcome leads to clinically relevant down- and up-staging which, in turn, affects the overall patient management.

The main limitation of this study is that none of the patients imaged had biopsy of the bone lesions. Therefore, our study lacked any histopathological correlation to confirm the diagnoses of malignant or benign lesion. Another major limitation was the lack of common reference standard in all patients as the decision on which imaging modality to use as the reference standard in some of the patients was left to the referring physician.

Future studies incorporating positron emission tomography (PET) tracers such as ^{18}F fludeoxyglucose (FDG) PET-CT and ^{18}F Fluoride FDG PET-CT will prove to be beneficial in choosing the appropriate imaging method for diagnosing skeletal metastasis.

Conclusion

Adding SPECT-CT to whole-body imaging improves both sensitivity and specificity significantly in diagnosing bone metastases in breast cancer patients. It significantly reduces the proportion of equivocal diagnosis in all regions of the skeleton. The most important outcome is derived from the alteration in patient management clinically by down- and up-staging of patients and a more precise identification of metastatic extent.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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