

## Multi-field-of-view SPECT is superior to whole-body scanning for assessing metastatic bone disease in patients with prostate cancer

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### ABSTRACT

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**Aim.** The aim of this study was to compare the diagnostic performance of whole-body bone scintigraphy (WBS) and multi-field-of-view single photon emission tomography (multi-FOV SPECT) with <sup>99m</sup>Tc-oxidronate (<sup>99m</sup>Tc-HDP) in patients with prostate cancer (PCa).

**Methods.** In a prospective study, WBS and SPECT acquisitions were performed in 194 patients with histologically confirmed PCa and serum prostate-specific antigen (PSA) levels above 10 ng/mL. Scans obtained using the two modalities were interpreted separately. Clinical and biochemical follow-up, radiological studies and biopsies served as benchmarks for the assessments. The impact of PSA level on WBS and SPECT results was also evaluated.

**Results.** The patient-based sensitivity, specificity, accuracy, PPV and NPV values of SPECT examinations were higher than those of WBS, especially in patients with serum PSA levels <40 ng/mL.

**Conclusion.** Multi-FOV SPECT proved to be more sensitive and specific than WBS in detecting bone metastases in PCa patients.

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### Introduction

Prostate cancer (PCa) is the most common malignancy in men. The most frequent sites of metastatic spread of PCa are the lymph nodes and bone; bone metastases are present in 90% of patients who die of this disease. The extent of osseous metastatic disease in PCa has been identified as an independent prognostic factor<sup>1</sup>. Normograms based on prostate-specific antigen (PSA) levels, Gleason score at biopsy, and clinical stage at presentation have been generated for pre-treatment risk stratification and for prognosis of local recurrence or distant metastatic spread<sup>2</sup>. Whole-body scintigraphy (WBS) has been found to be the most widely used method for evaluating skeletal metastases of PCa among patients with high-risk disease (i.e., PSA level >10 to 20 ng/mL and/or Gleason score >7), or those with elevated serum alkaline phosphatase levels, bone pain, or equivocal bone lesions on other imaging modalities<sup>3</sup>. Single photon emission computed tomography (SPECT) has been reported to have higher diagnostic accuracy than WBS for detecting malignant bone involvement and it also allows straightforward comparisons with other tomography-based techniques such as computed tomography (CT) and magnetic resonance imaging (MRI)<sup>4</sup>. However, SPECT imaging tends, in general, to be used in addition to WBS to evaluate equivocal focal uptakes<sup>5,6</sup>. In view of these considerations, the purpose of this study was 2-fold: first to evaluate the diagnostic accuracy of multi-field-of-view (multi-

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FOV) SPECT imaging of the axial skeleton in detecting bone metastases in patients with PCa, and second to compare SPECT with WBS examination in this population.

## Materials and methods

### Patients

WBS and SPECT scans were performed on the same day in 194 consecutive patients (mean age,  $72.4 \pm 9.7$  years) with histologically confirmed PCa and serum PSA  $>10$  ng/mL. This prospective study had local ethics committee approval, and all patients gave their written consent to take part in it.

### Imaging studies

Planar images of the entire skeleton (i.e., WBS) were acquired 2.5 hours after intravenous injection of 740 MBq of  $^{99m}\text{Tc}$ -oxidronate (TechneScan<sup>®</sup> HDP; Mallinkrodt Schweiz AG, Switzerland) using a dual-head camera (E-CAM; Siemens, Germany) equipped with LEHR collimators (scan speed 20 cm/min; matrix  $1024 \times 256$ ). A SPECT scan of the entire axial skeleton was performed after the WBS acquisition using the same dual-head gamma camera. The SPECT study consisted of 3 to 4 transaxial FOV tomographic acquisitions (from the vertex of the skull to mid femur). Sixty-four images were obtained for each tomographic acquisition on a  $128 \times 128$  matrix for 18 seconds, over a  $360^\circ$  arc, following a body-contouring profile. Raw data were reconstructed on the E-soft workstation (Siemens, Germany) using a dedicated protocol with a 3-dimensional iterative reconstruction algorithm (3D-OSEM: 8 subsets, 10 iterations, post-filtration by a Gaussian function with cut-off = 8 mm). Reconstructed data were automatically combined on the basis of the bed position in order to obtain a single tomographic series of the whole body. This combined series was then used to generate transaxial, coronal and sagittal slices of the skeleton and to create maximum intensity projection 3D images for clinical evaluation. Two board-certified nuclear medicine physicians evaluated all scans independently; disagreements were resolved by consensus. A scan showing normal skeletal distribution of  $^{99m}\text{Tc}$ -oxidronate was classified as normal. Any abnormal uptake of the radiopharmaceutical was classified as benign, malignant or equivocal, depending on its location and characteristics. Pelvic lesions were classed as benign when they were located around joints and as malignant otherwise. Vertebral lesions were classed as benign when they appeared as hot osteophytes or when they were located around joints, and as malignant when they involved the posterior portion of the vertebral body and peduncle, or the vertebra extensively. Rib lesions were classed as malignant when they appeared as elongated areas of up-

take and as benign (fractures) when they involved several ribs vertically. Any other abnormal radiopharmaceutical uptake was rated as equivocal. Equivocal lesions on WBS and/or SPECT were immediately evaluated by CT and/or MRI and diagnosed as benign when degenerative changes, fractures, or other benign bone lesions, such as cysts, were detected at the corresponding locations. All patients were monitored for at least 11 months (mean  $22 \pm 9$ ; range, 11-34 months), and their medical records were reviewed in an attempt to obtain a final diagnosis. The final diagnosis was based on clinical examinations, serial PSA measurements, repeated WBS or other imaging procedures and, if clinically warranted, bone biopsy.

### PSA measurement

A serum sample was obtained just before  $^{99m}\text{Tc}$ -oxidronate injection to measure PSA in a chemiluminescent assay on the Immulite 2000 fully automated platform.

### Statistical analysis

In a patient-based analysis, in which the final diagnosis was used as the benchmark, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in the diagnosis of bone metastases were calculated for both imaging modalities. Sensitivity, specificity, PPV and NPV were also evaluated for WBS and SPECT in a lesion-based analysis. In the statistical analysis we analyzed the results twice: categorizing the equivocal reading as suggestive for malignancy and, again, categorizing the equivocal reading as benign. The McNemar test was used to compare the detection of bone metastases by planar WBS and by SPECT. Distribution of serum PSA in patients with and without bone metastases at final diagnosis, WBS and SPECT were compared using the Mann-Whitney U-test. The chi-square test was used to compare the detection rate obtained with WBS and SPECT in patients with different PSA levels (10-20, 20-40, 40-60 and  $>60$  ng/mL). A *P* value  $<0.05$  was considered significant.

## Results

### Bone scan and SPECT results

*Patient-based analysis.* Sixty-eight of the 194 patients included in the study were found, on the basis of imaging findings, biopsy and clinical follow-up, to have bone metastases. Bone SPECT detected positive or equivocal findings in 61 and 4 patients, respectively. In the remaining 3 patients, the SPECT findings were classified as benign but the presence of bone metastases was established during follow-up. WBS detected positive or equivocal findings in 54 and 5 of 68 patients (all with positive SPECT scans) and tested negatively in 9 patients with

proved bone metastases (6 having positive SPECT). One hundred and twenty-six patients had no clinical or imaging evidence of metastatic spread to bone at the end of the follow-up period. In just one of these patients, the observation of  $^{99m}\text{Tc}$ -oxidronate uptake on SPECT was a false-positive result (as subsequently shown by benign MRI findings at the site of uptake and by the clinical behavior at follow-up). Of the remaining 125 patients, 121 had normal scans or benign lesions on SPECT examination, while 4 had equivocal lesions on SPECT with benign CT or MRI findings in the corresponding sites. Three of the 126 patients had false-positive WBS, as determined at follow-up and by detection of benign CT ( $n = 2$ ) or MRI ( $n = 1$ ) findings in the relative sites of  $^{99m}\text{Tc}$ -oxidronate uptake. One hundred and ten of the remaining 123 patients had normal findings or benign lesions on WBS, while 13 had equivocal lesions on WBS with benign CT and/or MRI findings in the corresponding sites. Compared with WBS, the bone SPECT examination showed significantly superior patient-based sensitivity, specificity and accuracy (Table 1 and Figure 1). Using the McNemar comparison test, the sensitivity and specificity of SPECT were significantly better than those of WBS when equivocal readings were categorized as malignant or as benign ( $P < 0.01$  in all cases).

**Lesion-based analysis.** Five patients had extensive disease with countless metastases on both WBS and SPECT and could therefore not be included in the lesion-based analysis. Two of these 5 patients with diffuse bone metastases who were excluded from the lesion-based analysis had distal femur metastases detected on WBS but outside the SPECT field of view. None of the other enrolled patients had metastases outside the SPECT field of view. Overall, 163 metastases were found in 63 patients; bone SPECT findings were positive in 157, equivocal in 3, and negative in 3 patients. Overall, 147 of 163 bone metastases were positive ( $n = 135$ ) or equivocal ( $n = 12$ ) at WBS examination. Consequently, 13 metastases were positive on SPECT but not on WBS. The sensitivity of SPECT was significantly higher than that of WBS in the lesion-based analysis, but the specificity was not when equivocal readings were considered as non-malignant (Table 2 and Figure 1). Using the McNemar comparison test, the sensitivity of SPECT was signifi-

cantly better than that of WBS when equivocal readings were categorized as malignant ( $P < 0.05$ ) or as benign ( $P < 0.01$ ). The specificity of SPECT was significantly better than that of WBS when equivocal readings were categorized as benign ( $P < 0.01$ ) but not when they were categorized as malignant.

#### Bone imaging and PSA level

Patients with bone metastases identified by SPECT had significantly lower PSA levels than those with bone metastases revealed by conventional WBS (Table 3). The sensitivity of WBS and SPECT did not differ in patients with PSA levels exceeding 40 ng/mL but the SPECT detection rate was significantly better in patients with lower PSA values, particularly those with PSA between 10 and 20 ng/mL (Table 3 and Figure 2).

## Discussion

The early detection or exclusion of bone metastases has a considerable impact on the clinical management of patients with PCa. From a therapeutic point of view, newly diagnosed patients with localized disease and no metastases may benefit from radical localized curative treatment; by contrast, in patients already harboring metastases at diagnosis, early initiation of androgen deprivation and bisphosphonate therapy is the most appropriate course, avoiding unnecessary surgery or radiotherapy. Thus, the primary aim of scintigraphic assessment in patients with PCa is to detect or exclude the presence of bone metastases as early as possible<sup>7</sup>. In the current prospective study, bone SPECT was found to be more sensitive than WBS, as reflected by its detection of 13 metastases missed by WBS alone. Identification of malignant bone involvement by SPECT (but not WBS) led to modification of the case management in 6 patients. The superiority of bone SPECT over WBS in detecting bone metastases was previously reported<sup>8</sup>. However, previous studies have generally tended to use a single SPECT view, providing tomographic data for a limited skeletal region, whereas few patients have been submitted to several SPECT views with prolonged acquisition protocols<sup>9</sup>. In our study, multi-FOV SPECT

**Table 1 - Diagnostic performance of WBS and SPECT: patient-based analysis**

Bone metastases (final diagnosis)	Confirmed (68 patients)			Excluded (126 patients)			Interpretation*				
	M	E	B/N	M	E	B/N	Sens (%)	Spec (%)	Acc (%)	PPV (%)	NPV (%)
Imaging classification											
WBS	54	5	9	3	13	110	86 (79)	87 (89)	84 (87)	78 (83)	94 (93)
SPECT	61	4	3	1	4	121	95 (89)	96 (99)	95 (96)	93 (98)	97 (98)

WBS, whole-body scintigraphy; SPECT, single photon emission tomography; M, metastases; E, equivocal; B/N, benign/negative; Sens, sensitivity; Spec, specificity; Acc, accuracy; PPV, positive predictive value; NPV, negative predictive value.

\*Normal and benign interpretation was considered nonmalignant. Equivocal and malignant interpretation was considered malignant. In parentheses, results analysis with normal, benign, and equivocal interpretation being considered nonmalignant.

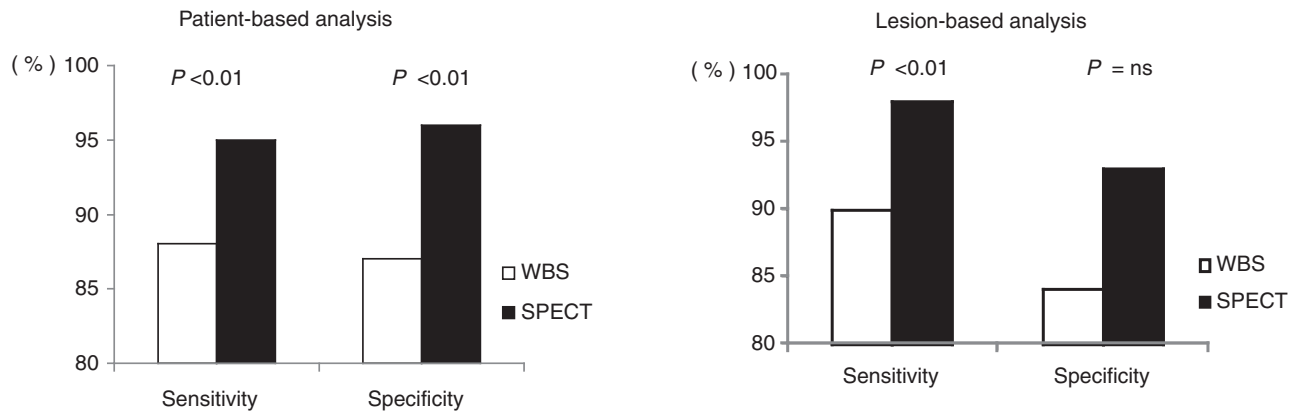


Figure 1 - Patient-based (left) and lesion-based (right) analysis of the sensitivity and specificity of WBS and SPECT (equivocal readings were considered as malignant).

**Table 2 - Diagnostic performance of WBS and SPECT: lesion-based analysis**

Bone metastases (final diagnosis)	Confirmed (163 lesions)			Excluded (82 lesions)			Interpretation*				
	M	E	B/N	M	E	B/N	Sens (%)	Spec (%)	Acc (%)	PPV (%)	NPV (%)
WBS	135	12	16	2	11	69	90 (82)	84 (97)	88 (88)	92 (98)	81 (71)
SPECT	157	3	3	3	2	77	98 (96)	93 (96)	97 (96)	97 (98)	96 (96)

WBS, whole-body scintigraphy; SPECT, single photon emission tomography; M, metastases; E, equivocal; B/N, benign/negative; Sens, sensitivity; Spec, specificity; Acc, accuracy; PPV, positive predictive value; NPV, negative predictive value.

\*Normal and benign interpretation was considered nonmalignant. Equivocal and malignant interpretation was considered malignant. In parentheses, results analysis with normal, benign, and equivocal interpretation being considered nonmalignant.

**Table 3 - Patients' PSA levels in relation to WBS and SPECT findings**

Bone metastasis	Confirmed	Excluded	P
WBS	34.6 (15.4-206) ng/mL	15.3 (10-42.5) ng/mL	<0.01
SPECT	26.4 (10-206) ng/mL	12.5 (10-38.7) ng/mL	0.03
P	<0.01	ns	

WBS, whole-body scintigraphy; SPECT, single photon emission tomography.

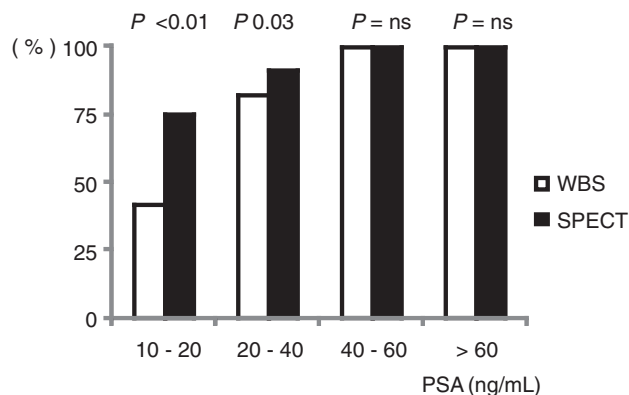


Figure 2 - Sensitivity of WBS and SPECT according to PSA concentration.

views of the axial skeleton were systematically acquired. Images were processed with an iterative algorithm rather than standard filtered back-projection, as this algorithm provides better noise properties and higher contrast and resolution<sup>10-12</sup>. Patient-based analysis showed that the sensitivity and PPV increased from 79-87% and 83-78% on WBS to 90-95% and 93-98% on multi-FOV SPECT, without any reduction in specificity. Lesion-based analysis was limited by the exclusion of 5 patients with diffuse skeletal involvement; SPECT, however, showed a significantly better sensitivity in the lesion-based analysis too (83-90% vs 96-98%); if equivocal readings were classified as benign the SPECT specificity significantly improved compared with that of WBS (84% vs 94%). It is well known that aspecific uptake in nonmalignant bone lesions negatively impacts on the specificity of bone scans; equivocal uptake has always been considered a limitation of bone scintigraphy, often necessitating further examinations, such as planar X-ray, CT or MRI, in order to differentiate malignant from nonmalignant lesions. Therefore, to obtain increased sensitivity without a reduction in specificity is an advantage in the management of these patients, making it possible to avoid further examinations and modifying the case management in a small but not negligible proportion of patients. The morphological char-

acteristics of bone lesions can also make an important contribution in the diagnostic analysis of bone scans, mainly by allowing the detection of cortical alterations and soft-tissue spreading; for these reasons, the implementation of hybrid modalities, such as SPECT/CT, is expected to further increase the diagnostic value of bone scans in the near future<sup>13</sup>. Multi-FOV SPECT imaging requires double-head gamma cameras and SPECT technology. These are widely used in the daily nuclear medicine practice; moreover, software for iterative reconstruction is available in modern workstations without any additional cost. However, the total acquisition time is increased from 15 to 43.30 minutes, adding 3 FOV SPECT views to a whole-body bone scan (64 images for 18 seconds over a 360° arc = 9.30 minutes for each view). This logistic issue could prevent the use of multi-FOV SPECT as a routine acquisition modality, particularly in small-sized nuclear medicine departments. As per our present data, performing multi-FOV SPECT acquisitions in patients with PCa and PSA levels below 40 ng/mL could allow the reduction of the gamma-camera workload while maintaining the diagnostic advantages of multi-FOV SPECT in this challenging patient subgroup<sup>14</sup>. Additionally, multi-FOV bone SPECT imaging will be mandatory to compare bone scan with whole body MRI and PET/CT examinations with <sup>18</sup>F-fluoride, <sup>18</sup>F-fluorocholine or <sup>11</sup>C-choline, now emerging as important techniques in the diagnosis of PCa bone metastases<sup>15-17</sup>.

## Conclusions

<sup>99m</sup>Tc-oxidronate multi-FOV SPECT was found to be a sensitive and specific tool for detecting bone metastases in patients with PCa and to perform better than WBS examination in this clinical field. Our data suggest that multi-FOV SPECT could play an important role in the assessment of patients with prostate cancer, especially when PSA levels are below 40 ng/mL. The specificity of bone SPECT is likely to improve further with the introduction of SPECT/CT techniques into clinical practice.

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