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Added Value of SPECT/CT to Planar Bone Scan in Evaluation of Suspicious Metastatic Bony Lesions in Breast Cancer.

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ABSTRACT:

Introduction: Planar bone scan (PBS) is a standard modality for detecting skeletal metastasis. Although PBS is very sensitive, it lacks specificity, especially when a solitary or few atypical osseous lesions depicted. The addition of SPECT/CT can greatly enhance diagnostic accuracy and help reclassify non-conclusive findings on PBS. In this work, we evaluated the added value of SPECT/CT in characterization of equivocal osseous lesions seen on conventional PBS in breast cancer patients.

Materials and Methods: This prospective study recruited patients known to have breast cancer referred for conventional planar bone scanning (PBS).Immediately after PBS was acquired, planar images were reviewed. If two nuclear medicine physicians agreed on the non-conclusive nature of the lesion(s), a targeted SPECT/CT was acquired in the same day, to cover the suspected area. Diagnostic performance indices from both modalities (PBS&SPECT/CT) were compared against the reference standard (clinical/imaging follow-up for at least 6-12 months).

Results: A total of 83 breast cancer patients were included in this study (81 females, 2 males) with median age 52 years (range: 32-84). The sensitivity, specificity and accuracy for PBS versus SPECT/CT were 89% vs. 100%, 30%vs. 87% &57%vs. 93%; respectively; ($P = 0.125$, <0.0001, <0.0001); respectively. SPECT/CT changed management in 36% of breast cancer patients by down-staging and upstaging their skeletal disease status.

Conclusion: Skeletal SPECT/CT offers an important diagnostic advantage over planar bone scan for characterization of inconclusive osseous lesions in patients with breast cancer and could significantly impact patient management.

Key Words: SPECT/CT, Equivocal lesions and Breast cancer

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INTRODUCTION:

Bone metastases are the most common malignant bone tumors seen in adults. Bone metastases may occur with all malignancies but are most common in carcinomas of the breast [1].The axial skeleton is involved more than the appendicular skeleton, mostly due to the presence of red bone marrow in the former [2].Detection of bone metastases in cancer patients is essential for accurate diagnosis and proper patient management [3].Bone scintigraphy is widely used to exclude or confirm bone metastases, despite its limited specificity in many cases [4].Degenerative changes frequently result in false positive scintigraphic findings that necessitate additional radiological imaging, mainly plain radiographic images [5]. However, the correlation between projection X-ray or even tomographic CT images and scintigraphic images remains challenging, and in many cases exact anatomical localization cannot be confidently assessed [6]. SPECT-CT system combines the functional benefit of SPECT with anatomical information of CT in a single setting allowing optimum co-registration of both image sets and could be well-utilized for accurately evaluating suspected bone metastasis [7]. Some studies have shown that the number of unclear lesions detected in whole-body planar scintigraphy and SPECT can be significantly decreased using SPECT/CT [8, 9]. Also, SPECT/CT has been shown to increase the accuracy of bone scanning and significantly impacts the clinical management decisions of cancer patients [8, 10]. However, only few reports focused on breast cancer population. The aim of this work was to evaluate the added value of SPECT/CT over conventional PBS in breast cancer patients.

MATERIAL AND METHODS:

Patients: This prospective study recruited patients known to have primary breast cancer referred for diagnosis/follow-up of bone metastases using conventional PBS. If PBS demonstrated suspicious solitary or few osseous lesions, a targeted SPECT/CT of the concerned region was performed and evaluated by two nuclear medicine physicians.

Imaging Protocol: At first, planar whole body scans were obtained in the anterior and posterior projections 2 hours after the IV injection of about 650-850 MBq of Tc-99m MDP. A dual-head γ-camera (Symbia T, Siemens Medical Solutions, Erlangen, Germany) equipped with parallel-hole high resolution low-energy collimators using a 15% energy window set at 140 kev was used. The table speed was 12 cm/min, matrix size 256x1024.SPECT/CT images of the concerned region were obtained in the same day. SPECT procedure was acquired employing a step and shoot protocol, 25 seconds∕ view for a total of 32views using a noncircular orbit over 360 degrees of rotation (180ºper head) and a matrix size of 128 x128.Immediately after completing SPECT acquisition, low-dose CT study was acquired with a tube current of 70 mAs, a tube voltage of 130 kV, employing a dose-reduction algorithm

(CARE Dose 4D, Siemens Medical Solutions, Erlangen, Germany).The CT dose index per volume (CTDI vol) was on average 7.6 mGy. CT images were reconstructed in 2-mm slices using bone and soft tissue kernels. After completion of acquisition, the images were reconstructed with attenuation and scatter correction using 3D iterative algorithm (OSEM 3D Flash, Siemens Medical Solutions, Erlangen, Germany).The reconstructed attenuation-corrected SPECT images and CT images were transferred to the viewing station (OsiriX MD, Pixmeo, Switzerland) for reviewing in axial, coronal, and sagittal planes.

Data interpretation: Two nuclear medicine physicians (Reader 1:8-year experience; Reader 2:12-year experience) scored each lesion on a subjective 5-point score for the probability of being malignant (1=benign, 2= probably benign, 3 = equivocal, 4=probably malignant & 5 = malignant). True & false results were identified in relation to the reference standard, which was based on subsequent clinical/imaging follow-up for at least 6-12 months. Both readers have prior knowledge of the aim of the study and clinical data of the patient (age, gender, primary tumor site).

Statistical analysis: Patient-based analysis was carried out. True-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) readings were identified on the basis of subsequent clinical /imaging validation as above-stated. Diagnostic performance parameters in the form of sensitivity, specificity, and negative predictive values (NPV), and positive predictive values (PPV), and accuracy of whole-body scintigraphy and SPECT/CT were calculated in relation to the reference standard. Because the reference standard is dichomatous (benign or malignant), while the diagnostic score is 5-points of probability, we decided to categorize patients with score 3 (equivocal reading) as malignant. The nonparametric McNemar test was used to evaluate the statistical significance of the differences in sensitivity and specificity (a two-sided P <0.05 was considered significant), whereas receiver-operating characteristic (ROC) analysis was used to compare the accuracy of the two modalities. Agreement between readers for each modality was measured using Kappa test and the level of agreement was categorized as poor (k value < 0), slight (k = 0 - 0.20), fair (k = 0.21 - 0.4), moderate (k = 0.41 - 0.6), substantial (k = 0.61-0.8) or perfect agreement (k = 0.81 – 1.0). Confidence interval around the agreement levels were calculated based on bootstrapping with 1000 - samples. Quantitative data were summarized and expressed as mean ± SD and median (range), whereas qualitative data were expressed as frequencies and percentages. The analyses were carried out using the SPSS, 21.0 (SPSS Inc., Chicago, Illinois, USA), MedCalc 11.0 (MedCalc, Ostend, Belgium), and Microsoft Excel 2003 (Microsoft, Redmond, Washington, USA).

RESULTS:

Patients' demographic data: During the period from January 2014 to December 2015, a total of 83 patients (2 male &81females) with median age 52 years (range: 32-84) were eligible for inclusion in that study. Of them, breast cancer was encountered bilaterally in 3 (4%), right-sided in 46 (55%) and left-sided in 34 (41%) *Table (1)*.

Table (1): Demographic data in breast cancer patients.

Characteristic	Results
Age "years"	
Mean ± SD	54±11.3
Median (range)	52 (32-84)
Gender:	
Female	81
Male	2
Site of breast cancer:	
Right Breast	46(55%)
Left Breast	34(41%)
Bilateral Breast	3(4%)
Total	83 (100%)

Planner Bone Scan:

(PBS) detected 113 lesions; while SPECT/CT detected 123 lesions which included all the lesions seen on PBS.

The majority of our patients had solitary lesion (n=50; 60%). In 33 patients, more than one lesion was seen per patient.

Two lesions were encountered in 26 patients (31%) and 7 patients (9%) had 3 equivocal lesions. Axial lesions were dominating the anatomical distribution of the encountered lesions n=81; (52 in the spine, 29 in skull, sternum and ribs). Thirty-three (27%) lesions were appendicular and 9 were proved to be extra-osseous by SPECT/CT.

Inter-observer agreement:

On planar imaging, both readers agreed on categorizing 58 lesions (16 as benign and 42 as malignant), resulting in fair level of agreement (k=0.38 [95%CI: 0.19-0.55]).On SPECT/CT, both readers concordantly classified 38 lesions as benign and 38 as malignant, with perfect agreement (k=0.83 [95%CI: 0.69-0.95]). The difference between the two levels of agreement was significantly higher for SPETC/CT (p < 0.001).Furthermore, PBS resulted in 34% (n=25) disagreement between the two readers regarding classifying lesions as benign or malignant compared to only 8% (n=7) for SPECT/CT.

Diagnostic performance: Bone metastases were confirmed in 37 patients (44.6%) and excluded in 46 patients (55.4 %). For this analysis, readings from reader 1 only were considered. PBS classified patients into 23 probably benign, 45 as equivocal and 15 as probably malignant. The number of patients with equivocal readings was significantly decreased from 45 (54 %) for PBS to only 10 patients (12%) for SPECT/CT.SPECT/CT correctly diagnosed bone metastasis in all patients positive for metastasis compared to 33 only for PBS, with sensitivity of 100% (95%CI: 95-100)

and 89% (95%CI: 75-97), respectively. Although SPECT/CT diagnosed disease in 4 additional patients that were false negative on PBS; however, the difference in sensitivity was not statistically significant (p=0.13).On the other hand, SPETC/CT correctly excluded disease in 40 patients, of them 26 were mis-categorized as false positive on PBS, with specificity of 87% (95%CI: 73-95) and 30% (95%CI: 18-46), respectively. The difference in specificity was statistically significant (p<0.0001) *(Table 2).*

Table 2: Cross tabulation of true and false results from planar and SPECT/CT.

Modality	SPECT/CT					
	Result	FN	TP	TN	FP	*P*
Planar	FN	**0**	**4**			0.13[*]
	TP	**0**	**33**			
	TN			**14**	**0**	<0.0001[#]
	FP			**26**	**6**	

* Difference for sensitivity, # Difference for specificity.

Impact of SPECT/CT on patients staging and management: SPECT/CT was able to recategorized false positive findings from PBS in 26/83 patients with subsequent osseous disease down-staging in 31.3%.Similarly, though less obvious,

SPECT/CT diagnosed disease in4/83 patients that were classified as non-metastatic by PBS with subsequent osseous disease upstaging and administration of palliative therapy *(Figure 1and 2).*
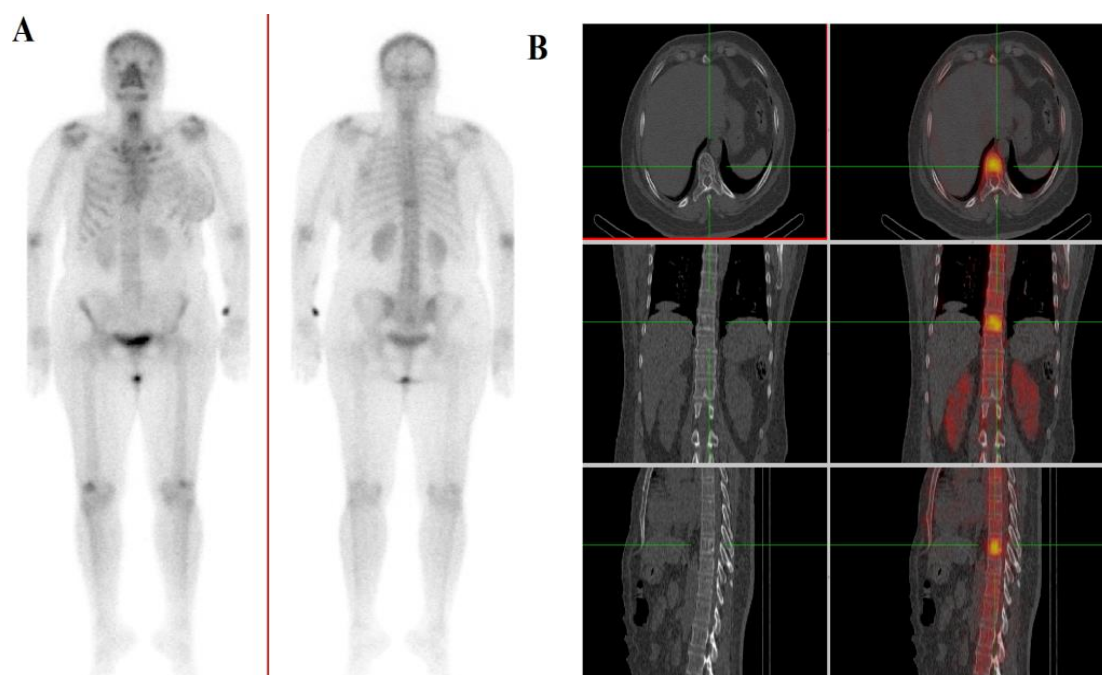
Figure 1 : 50 year old female with right breast cancer (A) PBS shows equivocal lesion in DV9 .(B) SPECT/CT images shows polka dot sign with a typical picture of hemangioma
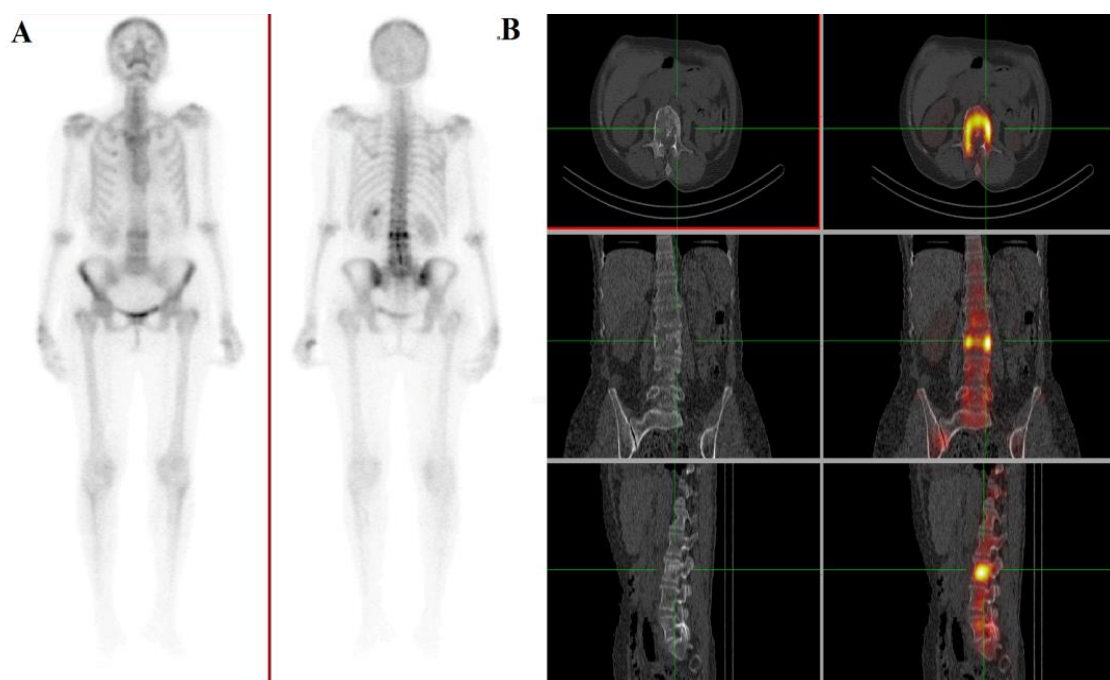

Figure 2: 58 year old female with left breast cancer (A) PBS shows equivocal lesion in LV3. (B) SPECT/CT images show multiple lytic lesions in the corresponding vertebra.

DISCUSSION:

A major disadvantage of planar bone scintigraphy is its low specificity due to tracer accumulation in benign bone lesions [11] which frequently results in considerable number of indeterminate or non-conclusive decisions in planar bone scans. The costs include more correlative imaging tests (typically CT or MRI) and/or more frequent follow-up visits [8]. Integrated SPECT-CT system is a well-established imaging modality that provides precise anatomical localization and better characterization of suspicious osseous lesions detected in planar scintigraphy by combining the functional benefit of SPECT with anatomical information of CT in a single setting; saving time and money [7]. SPECT/CT images help differentiating benign from malignant lesions; therefore decreasing number of equivocal lesions which reflects the patient management greatly [12]. In this work, we reported the agreement between two nuclear medicine physicians and diagnostic performance of SPECT/CT and planar scintigraphy in suspicious bony lesions in 83 known breast cancer patients (81 female and 2 male). It is well-known that objective reporting is desirable however, inter- and intra-observer variability is well-reported in literature for planar scintigraphy but less so for SPECT/CT (13-15). Our results showed that SPECT/CT significantly decreased the disagreement between reading decisions from 34% to 8%, which could significantly impact the uniformity of reporting in different institutions among readers with different level of experience. Our study showed increased sensitivity, specificity and accuracy of SPECT/CT compared to planar scintigraphy from 89%,30% and 57% for planar to 100%, 87%and 93% for SPECT/CT. Similar results were previously reported (1, 16, 17).The gain in diagnostic performance is mainly attributed to the improved specificity by co-registering the lesions with the integrated CT portion, which localizes benign uptake to sites of degeneration, arthritis or trauma. On the other hand, Sharma, et al. showed higher gain in sensitivity from 41% to 83% by adding SPECT/CT [18].Interestingly, the same authors, in a separate work, showed decreased sensitivity from 100% for planar scintigraphy to 92% for SPECT/CT in assessment of isolated vertebral lesions [19]. They considered, intermediate lesions (score 3) as benign.

In our analysis, this category was considered malignant, because in our practice, equivocal reporting usually results in subsequent intervention, either by correlative imaging, more frequent follow-up visits or even invasive biopsy.

Rager et al. showed the difference between considering the equivocal results as a benign and considering it as a malignant and its effect on sensitivity and specificity of SPECT/CT. They found that sensitivity increased when considering it as malignant while specificity decreased [19].

Similar results were reported by *Fleury et al*. who demonstrated that when considering equivocal lesions as malignant (pessimistic analysis), the higher was the sensitivity for both planar and SPECT/CT (93%, 100%) versus (74.4%, 97.7%) in optimistic analysis. However, when considering it as benign (optimistic analysis), the higher was the specificity (97.5%, 98.6%) versus (76.8%, 96.8%) in pessimistic [20].

Our results of modest increase in sensitivity come well in agreement with those reported by *Palmedo, et al*. as they showed an increase insensitivity from 91% to 98% for SPECT/CT [4].

Whereas, *Lofgren et al*. found that whole body SPECT/CT less sensitive than planar bone scan (62.5% vs.68.8%), albeit with higher specificity and accuracy [21].

They explained that their study was underpowered due to low prevalence of osseous metastasis in it (14%) which was lower than expected in clinical practice [21].

Numerous studies agreed that specificity significantly increased by addition of SPECT/CT [4, 19].

Also in the study by *Palmedoet al.*, specificity increased from 80.2% to 94% and in *Sharma et al*., from 36% to 100%.Our study showed similar results with increased specificity from 30% to 87%.

The gain in specificity results in notable down staging of osseous disease. About one third of our patients were correctly recategorized as free from osseous diseases by adding SPECT/CT which tremendously impacted their subsequent management by omitting unnecessary therapies.

On the other hand 4 patients (3%) were upstaged to metastatic status which also of clinical importance in managing the metastatic disease.

In 33 metastatic patients (39.8%) metastasis was confirmed with precise detection of the extent of metastasis.

These results come in agreement with *Palmedo et al*. work which showed down staging rate of 33.8% and upstaging of 2.1% with confirmation of metastasis in 34% of patients [4].

Finally, we have to admit the limitations of this study; which include inhomogeneity of the reference standard including CT, MRI and in some cases a follow-up bone scintigraphy. Theoretically the reference standard should be based on histopathology that would have required a bone biopsy for every lesion which is not justifiable either from a practical or ethical standpoint. Also, the interpretation of SPECT/CT scans was undertaken after interpretation of conventional PBS. Therefore, bias cannot be excluded. Another limitation is the introduction of interval therapy between the diagnostic scan and follow-up which could affect the pattern and outcome of the bony lesions. It is especially challenging when the encountered lesion shows a stationary course or improvement on follow up bone scan this result in difficult interpretation whether it was a malignant lesion with good response to therapy or a benign lesion from the start that is stable overtime. Future work is warranted to assess the interplay between treatments and outcome decisions. However, the advantages of this study included prospective nature, reasonable sample size, homogeneous patient population, uniform reporting by two observers and robust analysis.

CONCLUSIONS:

Our study showed significantly higher inter-reader agreement and diagnostic performance for SPECT/CT compared to PBS readings in patients with breast cancer. Addition of SPECT/CT could significantly impact management with potential for improved outcomes. Further work is needed to identify the sub-groups which could benefit the most from this powerful imaging modality.

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