Whole body bone SPET/CT can successfully replace the conventional bone scan in breast cancer patients. A prospective study of 257 patients

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Abstract

Objectives: Single photon emission tomography/computed tomography (SPET/CT) is usually recommended after ambiguous whole body bone scan (WBS) findings. We investigated the value of routine 2-field ("near" whole-body) SPET/CT application in breast cancer (BC) patients. **Subjects and Methods:** In this prospective study planar WBS and 2-field SPET/CT was performed in 257 consecutive BC patients referred for a bone scan. Whole body scan and SPET/CT were interpreted separately. Additional imaging studies and clinical follow-up for 30±24 months elucidated uncertain findings. **Results:** Bone metastases were confirmed in 65 patients (25.3%). Sensitivity, specificity, accuracy, positive and negative predictive value per-patient was 63.1%, 81.3%, 76.7%, 53.2% and 86.7% for WBS and 96.9%, 87.5%, 89.9%, 72.4% and 98,8% for SPET/CT; differences were statistically significant except for specificity. Respective values of sensitivity per-lesion were 47.6% and 98.9% (P<0.001). Eleven percent of true positive findings were noticed only in the low-dose CT images, while 7% only in SPET. Single photon emission tomography/CT exhibited higher specificity than WBS in the spine (94.8% vs. 88.7%, P=0.04). Whole body scan interpretation changed after SPET/CT in 74 (28.8%) patients. Thirty-two patients with positive/suspicious WBS turned to be metastases-free after the interpretation of SPET/CT while 42 with unremarkable WBS turned to be positive/suspicious. Of these cases, metastases were confirmed in one with negative and 23 with positive/suspicious SPET/CT. The SPET/CT results prompted treatment plan changes in 23 cases (8.9%). **Conclusion:** Whole-body bone SPET/CT scan outperformed WBS in terms of sensitivity, accuracy, positive and negative predictive value and impacted on patient management. Therefore, its use is recommended as a routine procedure in BC patients, even after a negative WBS.

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Introduction

The skeleton is the most common site of cancer colonisation from breast cancer (BC) and it also represents the position of the first secondary deposit of cancer in 26% to 50% of these patients. Actually, disseminated cancer cells can be detected in the bone marrow in about 30% of cases, even at early stages of BC and their presence is associated with a poorer prognosis. Clinically overt bone lesions will eventually appear in 50% to 70% of patients who relapse during the course of the disease [1-4]. Although isolated skeletal metastases affect overall patient survival less than visceral involvement [5] their complications are frequent and may have a dramatic impact on patients' quality of life [6]. Treatment to prevent or delay skeletal complications includes chemotherapy, bisphosphonates, receptor activator of nuclear factor kappa-B ligand (RANKL)-targeted agents, local radiotherapy or a combination of therapies [7]. The role of imaging in the early detection of bone metastases is essential. However, the choice of the most appropriate imaging modality for screening, initial work-up, assessment of response to treatment and patient surveillance is still controversial [1, 8]. Most current guidelines recommend no additional imaging studies for early-stage BC at initial presentation or for post-treatment follow-up of asymptomatic individuals with no specific findings on clinical examination [9-11].

Whole-body bone scan (WBS) is assumed to reveal metastases considerably earlier than radiographic methods [12], because it relies on metabolic alterations caused by tumour growth which precedes structural changes. The interpretation of WBS is based on the assessment of the radioactive tracer concentration in bone lesions without any visualization of the underlying anatomy. Therefore, the accuracy of the method is limited by frequent non-specific tracer uptake in various benign processes. On the other hand, st-

ructural changes shown on radiography are often difficult to assess without the corresponding functional information [13]. The classic planar WBS has been improved with the introduction of single photon emission tomography (SPET), which allows the visualisation of the three dimensional distribution of the radiopharmaceutical in the skeleton [14]. However, SPET still lacks the detailed anatomic correlation needed for differentiation of benign from malignant processes [15].

Nowadays, hybrid gamma cameras are able to combine SPET imaging and computerized tomography (CT) in one single construction (SPET/CT) [16]. The main idea of SPET/CT is to integrate functional and anatomical data in order to improve diagnostic accuracy. Until now, several studies have shown that the use of SPET/CT improves significantly the specificity of the nuclear bone scan by decreasing the number of the inconclusive results and increasing the diagnostic confidence of the interpreter [17-23]. Most experts, as well as the latest European Association of Nuclear Medicine (EANM) guidelines for bone scintigraphy, suggest the implementation of SPET/CT only in cases of abnormal or inconclusive findings of planar imaging [24-26]. However prespective studies with an increased number of patients and covering only the body central skeleton were not found by us in the medical literature or perhaps are very seldom.

The purpose of the present study was to investigate prospectively the value of systematic implementation of 2-field SPET/CT ("near" whole body, covering the central skeleton) in addition to WBS in a patient series with BC. Patient-and lesion-based results were analyzed as well as the clinical impact of these results on patient management.

Subjects and Methods

Patients

Prospective patient enlistment started in February 2011 and ended in March 2014 after inclusion of 257 patients (256 females and 1 male) with histopathologically proven BC. We recruited consecutive patients referred to our laboratory by the oncology department of our hospital for a bone scan. In order to ensure direct access to patients' records, referrals from other sites were excluded. Seventy-two of the participants underwent scintigraphy at the initial staging of the disease, while the remaining during their follow-up after therapy. Patient characteristics are detailed in Table 1. The study protocol was approved by the local ethics committee and a written informed consent was obtained from all patients.

Data acquisition and processing

All patients underwent a WBS followed by a 2-field SPET/CT sequence (spanning ~80cm), in order to include the whole vertebral column, the thorax, the pelvis and the proximal femur. An one-field SPET/CT would be able to scan a body area of only 40cm. Imaging took place approximately 3 hours after the intravenous (i.v.) administration of technetium-99m-hydroxydiphosphonate (Technescan, Mallinckrodt™) at an average dose of 655MBq (range 630-700MBq). The first part of the imaging was the conventional WBS (anterior and posterior images) with an approximate duration of 15-20 minutes and the second part was the 2-field SPET/CT imaging (duration 25-40 minutes). Regarding SPET/CT, the first 50 patients were imaged with the "Hawkeye" and the remaining with the "Hawkeye-4" hybrid system (both provided by GE Medical Systems). Both of the systems were dual-head g-camera models but the main difference conserned the low dose CT. The "Hawkeye-4" hybrid sustem was able to obtain 4 slices per rotation while the "Hawkeye" system only one.

Equipment, acquisition and reconstruction parameters, as well as study duration for each device are listed in Table 2. All images were viewed on a "Xeleris, version 2 or 3" workstation.

Table1. *Patient characteristics.*

Characteristic	No (%)
No of patients	257
Gender (female/male)	256/1 (99.6/0.4)
Age (mean±SD; range)	61.2±12.1; 23-83yrs
Breast cancer histology	
Ductal carcinoma	166 (64.6)
Lobular carcinoma	91 (35.4)
Initial stage of the disease	
0	2 (0.8)
IA	10 (3.9)
IB	24 (9.3)
IIA	66 (25.7)
IIB	47 (18.3)
IIIA	51 (19.8)
IIIB	23 (8.9)
IIIC	13 (5.1)
IV	21 (8.2)
Receptor status	
HER2(+)	83 (32.3)
ER(+)	184 (71.6)
PR(+)	181 (70.4)
Triple negative	50 (19.5)
Reason for bone scan referral	
Initial staging	72 (28.0)
Routine follow-up	98 (38.1)

continued

Known osseous metastases	21 (8.2)
Bone pain of new onset	58 (22.6)
Tumour marker elevation	29 (11.3)

HER2(+): Human epidermal growth factor receptor 2 positive; ER(+): Estrogen receptor positive; PR(+): Progesterone receptor positive

Image interpretation

Whole body scan and SPET studies were examined independently by one experienced nuclear medicine physician. Computed tomography images were interpreted by one experienced radiologist. Whole body scan, SPET and CT findings were characterized as non suspicious/unimportant (including lesions attributed to degenerative changes, fractures or other benign causes), suspicious (requiring further diagnostic investigation) or definite for bone metastases. Computed tomography abnormalities were further described as predominantly sclerotic or lytic. Detected lesions were assigned to 10 anatomical regions: Skull, vertebral column, ribs, sternum, clavicle, scapula, proximal humerus, proximal femur, pelvis and distal upper or lower extremities. Finally, fused SPET/CT images were viewed by a nuclear medicine physician and the radiologist during a joint session and a consensus was reached. Whole body scan and SPET/CT results were integrated in the official study report.

Table 2. *Equipment, acquisition and slice reconstructionparametersused in SPET/CT studies.*

Parameter	Hawkeye	Hawkeye-4
SPET		
Dual-head γ-camera model	Varicam	Infinia
Crystal thickness (inches)	5/8	3/8
Collimator	LEHR [a]	LEHR
Acquisition mode	Step-and-shoot	Step-and-shoot
Matrix size	128x128	128x128
Angular range (^{0})	360	360
No of projections	60	60
Angular step (^{0})	6	6
Frame time (sec)	15	10
Reconstruction (iterations/subsets)	OSEM [b] (2/10)	OSEM (2/10)
Scatter correction	No	yes
Post-filtering (frequency cut-off, order)	Butterworth (0.45/10)	Butterworth (0.45/10)
Resolution recovery [c]	No	Yes
Total acquisition time per field (min)	7.5	6
CT		
No of slices per rotation	1	4
Slice step (mm)	10	4.4
Acquisition mode	Axial	Helical
Rotation time (sec)	13.8	-
Velocity (rpm) [d]	-	2.6
Pitch	-	1.9
Matrix size	256x256	512x512
Voltage (kVp)	140	140
Current (mA)	2.5	2.5
Total acquisition time per field (min)	~10	~4

[a] LEHR: low-energy high-resolution collimator; [b] OSEM: ordered-subsets expectation maximization, [c] "evolution for bone" software by GE, Medical Systems; [d] rpm: revolutions per minute

Confirmation of skeletal metastases

Additional imaging studies, (diagnostic CT, MRI or ^{18}F-FDG PET/CT) were recommended and undertaken in all cases reported as ambiguous in the official report. Moreover, all patients were followed clinically for a mean±SD of 30±24 months (range 12-60 months). One or more bone scans (WBS plus SPET/CT) were performed in 239 patients during their follow-up in our department. No bone biopsies were undertaken. After complementary imaging studies, repeated bone scans and clinical follow-up uncertainties of the baseline bone scan were resolved. The follow-up ended in February 2017.

Statistics

Statistical differences were examined by the MacNemar's test for paired and by the chi-squared test for unpaired observations. Patient-based sensitivity, specificity, positive and negative predictive values (PPV, NPV) of WBS and SPET/CT were calculated. The sensitivity and specificity according to lesion-based analysis were also computed for each skeletal region.

Results

Patient-based analysis

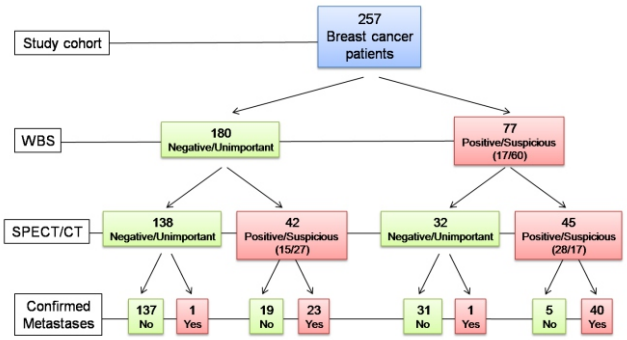

Figure 1. Flow-chart demonstrating changes in WBS interpretation induced by SPET/CT evaluation, with reference to bone metastases confirmation.

Sixty-five out of 257 patients (25.3%) were confirmed with bone metastases. Of these, 1.5%, 13.8% and 84.6% had been classified as stage I, II and III/IV at their initial presentation. Moreover, bone involvement was confirmed in 36.9% of patients with triple-negative as opposed to 16.6% of those not showing this receptor pattern (P<0.001). No difference in bone metastases rate was noticed between ductal and lobular BC (58.5% vs. 41.5%, P=0.2).

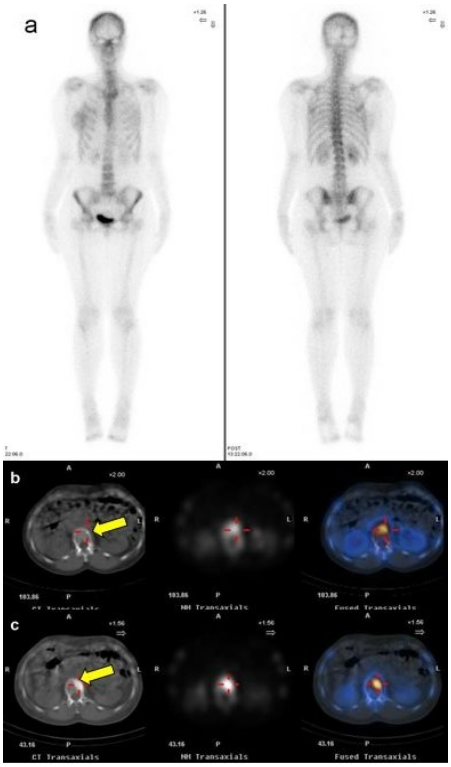

Figure 2. Images from a 37 years old female with lobular carcinoma of the left breast with liver and brain metastases at presentation (stage IV). Planar WBS (a) undertaken as part of the staging procedure was unremarkable. Low-resolution CT revealed a small osteoblastic lesion at the body of L1 vertebra which exhibited mild to moderate increase of metabolic activity (b). Single photon emission tomography/CT was interpreted as suspicious for metastasis. The evolution of the lesion is demonstrated on repeated SPET/CT study 10 months later (c), confirming the presence of a solitary bone metastasis (arrows).

Whole body scan interpretation on a per-patient basis yielded 180 (70.4%) negative/ unimportant, 60 (23.3%) ambiguous requiring further investigation and 17 (6.6%) definitely positive results. Respective SPET/CT findings were 170 (66.1%), 44 (17.1%) and 43 (16.7%). SPET/CT was able to elucidate uncertain WBS findings in 43 out of 60 cases (71.7%). However, 17 remained equivocal and moreover, suspicious findings requiring further investigation appeared in another 27 patients with negative WBS. Accordingly, SPET/CT changed WBS results in 74 patients (28.8%). More specifically, 42 patients with normal/unimportant WBS were classified as positive/suspicious for metastases after SPET/CT. Metastatic disease was confirmed in 23 and excluded in 19 of these. Conversely, 32 positive/suspicious WBS interpretations turned to normal/unimportant after SPET/CT. Metastatic disease was present in only 1 of these patients. The results are detailed in the flowchart of Figure 1. Case examples are displayed in Figures 2-4.

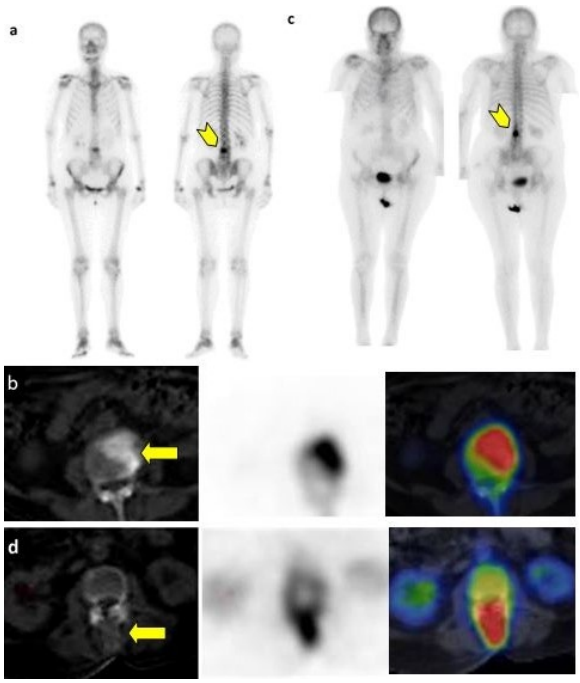

Figure 3. Two patients with similar WBS images but different SPET/CT findings. The first is a 65 years old female with ductal BC stage IIB at the time of the diagnosis, complaining of low back pain of recent onset. WBS (a) exhibited intense focal tracer accumulation at the lower lumbar spine (arrow head). The study was interpreted as suspicious for metastases. After SPET/CT (b) the aforementioned finding was attributed to L3-L4 intervertebral disc degeneration (arrow). The second is an 82 years old patient with ductal carcinoma referred for a bone scan because of tumour marker elevation. Like the previous example, suspicious WBS findings were focused on the lumbar spine (arrow head). In this case SPET/CT revealed a large osteolytic lesion at the spinous process of L3 vertebra (arrow) (d).

In order to determine the diagnostic efficacy of each technique, positive and indeterminate findings were summed together. The diagnostic performance of WBS and SPET/CT is presented in Table 3. Single photon emission tomography/CT exhibited higher sensitivity (96.9% vs. 63.1%), accuracy (89.9% vs. 76.7%), positive and negative predictive value (72.4% vs. 53.2% and 98.8% vs. 86.7%, respectively) compared with WBS, while specificity did not differ (87.5% vs. 81.3%).

Treatment plan changes were tailored by SPET/CT results in 23 patients. More specifically, in 18 patients the initiation of chemotherapy, intravenous bisphosphonates or denosumab was decided, while in another 5 local radiotherapy was opted on the basis of low-dose CT manifestations.

Table 3. *Patient-based analysis: diagnostic performance of WBS and SPET/CT.*

Diagnostic performance	WBS % (no)	SPET/CT % (no)	P
Sensitivity	63.1 (41/65)	96.9 (63/65)	<0.001
Specificity	81.3 (156/192)	87.5 (168/192)	ns
Accuracy	76.7 (197/257)	89.9 (231/257)	<0.001
PPV	53.2 (41/77)	72.4 (63/87)	0.011
NPV	86.7 (156/180)	98.8 (168/170)	<0.001

PPV/NPV: positive/negative predictive value; ns: not significant

Lesion-based analysis

The results are summarized in Table 4. Out of 970 lesions located in the central skeleton and detected by imaging modalities or verified during follow-up, 265 (27.3%) were classified as positive and 705 (72.7%) as negative for bone metastases. Another 76 lesions located in the skull or the distal extremities were detected by WBS alone. These were outside the SPET/CT field-of-view and were not included in the paired WBS-SPET/CT statistical comparison. None of the true positive WBS findings in these regions (n=23) was the sole positive lesion in the skeleton.

As shown in Table 4, the sensitivity of SPET/CT was significantly higher than WBS in most skeletal regions, notably in the vertebrae and the pelvis. Single photon emission tomography/CT proved more specific in the vertebral column. The overall accuracy of WBS and SPET/CT per-lesion was 78.1% and 94.4% (P<0.001).

Forty-eight out of 243 (19.8%) lesions detected by low-dose CT were described as predominantly lytic, whereas 195 (80.2%) as sclerotic. Of 262 true positive SPET/CT findings, most were evident on both image components, while 29 (11.1%) only on CT (11 lytic and 18 sclerotic) and 19 (7.3%) only on SPET.

Discussion

We investigated the incremental value of systematic 2-field SPET/CT ("near whole-body", like PET/CT) over conventional planar WBS in a relatively large series of BC patients. The presence of skeletal metastases was confirmed by additional imaging studies and a long period of clinical surveillance (30±24 months, range 12-60 months). During follow-up most of the patients returned in our department for a second or third bone scan (WBS SPET/CT was performed in all of these cases, as in the baseline examination). So, we had the opportunity to observe the evolution of bone lesions initially described as indeterminate (Figure 2). Due to the relatively "indolent" course of bone metastases in many BC patients, sometimes a lengthy surveillance period is needed in order to reach a final conclusion. On the other hand, lesions exhibiting a decline of metabolic activity in the absence of any therapeutic intervention could be safely attributed to benign causes.

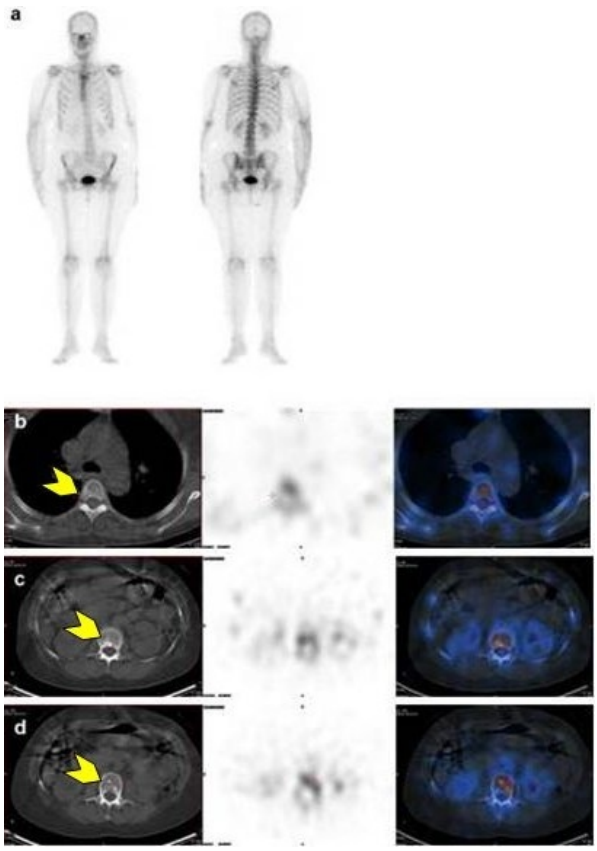

Figure 4. Normal WBS (a) in an asymptomatic 52 years old female referred for a bone scan during her regular follow-up 5 years after the diagnosis of ductal breast carcinoma, stage IIIB at presentation. Single photon emission tomography/CT revealed numerous metastases in the skeleton. Selective images are displayed here, showing an osteolytic lesion at the level of T4 (b, yellow arrow head) and small osteoblastic foci in L1 (c, yellow arrow head) and L2 vertebra (d, yellow arrow head).Local radiotherapy and intravenous bisphosphonates were recommended by the oncologists after SPET/CT results.

According to our results, SPET/CT outperformed WBS in terms of sensitivity, accuracy, PPV and NPV. Specificity was not significantly affected, except for the findings in the spine (Tables 3 and 4). Furthermore, the true extent of metastatic disease in the skeleton, when present, was better revealed by SPET/CT. Moreover, malignant lesions were further characterised by their radiographic appearance as primarily lytic or sclerotic. Both SPET and CT components of the hybrid sys-

Table 4. *Lesion-based analysis: Sensitivity and specificity of WBS and SPET/CT.*

	Sensitivity % (n)			Specificity % (n)		
Skeletal region	**WBS**	**SPET/CT**	**P**	**WBS**	**SPET/CT**	**P**
Vertebrae	39.8 (43/108)	100 (108/108)	<0.001	88.7 (339/382)	94.8 (362/382)	0.043
Ribs	61.1 (22/36)	94.4 (34/36)	0.027	82.2 (74/89)	89.9 (80/89)	ns
Sternum	64.3 (9/14)	100 (14/14)	ns	97.1 (33/34)	97.1 (33/34)	ns
Clavicle	100.0 (2/2)	100.0 (2/2)	ns	97.4.6 (37/38)	100.0 (38/38)	ns
Scapula	44.4 (8/18)	100 (18/18)	0.004	80.0 (12/15)	66.7 (10/15)	ns
Pelvis	36.1 (26/72)	98.6 (71/72)	<0.001	90.4 (104/115)	88.7 (102/115)	ns
Upper humerus	66.7 (2/3)	100 (3/3)	ns	71.4 (10/14)	92.9 (13/14)	ns
Upper femur	16.7 (2/12)	100 (12/12)	0.023	95.7 (22/23)	87.0 (20/23)	ns
Skull	100.0 (5/5)	-	-	100% (8/8)	-	-
Distal extremities	100.0 (18/18)	-	-	100.0 (45/45)	-	-
Total	47.6 (137/288)	98.9 (262/265)	<0.001	89.6 (684/763)	92.6 (653/705)	ns

ns: not significant

tem proved useful, since a number of malignant lesions were detected by only one technique (7% and 11%, respectively). Single photon emission tomography/CT modified WBS interpretation in 74 of 257 patients (28.8%). It succeeded in elucidating uncertain WBS results in 43 out of 60 patients (71.7%), thus avoiding supplementary investigation (Figure 3). More importantly, 42 of 180 (23.3%) normal/unimportant WBS studies turned to positive/suspicious once SPET/CT was inspected. Metastases were verified in 23 and refuted in 19 of these cases (Figure 1). Patient management was modified in 23 patients (8.9%) following SPET/CT results.

The two hybrid systems used in this study belong to the first-generation SPET/CT designs, in which the X-rays tube and detectors are mounted on the gamma-camera gantry. This led to increased CT acquisition time, particularly in the case of the older "Hawkey" construction (Table 2). Bearing in mind the time needed to conclude SPET data collection also, the total duration of the examination was prolonged. In order to reduce total study duration as possible, we used suboptimal angular sampling and frame time settings for SPET acquisition (Table 2). Nevertheless, the quality of SPET images was considered adequate, due to the implementation of resolution recovery in studies performed with the "Infinia" gamma-camera [27] and to the higher sensitivity of our particular "Varicam" model which is equipped with a 5/8-inch crystal. With the current and voltage CT settings used in this study (Table 2) the additional radiation exposure of the patients was relatively low. The average effective dose using "Hawkeye" is reported to be 0.9mSv for a chest CT scan and 1.5mSv for an abdomen-pelvis scan [28]. With "Hawkeye-4" doses are somewhat higher [29]. On the other hand, the inferior quality of obtained CT images, particularly with the "Hawkeye", certainly influenced the diagnostic confidence of the radiologist in interpreting CT studies. Many uncertain and false positive (FP) results could have been avoided by the use of high-quality images as those provided by the second-generation SPET/CT models.

Until now, SPET/CT is considered as a valuable tool to elucidate indeterminate WBS findings, but its systematic use (e.g. in face of a normal planar WBS)is not recommended. Cur-

rent EANM practice guidelines support this notion FAOZI [26]. These beliefs are grounded on the reported high sensitivity but relatively poor specificity of WBS. Indeed, many studies in literature, mostly relying on lesion-based analysis, have pointed out that by the integration of SPET and CT findings in a single fused image a significant number of suspicious WBS can be attributed to benign lesions [17-23]. Consequently, test accuracy is enhanced, mainly due to the improvement of specificity. As regards sensitivity, the incremental value of bone SPET/CT over WBS in cancer patients has not been corroborated. However, some recent studies using novel imaging modalities such as whole-body MRI, ^{18}F-FDG PET, ^{18}F-NaF PET or PET/CT have questioned the alleged high sensitivity of planar WBS [30-34].

The sensitivity and specificity of WBS per-patient was 63.1% and 81.3% in the present study. Respective figures per-lesion were 47.6% and 89.6%. Although specificity is within the reported range so far, sensitivity appears to be lower. As regards conventional bone scan in BC patients, a meta-analysis conducted by Shie et al. in 2008 estimated a 78% pooled sensitivity per-patient (95% CI: 67%-86%) and a pooled specificity of 79% (95% CI: 40%-95%) [35]. However, some of the studies included in this meta-analysis used SPET as an adjunct to planar WBS. Another recent meta-analysis in a similar population by Rong et al. (2013) encompassing studies other than those incorporated in the previous review, reported bone scan sensitivity and specificity in the range of 33%-100% and 55%-100%, respectively [30]. Obviously, the diagnostic performance of WBS in BC seems highly variable in the literature and eventually not incompatible with our results. Apart from image interpretation differences, another explanation for observed inconsistencies between studies could be the variable changes in the metabolic activity of bone lesions induced by therapy. Most lesions with low or absent activity will escape detection from planar imaging, but will be identified by SPET due to the higher contrast achieved by this technique, or by CT which depends on structural abnormalities only. This fact is probably reflected in the findings of the current work where 80% of detected lesions were predominantly sclerotic, probably some of them in the course of a healing process; it is known that most untreated bone metastases from BC are lytic [1, 3]. Actually, 21 patients of our study group were treated with intravenous bisphosphonates at the time of the baseline bone scan. From a clinical point of view, it is important to know the presence of bone metastases irrespective of their activity. Single photon emission tomography/CT offers the opportunity to detect lesions with minimal or no osteoblastic activity, assessing at the same time their response to therapy. Other reasons for the low sensitivity of WBS in this and other studies are the presence of small or pure osteolytic lesions (Figures 2 and 4). The early detection of small skeletal metastases may influence therapeutic decisions, while the identification of destructive lesions in weight-bearing bones may indicate the initiation of local radiotherapy.

Similar to our study design, Palmedo et al. (2014) implemented systematically 2-field SPET/CT after WBS in a series of 211 breast and 97 prostate cancer patients [36]. In their per-patient analysis they reported that with reference to WBS the specificity increased from 79% to 94% and the positive predictive value from 59% to 88% by the use of SPET/CT ($P<0.01$ for both comparisons). As regards sensitivity, they found a slight increase from 91% to 98% ($P>0.05$) in the BC subgroup. There was no significant difference in sensitivity between the two techniques in relation to the number of detected lesions. The discrepancy between the present and Palmedo's study cannot be fully explained. Perhaps it is due to differences in study cohort characteristics, patient treatment status and dissimilar bone scan interpretation criteria. However, it should be noted that Palmedo et al. (2014) recommended the replacement of WBS by whole-body SPET/CT in breast and prostate cancer patients.

Despite its drawbacks, planar WBS remains the imaging modality mostly employed worldwide in the detection of skeletal metastases from various malignancies, because it combines relatively high sensitivity, whole-body survey, low cost and broad availability [37]. Novel imaging methods promise improved diagnostic efficacy over the classic bone scan. Whole-body diffusion-weighted magnetic resonance ima-ging gathers many advantages; its widespread use is hampe-red though by increased cost, limited availability and lack of standardization of measurement parameters [38, 39]. Fluorine-18-FDG PET/CT has probably comparable sensitivity but higher specificity than WBS in BC patients [30, 34]. However, its role is controversial, because of the dependence of ^{18}F-FDG uptake on the sclerotic or lytic appearance of bone lesions and also on cancer histology [40, 41, 42]. So far, ^{18}F-Na-F PET/CT has consistently demonstrated higher sensitivity, specificity and accuracy and probably should replace conventional bone scan where it is available [32, 33, 43-46. Considering costs and accessibility, whole-body bone SPET/CT could be an alternative.

Limitations of the study

a) Although WBS and SPET/CT studies were interpreted separately, a bias in favour of the latter cannot be excluded.

b) The results of the lesion-based analysis should be viewed with caution, as it was not possible to confirm the nature of all detected focal abnormalities, even after additional imaging studies and long follow-up.

c) As already mentioned, the suboptimal quality of CT images produced by the SPET/CT devices used in this study may have somehow influenced our results. A relatively small proportion of patients (19%) was imaged with the "Hawkeye" system, which suffers from low-resolution of CT images and long acquisition time. Image quality was considerably better with the "Hawkey-4" device. Even with the latter, sometimes respiration-related artefacts in the thoracic spine interfered with CT interpretation.

d) The clinical significance of bone metastases discovered early in the course of the disease or the identification of metabolically "quiescent" lesions, is uncertain. Although oncologists of our institution took advantage of SPET/CT results and modified treatment plan in some cases, the impact of this strategy on the final patient outcome could not be validated.

In conclusion, the systematic use of SPET/CT as an adjunct to planar whole body bone scintigraphy improves significantly the diagnostic performance of the method in BC patients. Not only specificity for findings located in the spine, but also the overall sensitivity and accuracy of the test is enhanced, with important consequential implications for patient management. This benefit outbalances the relatively long examination time required by SPET/CT systems and the small additional radiation delivered to the patient. Two-field bone SPET/CT should become a routine procedure and eventually could replace planar whole body bone scan for the assessment of the central skeleton, at least in BC patients.

The authors declare that they have no conflicts of interest.

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Marble of Asclepius and his daughter Hygeia, Vatican Museums, Rome.