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## The Role of Whole-Body SPECT/CT Using Tc-99m MDP in Characterization of Osseous Lesion in Breast Cancer Patients.

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### ABSTRACT:

**Introduction:** breast cancer is the second greatest cause of death in women, affecting women of all ages, races, and geographical locations. Bone, lungs, and liver are the most common locations of distant metastases. The most extensively used approach for detecting bone metastases is whole-body bone scintigraphy with technetium 99m tagged diphosphonates.

**Objectives:** Compare the rate of detectability of bone metastases in breast cancer patients utilizing whole body single photon emission computed tomography / computed tomography against planar conventional bone scintigraphy.

**Material and methods:** prospective study included 50 female patients diagnosed with breast cancer, with an average age of  $46.9 \pm 15$  years. Planar bone scintigraphy was performed on the patients, followed by whole body SPECT/CT scans by

administering 1110 MBq of Tc-99m MDP intravenously. Full body scan was performed (table rate 12 cm/min). A total of 32 frames with 15 seconds per frame were used to collect SPECT and CT images of the entire body over a 360-degree arc with a 128\*128 matrix and iterative filtration (four iterations, four subsets, and Gaussian filter 8). Both modalities were read independently by two competent nuclear medicine experts.

**Results:** The sensitivity, specificity, positive predictive value, and negative predictive value of Planar bone scintigraphy and W.B. SPECT/CT images were 52.2 % Vs 87 %, 92.6 % Vs 96.3 %, 85.7 % Vs 95.2 %, and 69.4 % Vs 89.7 %, respectively. The difference in sensitivity between the two modalities was statistically significant (P-value = 0.001), whereas the difference in specificity was statistically inconsequential (P-value = 0.5).

**Conclusions:** whole-body SPECT/CT bone scintigraphy improves the sensitivity of the bone scan for detecting osseous metastases

and minimizes the number of equivocal lesions.

**Key Words:** Bone metastases, Planar bone scintigraphy, Whole-body SPECT/CT bone.

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## INTRODUCTION:

Breast cancer is the second greatest cause of death in women, affecting women of all ages, races, and geographical locations <sup>(1)</sup>.

Bone, lungs, and liver are the most common locations of distant metastases <sup>(2)</sup>.

The prognosis varies depending on whether there are a single or numerous metastatic lesions <sup>(3)</sup>.

Early diagnosis of osseous involvement is critical in the evaluation of patients with breast cancer since it affects their treatment options. The most extensively used approach for detecting bone metastases is whole-body bone scintigraphy (WBBS) with technetium-99m tagged diphosphonates <sup>(4)</sup>. The diagnostic accuracy, sensitivity, and specificity of this modality are influenced by the integration of hybrid single photon emission computerized tomography and computed tomography (SPECT/CT) <sup>(5)</sup>. SPECT/CT combines two distinct technologies, SPECT is a tomographic scintigraphic technology that uses the detection of single photon emissions from

radionuclides delivered into the body to create a computer-generated image of local radioactive tracer distribution in tissues.

The CT portion of the exam is used to pinpoint the location of the lesion and correct for attenuation <sup>(6)</sup>.

SPECT/CT pictures improve the contrast enhancement of lesion to background activity and enable for better identification of complicated structures such as the bony pelvis and spine <sup>(7)</sup>. SPECT allows for more precise tracer activity localization, which improves diagnostic specificity <sup>(8)</sup>.

SPECT/CT pictures can classify roughly 92% of ambiguous lesions in planar images, increasing the usefulness of bone imaging and eliminating the need for more expensive imaging such as MRI.

**Objectives:** Compare the rate of detectability of bone metastases in breast cancer patients utilizing whole body single photon emission computed tomography/computed tomography (WB SPECT/CT) against planar bone scintigraphy.

## MATERIAL AND METHODS:

From September 2018 through March 2019, this prospective study was conducted at Cairo University's NEMROCK center. It included 50 female patients diagnosed with breast cancer, with an average age of  $46.9 \pm 15$  years, who were referred for bone scintigraphy for staging, restaging, or follow-up. Planar bone scintigraphy was performed on the patients, followed by full body SPECT/CT scans. The images were anonymized before being shown to two readers. To reduce recall bias, both modalities were read in separate sessions. All adult female patients with breast cancer who are undergoing routine bone scintigraphy for metastatic work-up or follow-up are eligible. All of the patients were able to sleep for about 35 minutes in a stable position. The scan was performed by administering 1110 MBq of Tc99m MDP intravenously, followed by consuming around 2 and a half liters of water while voiding urine continuously. After the injection, the acquisition time was 2 to 4 hours. Before scanning, patients were instructed to void. Patients were urged to remove any metal objects from their homes. Patients sat in a supine position with their arms down. The photon peak was centered at

140 KeV with a 20 % window in both front and posterior views, with a matrix of  $1024 \times 256$ . A full body scan was performed (table rate 12 cm/min). A total of 32 frames with 15 seconds per frame were used to collect SPECT and CT images of the entire body over a 360-degree arc. SPECT scans of the head, neck, and chest, then of the belly, then of the pelvic to the knees. The photos were captured with a  $128 \times 128$  matrix and iterative filtration (four iterations, four subsets, and Gaussian filter 8). With a slice thickness of 1mm, an 80-mA current, and a voltage of 130 KV, a non-contrast CT scan was performed. The SPECT/CT capture took about 35 minutes in total. The CT-based attenuation maps were used to provide attenuation correction to these pictures. Flash 3D software was used to recreate the corrected SPECT pictures. Following that, axial, coronal, and sagittal tomographic slices were created and presented. We visually assessed fused emission and transmission images for co-registration accuracy. Studies that had a lot of mis-registration were removed from the analysis. Image interpretation: Both modalities were read independently by two competent nuclear medicine experts.

To avoid recall bias, images were appraised in separate sessions. The clinical history of the patients was revealed to the readers, but the data from other imaging modalities was kept hidden.

The planar and SPECT images were reviewed separately using a grey linear scale display on a specific work station "Mac." Both linear grey scale and color fusion displays were used to review the SPECT/CT scans. "Skull, clavicles and scapulae, humeri, sternum, ribs, cervical spine, dorsal spine, lumbar spine, bony pelvis, sacrum, and both femora" were the 11 locations studied. Each location was given a score ranging from "zero" to "five," with 0 denoting "free." 1 indicates a benign lesion(s), 2 indicates a likely benign lesion(s), and 3 indicates an ambiguous lesion (s) 4 indicates that the lesion is most likely cancerous (s) The number 5 denotes a malignant tumor (s).

For areas of physiological MDP uptake, a score of "0" was assigned. Lesions that did not follow the physiological MDP uptake pattern but could be associated with MDP uptake related to cartilage, joints, or the uptake appearance was indicative of a benign etiology were given a score of "1" or "2." A score of "4" was given if there was focal intense uptake within a bone with

involvement of a nearby joint or a solitary area of focal uptake, while a score of "5" was given to lesions with focal intense uptake within the body or the pedicle of the vertebra or other bones involvement without extension to a nearby joint, as well as a suspicious accumulation pattern as random distribution in the skeleton.

The lesion was given a "3" if the readers couldn't tell whether it was benign or cancerous. Uptake along the edge of the vertebral body near the intervertebral disc, uptake extending outside the vertebral body outline, or focused uptake in the facet joints were all rated as "1" on the SPECT scan (sparing the pedicles). If there was focal uptake identified just proximal to a joint or within a vertebral body within the intervertebral disc area without expansion beyond the body contour, a score of "2" was assigned. Uptake areas were given a score of "5" if discrete uptake was identified inside the vertebral body and pedicles, and a score of "4" if uptake involving a vertebral body and extending into the pedicles.

The definite diagnosis was based on the results of a SPECT/CT examination that showed an area of uptake. When a CT study revealed a benign feature, such as arthritic changes, an area of aberrant uptake was considered benign.

If the CT study revealed lytic, sclerotic, or mixed lytic/sclerotic lesions, the area of uptake was declared malignant.

The number of lesions in both modalities was counted for each region after it was scored. We divided the lesions seen in SPECT/CT pictures into three categories based on the contribution of the decision made based on SPECT images alone, CT images alone, or a combination of the two. The results of the SPECT/CT are then compared to those of other diagnostic imaging modalities such as CT, MRI, or, if available, PET/CT.

## RESULTS:

The study included 50 female pathologically-proven breast cancer patients with mean age 46.9 years  $\pm$  9. 27 patients had left breast cancer, 22 patients had right breast cancer, and only one patient had bilateral breasts neoplasm. In terms of pathology, 40 patients (80 %) were diagnosed with infiltrative Ductal carcinoma (IDC), 9 patients (18%) with infiltrative lobular carcinoma (ILC) and one patient (2%) diagnosed with IDC on top of Pagets' disease (*Table 1*).

**Table (1):** Demographic Data of 50 patients with breast cancer.

Age	46.9 Years $\pm$ 9		Pathology	
Left Breast Cancer	27 Patients (54%)		Infiltrative Ductal Carcinoma	40 Patients (80%)
Right Breast Cancer	22 Patients (44%)		Infiltrative lobular Carcinoma	9 Patients (18%)
Bilateral Breast Cancer	1 Patient (1%)		Infiltrative Ductal Carcinoma on top of Pagets' Disease	One Patient (2%),

On clinical and imaging follow-up data, 23 patients (46%) out of 50 were found to have osseous metastasis, while 27 patients (54%) were found to be osseous metastasis-free. In the CT part of the study, SPECT/CT revealed features of sclerotic and lytic lesions with abnormal tracer uptake consistent with metastases, and the patients were subjected to CT with contrast, which revealed metastatic disease in all of them (*Table 2*).

Another patient with rib lesions was diagnosed as traumatic in PBS, but the SPECT/CT revealed mixed lytic and sclerotic nature, which was consistent with the CT with contrast that the patient had done, indicating that the lesions were metastatic. Also, in one patient, PBS failed to detect small foci of sclerosis in the femora that was found by SPECT/CT and the patient had an MRI that revealed changed marrow signal consistent with metastatic origin. Furthermore, the PBS missed two lesions in the sacrum, whereas the SPECT/CT detected sclerotic spots that were later shown to be metastatic by CT with contrast.

Two patients were found to have changed bone marrow signal in the lumbar vertebrae in the MRI after being mistakenly negative in both the PBS and SPECT/CT.

Two individuals were diagnosed mistakenly positive in PBS, one in the sacroiliac region, which was later determined to be sacroiliitis by MRI, and the other in the dorsal spine, which was later determined to be degenerative alterations by SPECT/CT and CT with contrast (*Table 2*).

Only one instance was identified as a false positive by SPECT/CT in the sacroiliac area, which was later confirmed by MRI to be sacroiliitis. The sensitivity, specificity, positive predictive value, and negative predictive value of PBS and W.B. SPECT/CT images were 52.2 % Vs 87 %, 92.6 % Vs 96.3 %, 85.7 % Vs 95.2 %, and 69.4 % Vs 89.7 %, respectively, as shown in *Table (2)*. The difference in sensitivity between the two modalities was statistically significant (P-value = 0.001), whereas the difference in specificity was statistically inconsequential (P-value= 0.5).

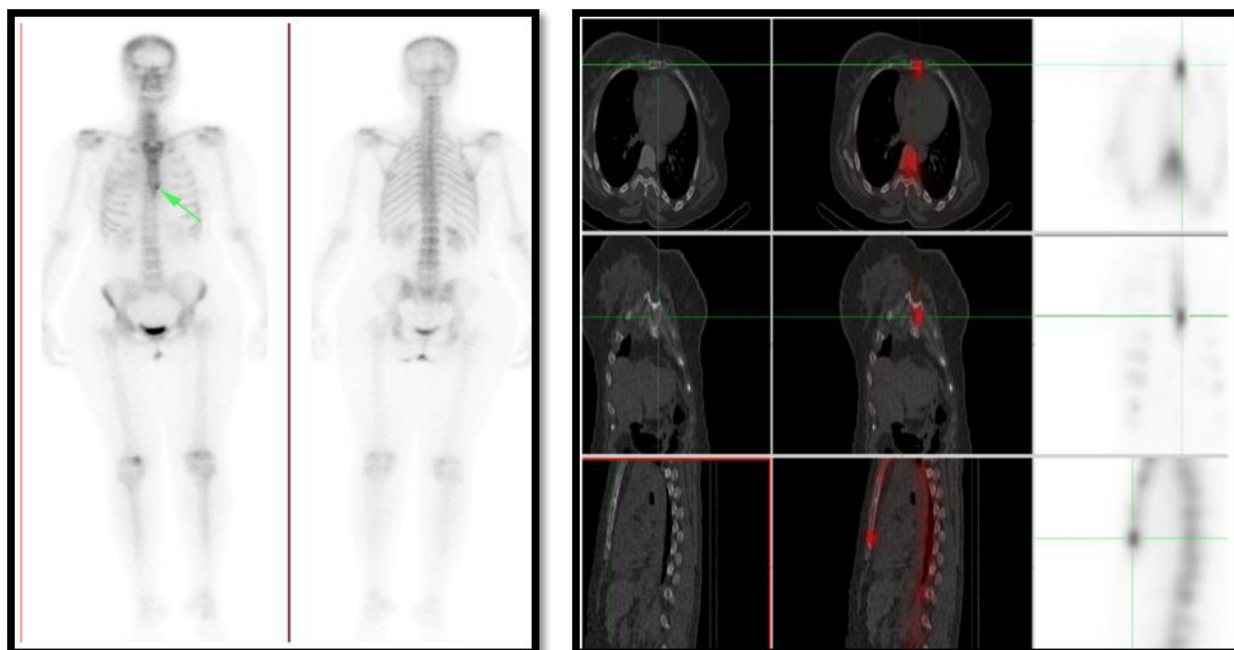
Analyses based on location: The skull, scapulae and clavicles, humeri, sternum, ribs, cervical spine, dorsal spine, lumbar spine, pelvic bones, sacrum, and femora were separated into eleven zones. Because site-based analysis is difficult, we limited our analysis to patients and sites that had additional imaging modalities to validate the type of the lesions, as shown in *Table (3)*.

**Table (2):** Diagnostic performance of planar bone scintigraphy and whole-body SPECT/CT in detection of osseous metastases in 50 patients with breast cancer.

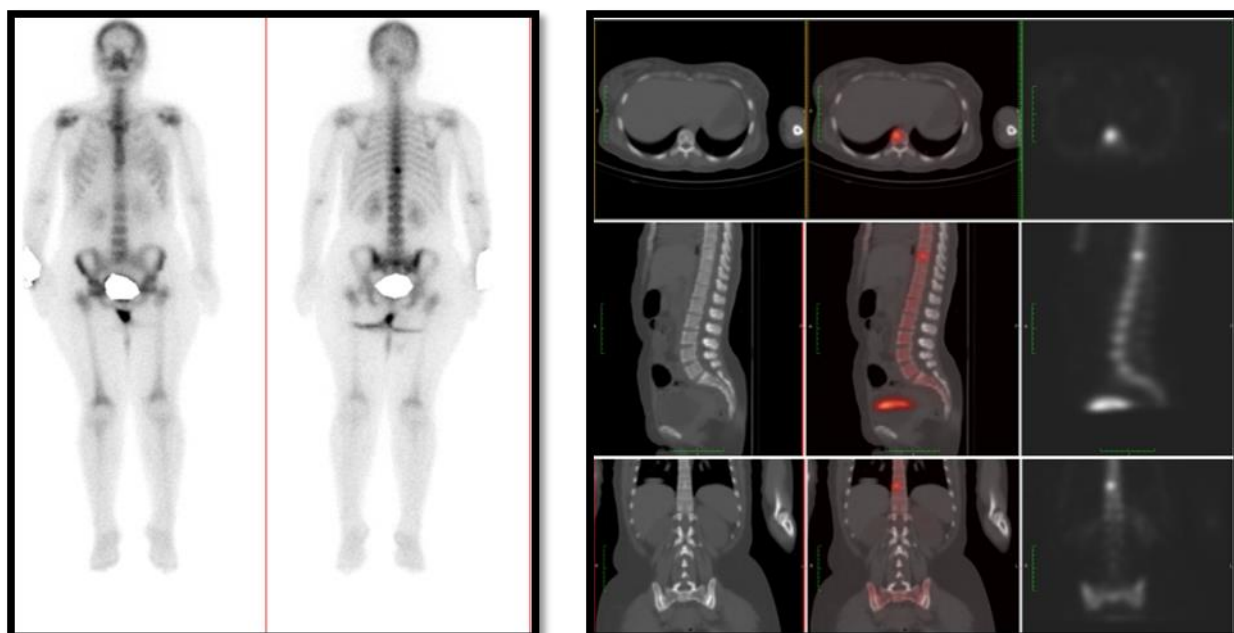
	Planar Bone Scintigraphy	W.B. SPECT/CT
False Negative	11	2
True Positive	12	21
True Negative	25	26
False Positive	2	1
Sensitivity	52.2%	87%
Specificity	92.6%	96.3%
Positive Predictive Value	85.7%	95.2%
Negative Predictive Value	69.4%	89.7%
Accuracy	74%	92%

**Table (3):** Site based analysis of the metastatic lesions in 50 patients with breast cancer.

Site	No. of cases	Planar bone scintigraphy				W.B. SPECT/CT				p-value
		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	
Sternum	13	100%	91.7%	50%	100%	100%	91.7%	50%	100%	0.015
Ribs	17	83.3%	90.9%	83.3%	90.9%	100%	90.9%	85.7%	100%	0.002
Dorsal spine	25	52.9%	100%	100%	50%	94.1%	100%	100%	88.9%	0.0001
Lumbar spine	26	46.2%	100%	100%	65%	84.6%	100%	100%	86.7%	0.0001
Pelvic bones	16	70%	83.3%	87.5%	62.5%	100%	83.3%	90.9%	100%	0.001
Sacrum	16	14.3%	100%	100%	60%	100%	100%	100%	100%	0.001

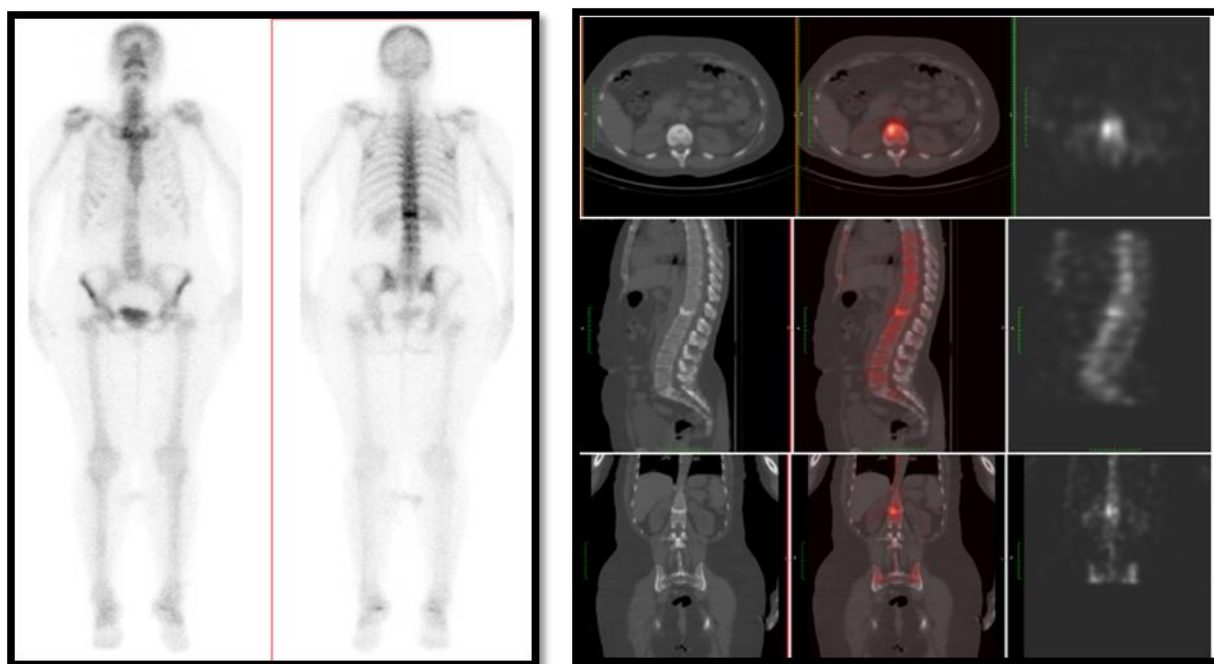


**Figure (1):** 35-year-old female patient with newly diagnosed right breast cancer not operated referred for staging. **Bone scan** revealed solitary equivocal osseous lesion at the lower part of the sternum with score (3) "Equivocal". **SPECT/CT images** showed solitary osseous lesion at the sternum with underlying lytic lesion in low dose CT images, score (5) "Malignant".



**Figure (2):** 29-year-old female patient with newly diagnosed left breast cancer not operated referred for metastatic work-up. **Bone scan** revealed solitary equivocal osseous lesion at the 9th dorsal vertebra with score (3) "Equivocal". **SPECT/CT images** showed solitary osseous lesion at DV9 with underlying sclerotic lesion in low dose CT images, score (5) "Malignant".





**Figure (3):** 42-year-old female patient with diagnosed right breast cancer, right modified radical mastectomy was performed, no chemotherapy or radiotherapy referred for metastatic work-up. **Bone scan** revealed solitary equivocal osseous lesion at the first lumbar vertebra with score (3) "Equivocal". **SPECT/CT images** showed vertebral compression fracture with score (1) "Benign".

## DISCUSSION:

This prospective study comprised 50 adult female patients with pathologically established breast cancer who were treated in the Nuclear Medicine unit at Kasr Al-Ainy Hospital (NEMROCK), Cairo University, between September 2018 and March 2019. The goal of this study was to see if W.B. SPECT/CT had an added value to PBS in detecting osseous metastases in breast cancer patients. Sensitivity, specificity, positive predictive value, and negative predictive value for PBS and W.B. SPECT/CT pictures

were 52.5 % vs 87 %, 92.6 % vs 96.3 %, 85.7 % vs 95.2 %, and 69.4 % vs 89.7 %, respectively. Fleury et al. investigated the benefits of trunk SPECT/CT vs planar bone scan in a study of more than 300 individuals with breast and prostate cancer. SPECT/CT improved the performance of planar bone scans by increasing sensitivity, specificity, PPV, and NPV from (93 %, 76.8%, 37.7%, and 98.7%) to (93 %, 76.8%, 37.7%, and 98.7%).

(100 %, 96.8 %, 82.7 %, and 100 %), however no significant difference in specificity between the two modalities in our investigation <sup>(9)</sup>. Similarly, *Olivier Rager et al.*, compared whole body SPECT/CT with planar bone scan with targeted SPECT/CT. They studied 212 patients, 70 of whom had prostate cancer, 50 of whom had breast cancer, and 92 of whom had other cancers. In 43 patients (20%). They concluded that W.B. SPECT/CT had higher sensitivity than PBS linked with targeted SPECT/CT with no significant difference in their specificity, which was consistent with our findings <sup>(10)</sup>. Also, *Palme do et al.*, Studied 353 individuals, 211 of whom had breast cancer and 97 of whom had prostate cancer.

In 72 cases, bone metastases were confirmed. Planar scintigraphy had a sensitivity and specificity of 93 % and 78 % for WBP and 97 % and 94 % for W.B. SPECT/CT, respectively. Specificity and positive predictive value were significantly better with SPECT/CT (P value 0.05) <sup>(11)</sup>. Gad *Abikher et al.*, looked at the detectability rates of planar bone scintigraphy and whole-body SPECT in 92 breast cancer patients. In 34 cases, bone metastases were discovered. Only one instance was diagnosed by SPECT that was

not diagnosed by planar bone scintigraphy <sup>(11)</sup>. There was no statistically significant difference in the detectability of bone metastases between planar bone scan and whole-body SPECT.

*Utsonomiya et al.*, Conducted a retrospective study to determine whether hybrid SPECT/CT is useful or not in the diagnosis of metastatic disease in 45 patients with various tumors, including breast cancer. They discovered that fusion of SPECT/CT images improved diagnostic accuracy when compared to separate bone SPECT and CT images in distinguishing benign from malignant lesions <sup>(12)</sup>.

This was consistent with our findings, as we found that two patients were falsely negative in both PBS and W.B. SPECT/CT but had altered marrow signal in the lumbar vertebrae on MRI. *Hanney et al.*, reported on the increased usefulness of half-body SPECT in 20 patients, where SPECT altered the location and clinical relevance of lesions revealed by planar bone scintigraphy <sup>(13)</sup>. Similarly, we demonstrated the incremental usefulness of hybrid SPECT/CT and the contribution of the CT component in defining lesions that were unclear on planar projections, albeit in a smaller number of patients.

We confidently examined and accurately excluded bone metastases in the pelvic bones using SPECT/CT scans. The dorsal spine, lumbar spine, pelvic bones, and sacrum had the highest sensitivity in our study's site-based analysis. SPECT/CT was able to accurately interpret 96 % of lesions in the vertebrae seen using a bone scan, according to *Sharma et al.*. The pelvic bones were analysed with SPECT/CT imaging, and 7 of our patients had metastatic deposits in the sacrum, 6 of which were missed on PBS<sup>(2)</sup>. The artefact was definitely excluded by SPECT/CT. Our research found that the use of SPECT/CT reduced ambiguous lesions from 38 to 2 lesions, with a significant P-value (0.001), reducing the need for further imaging such as MRI and so saving time and money.

Also, *Palmedo et al.*, found a decrease in equivocal lesions from 157 lesions (18.7%) in planar bone scintigraphy to 29 lesions (3.5%) after adding SPECT/CT<sup>(14)</sup>.

*Sharma and Punet.* conducted a study in which 102 patients with 115 equivocal lesions on planar scintigraphy underwent SPECT and SPECT-CT of a selected volume, and found that SPECT-CT is superior to planar scintigraphy and SPECT alone for characterizing equivocal bone scintigraphy lesions in patients with breast cancer, and can have a significant impact on

patient management<sup>(6)</sup>.

*Ndlovu et al.*, looked at 42 patients with various cancers, 22 of whom had breast cancer. Patients and lesions of equivocal nature were shown to be much reduced with SPECT/CT as compared to SPECT alone, from 31% to 9% in equivocal lesions<sup>(15)</sup>. This agreed with our findings, except instead of comparing planar bone scintigraphy to SPECT/CT, they compared planar bone scintigraphy to SPECT alone.

*Eloteify, L M et al.* Studied 83 breast cancer patients (81 females, 2 males) with median age 52 years referred for conventional planar bone scanning. Targeted SPECT/CT was acquired in the same day for equivocal lesions. The sensitivity, specificity and accuracy for PBS versus SPECT/CT were 89% vs. 100%, 30% vs. 87% & 57% vs. 93%; respectively. In our study we replaced the targeted SPECT/CT by whole body SPECT/CT. Our result included sensitivity, specificity, positive predictive value, and negative predictive value of PBS and W.B. SPECT/CT images were 52.2 % Vs 87 %, 92.6 % Vs 96.3 %, 85.7 % Vs 95.2 %, and 69.4 % Vs 89.7 %, respectively. The whole-body SPECT/CT didn't offer extra advantage regarding sensitivity and specificity. The rationale for this, is that the equivocal lesions are mostly solitary and targeted SPECT/CT is often enough<sup>(15)</sup>.

### **Limitation:**

This study has a few limitations. Longer period of follow-up is required to investigate specific outcome. Many diagnostic studies lack a real and/or standardized reference test, with biopsy being a questionable technique from both an ethical and, in many cases, a

practical one. Low-dose CT was also a concern, as some lesions showed increased tracer absorption on SPECT but no underlying CT change, making diagnosis more challenging.

### **CONCLUSIONS:**

In breast cancer patients, whole-body SPECT/CT bone scintigraphy improves the sensitivity of the bone scan for detecting osseous metastases through minimizes the

number of equivocal lesions and detected higher number of mostly malignant lesions compared to planar bone scintigraphy

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