Original Study

^{68}Ga-PSMA PET/CT Replacing Bone Scan in the Initial Staging of Skeletal Metastasis in Prostate Cancer: A Fait Accompli?

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Abstract

We compared the findings of technetium-99m–10-metacyloyloxydecyl dihydrogen phosphate (^{99m}Tc-MDP) bone scintigraphy and ^{68}Ga–prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) in 113 patients who underwent initial skeletal staging for prostate cancer. ^{68}Ga-PSMA PET/CT was found to be better than ^{99m}Tc-MDP bone scintigraphy because of ability to additionally detect lytic and bone marrow lesions. ^{68}Ga-PSMA PET/CT could potentially replace bone scan for initial staging of skeletal metastases.

Purpose: ^{68}Ga ligands targeting prostate-specific membrane antigen (PSMA) are rapidly emerging as a significant step forward in the management of prostate cancer. PSMA is a type II transmembrane protein with high expression in prostate carcinoma cells. We prospectively evaluated the use of ^{68}Ga-PSMA positron emission tomography/computed tomography (PET/CT) in patients with prostate cancer and compared the results to those for technetium-99m (^{99m}Tc)-10-metacyloyloxydecyl dihydrogen phosphate (MDP) bone scintigraphy (BS). **Patients and Methods:** A total 113 patients with biopsy-proven prostate cancer referred for standard-of-care BS were prospectively enrolled onto this study. ^{68}Ga-PSMA PET/CT was performed after BS. Metastasis diagnosed on each technique was compared against a final diagnosis based on CT, magnetic resonance imaging, skeletal survey, clinical follow-up, and histologic correlation. **Results:** Ninety-one bone lesions were interpreted as bone metastases in 25 men undergoing ^{68}Ga-PSMA PET/CT compared to only 61 lesions in 19 men undergoing ^{99m}Tc-MDP BS. Of the 7 bone scans that missed skeletal metastases, 54% of these missed lesions were due to either marrow or lytic skeletal metastases. The median standardized uptake value in all malignant bone lesions was 13.84. ^{68}Ga-PSMA PET/CT showed significantly higher sensitivity and accuracy than BS (96.2% vs. 73.1%, and 99.1% vs. 84.1%) for the detection of skeletal lesions. For extraskeletal lesions, ^{68}Ga-PSMA PET/CT showed an additional 96 unexpected lesions with a median standardized uptake value of 17.6. **Conclusion:** ^{68}Ga-PSMA PET/CT is superior to and can potentially replace bone scan in the evaluation for skeletal metastases in the clinical and trial setting because of its ability to detect lytic and bone marrow metastases.

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Table 1 Age Distribution, Gleason Scores, and PSA of Study Participants

Characteristic	Value
Age (Years)	
Mean ± SD	66.65 ± 7.98
Age Range	43-88
<65 years	40 (35.4)
≥65 years	73 (64.6)
Gleason Score	
<7	10 (8.8)
7	42 (37.2)
>7	61 (54.0)
PSA	
<10 ng/mL	15 (13.3)
10-20 ng/mL	13 (11.5)
>20 ng/mL	85 (75.2)

Data are presented as n (%) unless otherwise indicated.
Abbreviation: PSA = prostate-specific antigen.

Introduction

Prostate cancer is among the foremost cancers faced by men and is among the leading causes of cancer-related deaths worldwide.[1,2] Early detection through screening and resultant treatment at an organ-confined stage results in an improvement of the expected 5-year survival to 100%.[3]

Accurate early staging of prostate cancer is crucial to patient risk stratification. The accurate detection of disease, either confined to the prostate gland or with extraglandular spread to the lymph nodes or skeleton, is essential in determining the most appropriate patient-specific therapeutic strategy.[4,5]

Imaging modalities including computed tomography (CT), magnetic resonance imaging, and ultrasound play an important role in the initial staging of prostate cancer. However, the optimal imaging modality in the initial staging of prostate cancer is still under debate because of the variable sensitivity and specificity of these imaging modalities.[6,7]

Bone scintigraphy (BS) in initial staging is reserved for patients with elevated prostate-specific antigen (PSA) and an increased Gleason score. Although bone scan may have good sensitivity for the detection of osteoblastic skeletal metastases, it has reduced specificity.[8]

Positron emission tomography (PET)/CT offers increased image resolution and diagnostic confidence as compared to single-photon imaging with a gamma camera. Some of the PET/CT tracers used in the staging of prostate cancer include ^{18}F-NaF and ^{18}F/^{11}C-choline. ^{18}F-NaF demonstrates increased sensitivity for the detection of skeletal metastases but is not informative regarding soft tissue involvement. ^{18}F-flouro-choline has demonstrated low specificity and sensitivity in the setting of low PSA.[9]

^{68}Ga ligands targeting prostate-specific membrane antigen (PSMA) are rapidly emerging as a significant step forward in the management of prostate cancer. PSMA is a type II transmembrane protein with high expression in prostate carcinoma cells.[10] PSMA overexpression by prostate cancer cells is further enhanced in increasing tumor grade and metastases, and by hormone refractoriness.[11,12]

The clinical utility of ^{68}Ga-PSMA PET/CT has been reported in limited-stage disease as well as suspected recurrence. Accurate exclusion of extraprostatic disease is essential in treatment planning in prostate-limited disease before undergoing localized therapy. ^{68}Ga-PSMA has been found to be superior to conventional imaging in the identification nodal disease in patients with moderate- to high-risk prostate cancer.[13] However, there is limited literature on the clinical utility of ^{68}Ga-PSMA PET/CT in the assessment for skeletal metastases in the primary staging of prostate cancer.

We prospectively evaluated the diagnostic performance of ^{68}Ga-PSMA-11 PET/CT in patients with high-risk prostate cancer and compared the results with those for technetium-99m (^{99m}Tc)−10-metacyloyloxydecyl dihydrogen phosphate (MDP) BS.

Table 2 ^{99m}Tc-MDP Bone Scan Findings of Study Participants

Characteristic	N (%)	SUV_{max} (Mean ± SD)
Finding		
Positive	30 (26.5)	
Negative	83 (73.5)	
Total no. of skeletal lesions	61	
^{68}Ga-PSMA PET/CT		
Positive	111 (98.2)	
Negative	2 (1.8)	
Localized disease only	69 (61.1)	12.6 ± 9.6
Metastatic disease	42 (37.2)	14.52 ± 10.6
Skeletal metastatic disease	25 (22.1)	12.75 ± 9.4
Total skeletal lesions	91	14.4 ± 13.3
Additional soft tissue lesions	96	17.6 ± 13.1
Soft tissue disease only	14 (12.3)	16.8 ± 11.9

Abbreviations: CT = computed tomography; MDP = 10-metacyloyloxydecyl dihydrogen phosphate; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; SUV_{max} = standardized maximum uptake value; ^{99m}Tc = technetium-99m.

Patients and Methods

The study was approved by the local research ethics committee.

One hundred thirteen men (mean age, 66.65 years; range, 43-88 years) with biopsy-proven prostate cancer referred for standard-of-care BS were prospectively enrolled onto this study. Exclusion criteria included no histology result and having started any prostate cancer−related therapy.

BS was performed as per standard protocol.[14] Patients underwent whole-body, static, and lumbar single-photon emission computed tomography (SPECT) imaging 2 to 3 hours after injection of 30 mCi ^{99m}Tc-MDP. Additional SPECT/CT images were acquired as indicated for localization of uncertain uptake.

^{68}Ga-PSMA-11 was prepared in house as previously described by us.[15] Whole-body PET/CT images from vertex to midthigh were acquired on a Biograph 40 PET/CT scanner (Siemens, Munich, Germany) 60 minutes after injection of ^{68}Ga-PSMA-11. The median injected activity was 3.7 mCi (range, 1.24-8.25 mCi). Noncontrast low-dose CT scans were simultaneously acquired for attenuation correction and anatomic localization.

Table 3 Diagnostic Performance of Bone Scan and PSMA PET/CT in Detecting Skeletal Metastasis

Characteristic	Positive (N = 26), N (%)	Negative (N = 87), N (%)	Total (N = 113)	χ^2	*P*
Bone Scan					
Positive	19 (63.3)	11 (36.7)	30	37.491	<.001*
Negative	7 (8.4)	76 (91.6)	83		
PSMA PET/CT					
Positive	25 (100.0)	0	25	107.419	<.001*
Negative	1 (1.1)	87 (98.9)	88		

Abbreviations: CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.
*Statistically significant at $P < .05$.

Image Analysis

Using both modalities, we counted a maximum of 5 skeletal lesions. Additionally on the ^{68}Ga-PSMA-11 PET/CT scans, we also counted a maximum of 5 soft tissue metastases.

Two experienced nuclear physicians unaware of the results of the studies independently reviewed either the bone scan or PET/CT studies. Focal uptake greater than background and not in keeping with physiologic uptake was deemed to be positive for prostate cancer involvement on ^{68}Ga-PSMA-11 PET/CT. BS was interpreted as per standard guidelines.[14] Disagreement was resolved by consensus.

Metastasis diagnosed on each of these techniques was compared against a final diagnosis based on histologic correlation and clinical follow-up.

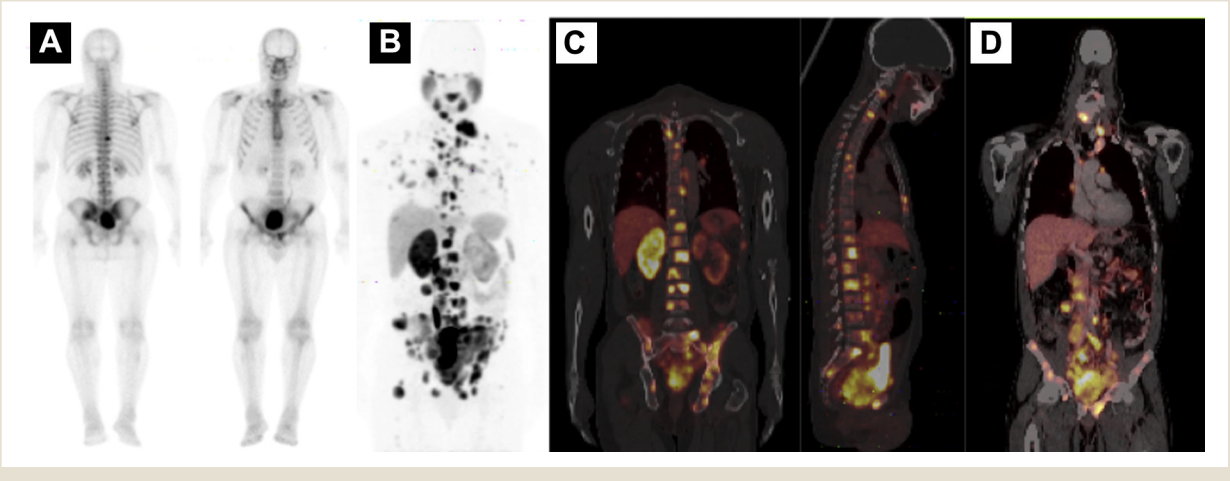
Statistical Analyses

Descriptive statistics of the demographic and clinical characteristics of the study population were done. A 2-by-2 contingency table was used to obtain the sensitivity, specificity, positive predictive value, and negative predictive value as well as the accuracy of ^{68}Ga-PSMA-11 PET/CT and BS for the detection of skeletal metastases. The diagnostic performances of the 2 imaging modalities at different Gleason scores of < 7, 7, and ≥ 7 were determined. Similar evaluation was done for the diagnostic performances of the 2 imaging modalities at different PSA levels (<10, 10-20, and > 20 ng/mL) as well as their performances in different groups depending on age at time of diagnosis: < 65 years and ≥ 65 years. The diagnostic performances for the entire cohorts of ^{68}Ga-PSMA-11 PET/CT and BS for the detection of bone metastases were compared by chi-square test. Chi-square test was also used to test if any significant difference existed in tests' abilities to detect skeletal metastases at different Gleason scores and PSA levels as well as in patients in different age groups. The significance level was set at $P < .05$. Statistical analysis was done by SPSS Statistics 21.0 (IBM, Armonk, NY).

Results

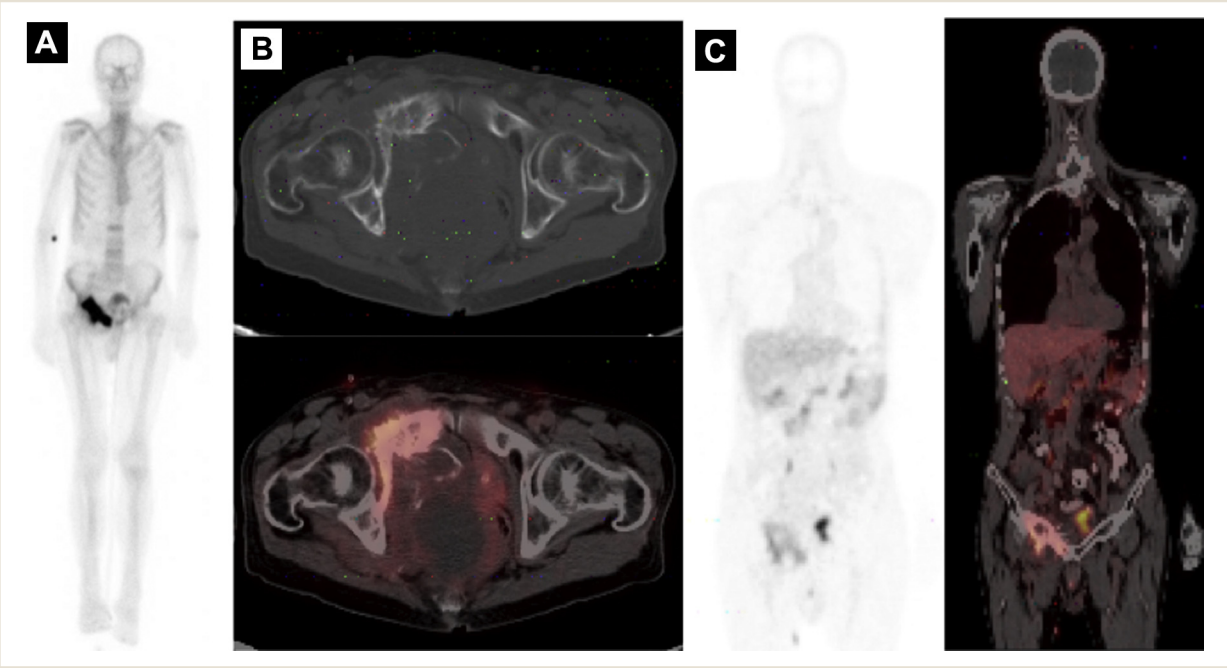
One hundred eleven patients (98.2%) demonstrated positive uptake for prostate cancer on ^{68}Ga-PSMA-11 PET/CT, with only 2 patients not demonstrating uptake despite histology demonstrating prostate cancer involvement. Patient and lesion characteristics are

Figure 1 Patient With Single Osteoblastic Skeletal Lesion in Thoracic Vertebrae. (A) Bone Scan of 58-Year-Old Man With Gleason 4 + 5 Disease Demonstrated Single Osteoblastic Skeletal Lesion in Thoracic Vertebrae. ^{68}Ga-PSMA-11 PET/CT Maximum Intensity Projection (B) and Fused Coronal and Sagittal Images (C, D) Demonstrated Widespread Skeletal and Nodal Lesions, Which Were Not Visualized on Bone Scan, Which is Why ^{68}Ga-PSMA PET/CT Should Replace Bone Scan



Abbreviations: CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

Figure 2 Patient With Pelvic Osteoblastic Skeletal Metastases. (A) Bone Scan of 73-Year-Old Man With Gleason 5 + 5 Disease Demonstrated Pelvic Osteoblastic Skeletal Metastases. ^{68}Ga-PSMA-11 PET/CT Pelvic CT Bone Window and PET/CT Fused Axial (B) and Coronal PET and PET/CT Fused (C) Images Demonstrated Low-Grade Tracer Uptake in Pelvic Skeletal Lesion, Less Than Liver Uptake, Which was Deemed Negative



Abbreviations: CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

listed in Table 1. Sixty-nine (61.1%) of the ^{68}Ga-PSMA-11 PET/CT scans demonstrated prostate-confined disease, whereas 42 (37.16%) demonstrated metastatic disease. A total of 91 bone lesions were interpreted as bone metastases in the 25 men who underwent ^{68}Ga-PSMA-11 PET/CT, compared to only 61 lesions in 19 men on BS. The median maximum standardized uptake value in all malignant bone lesions was 13.84 (Table 2).

^{68}Ga-PSMA-11 PET/CT was positive for skeletal metastases in 7 (8.4%) of the negative BS, whereas 11 (36.7%) of the positive BS were negative by ^{68}Ga-PSMA-11 PET/CT (Table 3; Figures 1, 2, and 3). ^{68}Ga-PSMA-11 PET/CT showed significantly higher sensitivity and accuracy than BS (96.2% vs. 73.1%, and 99.1% vs. 84.1%) for the detection of skeletal lesions (Table 4).

For extraskeletal lesions, ^{68}Ga-PSMA-11 PET/CT showed 96 unexpected metastatic lesions with a mean standard uptake value of 17.6 (Table 2).

Ten patients (8.8%) had a Gleason score of < 7, whereas 42 (37.2%) and 61 (54.0%) had Gleason scores of 7 and ≥ 7, respectively. A total of 13.3% of patients had PSA < 10 ng/mL, whereas 11.5% and 75.2% presented with PSA 10 to 20 ng/mL and > 20 ng/mL, respectively. A total of 30 bone scans (26.5%) were positive for skeletal metastases on BS, whereas 83 (73.5%) were negative (Table 2).

Discussion

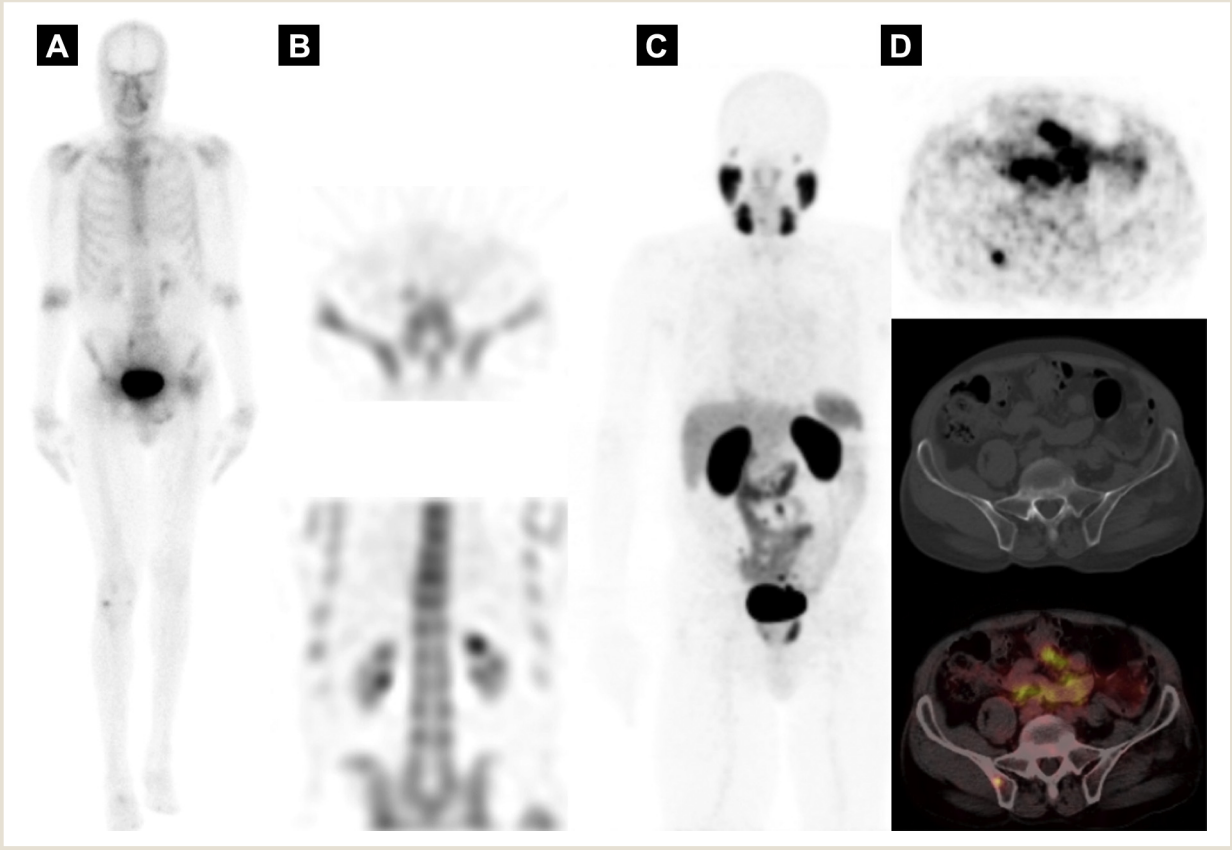
PET/CT has demonstrated higher image resolution and diagnostic confidence compared to gamma imaging; however, this comes at a higher cost. In a resource-constrained setting, it may not be feasible to do a ^{68}Ga-PSMA PET/CT study in all patients with prostate cancer. BS is recommended as part of an initial assessment in patients with intermediate- to high-risk prostate cancer to exclude skeletal metastases.[16,17] We prospectively aimed to identify subsets of patients who may benefit from a ^{68}Ga-PSMA-11 PET/CT study as part of their routine baseline imaging.

In a retrospective series, Pyka et al[18] demonstrated a higher ^{68}Ga-PSMA sensitivity and specificity compared to bone scan of 100% and 100% versus 71.4% and 65.2%, respectively, for the detection of skeletal metastases in the initial staging of prostate cancer, which was similar to our findings. Similarly, Thomas et al,[19] in a study population comprising patients being assessed for appropriateness for radium dichloride therapy, demonstrated that ^{68}Ga-PSMA was superior to BS in the detection of skeletal metastases in prostate cancer, with ^{68}Ga-PSMA detecting nearly double the amount of skeletal lesions compared to BS. Our study confirmed similar results even when having limited lesions to 5.

Age is one of the risk factors in prostate cancer.[20] Patients with onset of prostate cancer before age 65 have a higher risk of having genetic mutations that may confer a risk of more aggressive prostate cancer.[21-24]

Six (15%) of 40 patients aged < 65 presented had skeletal metastatic disease, whereas 20 patients (27.4%) aged ≥ 65 presented with metastatic disease. BS missed 2 patients with skeletal metastatic disease in the group aged < 65 compared to 5 patients aged ≥ 65 (Tables 5 and 6). ^{68}Ga-PSMA-11 PET/CT outperformed BS, with a

Figure 3 Uptake for Osteoblastic Skeletal Metastases. (A) Whole-Body Bone Scan Image of 54-Year-Old Man With Gleason 4 + 4 Disease and (B) Axial and Coronal SPECT Images Did Not Demonstrate Uptake Typical for Osteoblastic Skeletal Metastases. ^{68}Ga-PSMA PET/CT Maximum Intensity Projection Image (C) and Axial PET (D) PET, CT, and Fused PET/CT Image Demonstrated Marrow Metastases in Right Ilium



Abbreviations: CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; SPECT = single-photon emission computed tomography.

higher sensitivity and accuracy of 100% and 100%, versus 66.7% and 82.5%, respectively, in the < 65 year age group (Figure 1, Table 6).

Various risk classification systems have been developed in an attempt to risk-stratify prostate cancer patients before therapy. Some of the risk factors used include PSA and Gleason score.[25,26] The majority of our patients presented with Gleason score ≥ 7. Of those patients with Gleason score < 7, none had Gleason score < 6. Only a single patient within this cohort presented with skeletal metastases, whereas BS did not miss any skeletal metastases. The low yield for skeletal metastases in this patient cohort is not surprising and is in keeping with what has been described in the literature.[27]

^{68}Ga-PSMA-11 PET/CT had a significant impact in the Gleason ≥ 7 group (Table 7) and was able to correctly reclassify 10 false-positive and 7 false-negative findings on BS (Table 8). ^{68}Ga-PSMA-11 PET/CT did demonstrate a single false-negative finding within this group, however. It was a patient with Gleason score 10 on histology with pelvic bone metastases noted on bone scan that demonstrated low-grade tracer uptake on PET/CT that was deemed negative (Figure 2). Although cellular PSMA expression is increased with increasing prostate cancer aggressiveness, it is anticipated that with higher Gleason scores, there may be a down-regulation of PSMA cellular expression as cells become more poorly differentiated.[11,28]

Skeletal metastases occur less frequently in patients with PSA < 10 ng/mL; an increasing detection rate of skeletal metastases is expected with rising PSA value (Table 9).[29-31] Fifteen patients (13.2%) presented with PSA < 10 ng/mL; BS missed skeletal metastases in only a single patient in this group while incorrectly assessing 4 patients as

Table 4 Accuracy of Bone Scan and PSMA PET/CT in Detecting Skeletal Metastasis

Evaluation	Bone Scan (%)	PSMA PET/CT (%)
Sensitivity	73.1	96.2
Specificity	87.4	100.0
Positive predictive value	63.3	100.0
Negative predictive value	91.6	98.9
False positive	12.6	0.05
False negative	26.9	3.8
Accuracy	84.1	99.1

Abbreviations: CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

Table 5 Diagnostic Performance of Scans in Detecting Skeletal Metastasis by Age Group

Characteristic	Positive (N = 26), N (%)	Negative (N = 87), N (%)	Total (N = 113)	χ^2	*P*
Age <65 Years					
Bone Scan					
Positive	4 (44.4)	5 (55.6)	9	7.897	.005*
Negative	2 (6.5)	29 (93.5)	31		
Total	6	34	40		
PET/CT					
Positive	6 (100.0)	0	6	40.000	<.001*
Negative	0	34 (100.0)	34		
Total	6	34	40		
Age ≥65 Years					
Bone Scan					
Positive	15 (71.4)	6 (28.6)	21	28.734	<.001*
Negative	5 (9.6)	47 (90.4)	52		
Total	20	53	73		
PET/CT					
Positive	19 (100.0)	0	19	68.066	<.001*
Negative	1 (1.9)	53 (98.1)	54		
Total	20	53	73		

Abbreviations: CT = computed tomography; PET = positron emission tomography.
*Fisher exact test, $P < .05$.

having skeletal metastases. ^{68}Ga-PSMA-11 PET/CT was able to detect 7 false-positive and 6 false-negative findings for skeletal metastases on BS in patients with PSA ≥ 10 ng/mL (Table 10).

The development of skeletal metastases progress from red marrow seeding, osteoclastic activation, and then osteoblastic activation.[32] BS will not detect bone marrow metastases and has a low sensitivity for lytic skeletal lesions and early sclerotic lesions. ^{68}Ga-PSMA PET/CT's superiority over BS was further highlighted by the fact that of the 7 BS that missed skeletal metastases, 6 (54%) missed skeletal lesions were due to either marrow or lytic skeletal metastases on ^{68}Ga-PSMA PET/CT (Table 11). Figure 3 shows a missed skeletal metastasis on BS that was due to a marrow lesion identified on ^{68}Ga-PSMA PET/CT. Of the 11 BS that were incorrectly interpreted as bone metastases, 13 (72%) of these lesions were determined to be due to osteodegenerative changes.

Though our study focused on reviewing the diagnostic performance between ^{68}Ga-PSMA-11 PET/CT and bone scan in detecting skeletal metastases, lymph nodes are among the common sites of prostate cancer metastases after the skeleton.[33] An additional value of imaging with ^{68}Ga-PSMA-11 is detecting lymph node and soft tissue disease. In our study, ^{68}Ga-PSMA-11 PET/CT detected soft tissue metastases in 14 patients (12.3%) who had negative bone scans. In total, an additional 96 soft tissue lesions were detected in our study (Table 2). Interestingly, no additional soft tissue lesions outside of the prostate were noted in patients falsely assessed as having skeletal metastases on BS.

^{68}Ga-PSMA, however, has significant shortcomings, including its short half-life and the fact that ^{68}Ga is obtained from a germinium-68/gallium-68 generator, which can only be eluted for a limited number of times per day, with each elution only being sufficient for imaging up to 2 patients at a time. This significantly limits the

Table 6 Accuracy of Bone Scan and PSMA PET/CT in Detecting Skeletal Metastasis by Age Group

Evaluation	Bone Scan (%)		PSMA PET/CT (%)	
	<65 Years	≥65 Years	<65 Years	≥65 Years
Sensitivity	66.7	75.0	100.0	95.0
Specificity	85.3	88.7	100.0	100.0
Positive predictive value	44.4	71.4	100.0	100.0
Negative predictive value	93.5	90.4	100.0	98.1
False positive	14.7	11.3	0	0
False negative	33.3	25.0	0	5.0
Accuracy	82.5	84.9	100.0	98.6

Abbreviations: CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

Table 7 Comparison and Evaluation of Diagnostic Performance of Bone Scan and PSMA PET/CT in Detecting Skeletal Metastasis Based on Gleason Score

Characteristic	Positive (N = 26), N (%)	Negative (N = 87), N (%)	Total (N = 113)	χ^2	*P*
Gleason Score < 7					
Bone Scan					
Positive	1 (50.0)	1 (50.0)	2	4.444	.200[F]
Negative	0	8 (100.0)	8		
Total	1	9	10		
PET/CT					
Positive	1 (100.0)	0	1	10.000	.100[F]
Negative	0	9 (100.0)	9		
Total	1	9	10		
Gleason Score 7					
Bone Scan					
Positive	3 (33.3)	6 (66.7)	9	3.394	.101[F]
Negative	3 (9.1)	30 (90.9)	33		
Total	6	36	42		
PET/CT					
Positive	6 (100.0)	0	6	42.000	<.001*
Negative	0	36 (100.0)	36		
Total	6	36	42		
Gleason Score > 7					
Bone Scan					
Positive	15 (78.9)	4 (21.1)	19	29.400	<.001*
Negative	4 (9.5)	38 (90.5)	42		
Total	19	42	61		
PET/CT					
Positive	18 (100.0)	0	18	56.446	<.001*
Negative	1 (2.3)	42 (68.9)	43		
Total	19	42	61		

Abbreviations: CT = computed tomography; F = Fischer exact test; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.
*Fisher exact test, $P < .05$.

ability of ^{68}Ga-PSMA to meet the demand for imaging in prostate cancer. Therefore, ^{18}F-PSMA ligands have gained traction as ideal PET tracers because of their favorable physical properties, which allow for delayed imaging and higher activity to be administered to the patient, thus resulting in improved sensitivity for the detection of prostate cancer deposits.[34] In resource-limited settings, ^{99m}Tc-PSMA agents have become an attractive alternative to the PET PSMA tracers because of the widespread availability of ^{99}Mo/^{99m}Tc

Table 8 Accuracy of Bone Scan and PET/CT by Gleason Score

	Bone Scan (%)			PET/CT (%)		
	Gleason Score			Gleason Score		
Characteristic	<7	7	>7	<7	7	>7
Sensitivity	100.0	50.0	78.9	100.0	100.0	94.7
Specificity	88.9	83.3	90.5	100.0	100.0	100.0
Positive predictive value	50.0	33.3	78.9	100.0	100.0	100.0
Negative predictive value	100.0	90.9	90.5	100.0	100.0	97.7
False positive	11.1	16.7	9.5	0	0	0
False negative	0.0	50.0	21.1	0	0	5.3
Accuracy	90.0	78.6	86.9	100.0	100.0	98.4

Abbreviations: CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

Table 9 Comparing Diagnostic Performance of Bone Scan and PSMA PET/CT in Detecting Skeletal Metastasis by PSA Group

Characteristic	Positive (N = 26), N (%)	Negative (N = 87), N (%)	Total (N = 113)	χ^2	*P*
PSA < 10 ng/mL					
Bone Scan					
Positive	2 (33.3)	4 (66.7)	6	1.111	.525[F]
Negative	1 (11.1)	8 (88.9)	9		
Total	3	12	15		
PET/CT					
Positive	3 (100.0)	0	3	15.000	.002*[F]
Negative	0	12 (100.0)	12		
Total	3	12	15		
PSA 10-20 ng/mL					
Bone Scan					
Positive	2 (33.3)	4 (66.7)	6	2.758	.192[F]
Negative	0	7 (100.0)	7		
Total	2	11	13		
PET/CT					
Positive	2 (100.0)	0	2	13.000	.013*[F]
Negative	0	11 (100.0)	11		
Total	2	11	13		
PSA > 20 ng/mL					
Bone Scan					
Positive	15 (83.3)	3 (16.7)	18	42.195	<.001*
Negative	6 (9.0)	61 (91.0)	67		
Total	21	64	85		
PET/CT					
Positive	20 (100.0)	0	20	79.707	< .001*[F]
Negative	1 (1.5)	64 (98.5)	65		
Total	21	64	85		

Abbreviations: CT = computed tomography; F = Fischer exact test; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.
*Fisher exact test, $P < .05$.

generators and gamma cameras. Among the available gamma imaging radionuclides, ^{99m}Tc-hydrazinonicotinamide-PSMA has the added advantage of being easier to label and having a good senility in the detection of prostate cancer deposits.[35]

Limitations

Our study has several limitations. Histopathologic evaluation of all detected metastatic lesions was not possible. In addition, positive uptake of ^{68}Ga-PSMA-11 was assumed to be pathologic (metastatic)

Table 10 Accuracy of Bone Scan and PET/CT by PSA Group

	Bone Scan (%)			PET/CT (%)		
	PSA (ng/mL)			PSA (ng/mL)		
Characteristic	<10	10-20	>20	<10	10-20	>20
Sensitivity	66.7	100.0	71.4	100.0	100.0	95.2
Specificity	66.7	63.6	95.3	100.0	100.0	100.0
Positive predictive value	33.3	33.3	83.3	100.0	100.0	100.0
Negative predictive value	88.9	100.0	91.0	100.0	100.0	98.5
False positive	33.3	36.4	4.7	0.0	0.0	4.8
False negative	33.3	0.0	28.6	0.0	0.0	0.0
Accuracy	66.7	69.2	89.4	100.0	100.0	98.8

Abbreviations: CT = computed tomography; PET = positron emission tomography; PSA = prostate-specific antigen.

Table 11 Characteristics of False-Negative and False-Positive Lesions Found on Bone Scan With ^{68}Ga-PSMA PET/CT

Characteristic	N (%)
False-Negative Lesions	11
Bone marrow lesions	3 (27%)
Lytic lesions	3 (27%)
Equivocal sclerotic lesions	5 (46%)
Additional soft tissue lesions	13
False-Positive Lesions	18
Osteodegenerative	13 (72%)
No significant morphologic finding	5 (28%)
Additional soft tissue lesions	0

Abbreviations: CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen.

on the basis of follow-up imaging. Correlation with other imaging modalities and histology was possible, but it is also possible that some of the uptakes could be falsely positives.[36,37] SPECT/CT improves BS sensitivity and lesion detection; however, it was not always possible to routinely conduct SPECT/CT imaging on all bone scans because of logistic constraints.[14]

Conclusion

^{68}Ga-PSMA PET/CT is superior to and can potentially replace BS in the clinical and trial setting. ^{68}Ga-PSMA-11 PET/CT demonstrated reduced false-positive findings and had higher sensitivity and accuracy compared to BS, including the detection of lytic and bone marrow metastases. Extraskeletal lesions detected on ^{68}Ga-PSMA-11 PET/CT could further affect patient management.

Clinical Practice Points

- ^{68}Ga-PSMA-PET/CT is of benefit in primary staging in high-risk disease according to D'Amico classification and can detect biochemical recurrence with low PSA values (0.2-10 ng/mL).
- Few data exist on the utility of ^{68}Ga-PSMA ligands in the initial assessment of skeletal disease in high-risk prostate cancer patients. ^{68}Ga-PSMA PET/CT is superior to bone scan in the assessment for skeletal lesions because it detects more skeletal lesions, including bone marrow and lytic lesions, that may be missed by bone scan. In addition, ^{68}Ga-PSMA PET/CT was able to detect soft tissue lesions, which could affect patient management.
- PSMA-labeled tracers (including the more readily available ^{99}mTc-, ^{18}F-, and ^{68}Ga-based tracers) could potentially replace bone scintigraphy in the evaluation of skeletal metastases in both clinical and trial settings.
- Unlike bone scan, which has not been routinely used for monitoring systemic treatment in patients with advanced prostate cancer, ^{99}mTc-, ^{18}F-, or ^{68}Ga-PSMA could play an important role in treatment response evaluation. PSMA-based imaging could also play an important role in active surveillance, especially in combination with multiparametric magnetic resonance imaging.
- PSMA-based imaging may form the basis for selection of patients for targeted radionuclide therapy and may prove important in evaluation of treatment response in such patients.

Disclosure

The authors have stated that they have no conflict of interest.

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