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Comparing ^{99m}Tc-PSMA to ^{99m}Tc-MDP in Prostate Cancer Staging of the Skeletal System

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Purpose: This prospective study was aimed at assessing the ability of ^{99m}Tc-PSMA scan to detect bone metastases in prostate cancer (PCa) against ^{99m}Tc-MDP scan as a standard and assess the correlation of these modalities in PCa staging of bone involvement.

Patients and Methods: Forty-one patients (41) with histologically confirmed PCa were scanned using both methods. Planar imaging was performed with additional regional SPECT/CT 3 to 4 hours posttracer injection. Scans were reported as positive, negative, or equivocal. In the case of positive scans, lesions were quantified by each of the 3 reporters separately. Planar and SPECT/CT images were reported together to obtain the final report on each scan.

Results: Our preliminary results showed no significant difference in the detection of bone metastases between the 2 scans. ^{99m}Tc-PSMA detected 52 of the 55 bone lesions detected on ^{99m}Tc-MDP. However, ^{99m}Tc-PSMA provided extra information by reporting lymph nodal metastases in 7 patients and residual disease in the prostate in 2 patients with biochemical progression after radical therapy. In 1 patient, the PSMA scan resulted in change in management with patient now on ^{177}Lu-PSMA radioligand therapy. Equivocal findings were reported in 4 patients on ^{99m}Tc-MDP and none on ^{99m}Tc-PSMA.

Conclusions: ^{99m}Tc-PSMA was comparable to ^{99m}Tc-MDP in detection of bone metastases and demonstrated an additional benefit of providing information on visceral disease. ^{99m}Tc-PSMA may be a better alternative to ^{99m}Tc-MDP in staging, restaging, and assessment of patients with biochemical progression after radical therapy of PCa in a resource-limited setup like ours while also assisting to detect patients eligible for PSMA-labeled radioligand therapy.

Key Words: PSMA scan, bone scan, SPECT/CT, urology, radioligand therapy

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Prostate cancer (PCa) is the most common noncutaneous cancer in men with a lifetime risk of 12.5%.[1] Although only 6% of men with PCa have metastatic disease at diagnosis, 90% of men who die of PCa have metastatic disease to bone.[2] The high rate of bone metastases has led to the incorporation of bone imaging in most published national and international treatment guidelines.[3–6] Imaging of bone metastases in PCa has traditionally involved the use of the bone-seeking ^{99m}Tc-MDP, which is highly sensitive for detection of bone lesions.[7] ^{99m}Tc-labeled prostate-specific membrane antigen (PSMA) is a newer agent used for imaging in PCa. It has the advantage of being able to demonstrate both visceral and bone lesions.[8,9] To our knowledge, there is currently only 1 study comparing the sensitivity of ^{99m}Tc-MDP bone scan with that of ^{99m}Tc-PSMA in detecting bone metastases in PCa.[8]

^{99m}Tc-MDP bone scintigraphy is the cornerstone of skeletal nuclear medicine imaging and has been regarded as the standard of reference in detection of bone metastases in PCa patients.[10] ^{99m}Tc-MDP is a bisphosphonate derivative, which localizes within the hydroxyapatite portion of the bony matrix by chemical adsorption (chemisorption).[11] It is highly sensitive, readily available, and cost-effective, and it has been the standard method for nuclear imaging of the skeletal system for decades.[12] There is a need to affordably improve imaging of metastases in PCa as scintigraphy with ^{99m}Tc-MDP is associated with limited sensitivity in patients with low prostate-specific antigen (PSA),[13,14] long PSA doubling time,[15] lytic bone lesions,[16] and in assessing biochemical progression after radical prostatectomy.[17]

Modern clinical management of PCa increasingly relies on exploiting the PSMA as a molecular target both for imaging and for treatment of PCa.[6,18–21] PSMA is a type II integral membrane glycoprotein with an intracellular component, a transmembrane component, and a large extracellular domain.[22] ^{99m}Tc-PSMA is able to detect both soft tissue and skeletal metastases, and it has been reported in a study by Rathke et al[8] that ^{99m}Tc-PSMA scintigraphy demonstrates a reduction of the number of equivocal findings in comparison to ^{99m}Tc-MDP bone scan. The limitation to the available literature is that, in many instances, a comparison is made between PET/CT and SPECT/CT.[23–26] The higher spatial resolution on PET[27,28] is a confounding factor, which this study eliminated by comparing the 2 tracers using SPECT/CT imaging. The SPECT/CT-to-SPECT/CT comparison in this study is also important because many centers in our setting can only afford SPECT/CT scanners due to the high cost of PET/CT scanners and tracers.

The aim of this prospective study was to compare the detection rate of bone metastases of ^{99m}Tc-PSMA to that of ^{99m}Tc-MDP in PCa and correlate the findings with patient factors such as age, disease stage, Gleason score, and PSA.

To achieve this, male patients with PCa in KwaZulu-Natal were recruited to do both scans within a period of 28 days. The scans were scrutinized for the comparative detection rate of positive, equivocal, and negative findings by experienced certified nuclear medicine physicians overall having more than 7 years' experience in the field.

PATIENTS AND METHODS

Forty-one male patients referred for staging/restaging of PCa with either ^{99m}Tc-MDP or ^{99m}Tc-PSMA were recruited for the second

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scan to be performed within 28 days of the first. Participants underwent both scans with whole-body and regional SPECT/CT scans. The scans were performed within a mean time interval of 21 days of each other. The study was undertaken in the Nuclear Medicine Department of Inkosi Albert Luthuli Central Hospital in KwaZulu-Natal. Patients with histologically confirmed PCa, regardless of disease stage and prior interventions, were included. All patients signed a written informed consent form. The BREC (Biomedical Research Ethics Committee) approved this evaluation (BREC reference number BE381/19).

Radiopharmaceuticals

The labelling of ^{99m}Tc was done using the supplier-provided HYNIC-IPSMA ligand kit according to the provided protocol. Quality control (QC) for ^{99m}Tc-labeled PSMA was performed by thin-layer chromatography, and the only radiopharmaceutical with radiochemical purity of greater than 95% was used. For ^{99m}Tc-MDP, the QC is performed by the suppliers, and only kits that have passed QC are supplied to the departments.

Imaging Protocol

For the ^{99m}Tc-MDP scan, each candidate was injected with a standard dose of 740 MBq (20 mCi) of ^{99m}Tc-MDP followed by 3 to 4 hours postinjection delayed whole-body imaging. The patients were imaged in the supine position on the camera bed with both arms along the sides and feet slightly internally rotated. Camera matrix size was set at 256 × 1024 for both detectors, and the zoom was set 1.00 and image processing was done with planar enhancement processor at 30% enhancement. SPECT/CT imaging was done in selected regions of interest determined by the tracer uptake on the planar/whole-body images. Regional SPECT/CTs were matched in both scans, and the region of interest was guided by the first scan in sequence. For CT, 3.0-mm slices with an extended field of view (650) were used (iterative reconstruction was used for both SPECT and CT).

For ^{99m}Tc-PSMA scan, a standard dose of 555 MBq (15 mCi) of ^{99m}Tc-PSMA was injected intravenously followed by delayed 3 to 4 hours imaging. Whole-body planar imaging and regional SPECT/CT scans were obtained as above. The patients positioning and camera settings were the same as that of ^{99m}Tc-MDP scan. In addition to the above regional SPECT/CT, ^{99m}Tc-PSMA scans had a mandatory pelvic SPECT/CT scans for assessment of the prostatic bed and lymph nodes.

Reporting of Findings

The studies were evaluated by 3 experienced certified nuclear medicine physicians to evaluate the number, location, and characteristics of the skeletal metastases. All the scans were anonymized and reviewed by each physician independently to avoid subjective bias. Concordance in discrepant results was achieved by consensus. The findings were reported as positive, negative, or equivocal. Uptake was considered to be positive for metastasis if it was seen in an area less likely to be due to trauma, contamination, or degenerative, widespread pattern and/or having typical sclerotic/lytic changes on CT. Uptake was considered to be negative for metastases if it localized to areas of benign change or contamination. Uptake was considered to be equivocal for metastasis if it localized to areas that did not display typical benign or metastatic changes. In the case of positive findings, the total number of identified lesions was recorded. The CT was used (fused with a SPECT) for further characterization of equivocal findings to determine the likelihood of metastasis. In addition, results were correlated with age, disease stage, serum PSA, and Gleason score.

Best Valuable Comparator

To assess the performance of the 2 scans independently, a criterion standard would be required. Owing to ethical and practical reasons, bone histology was not performed as the criterion standard, and a best valuable comparator (BVC) was used as a standard of comparison. The BVC was defined as in previous investigations,[8,23,25] using a combination of all available information including ^{99m}Tc-PSMA and ^{99m}Tc-MDP bone scans (initial and interval scans), SPECT/CT, PET/CTs, CT scans, and clinical data.

Statistical Analysis

Patient demographic characteristics were summarized using descriptive statistics. Furthermore, testing the differences in mean (±SD) number of lesions observed on ^{99m}Tc-MDP to that of ^{99m}Tc-PSMA was performed using exact Wilcoxon matched pairs signed rank test. To accommodate the high frequency of zero lesions among several patients in the study, a zero-inflated negative binomial regression was used to model the association between the number of soft tissue metastases on ^{99m}Tc-PSMA and several patient-related factors. Furthermore, a logistic model was used to determine factors associated with ^{99m}Tc-PSMA uptake in the prostate gland. Sensitivity, specificity, and area under the curve (AUC) were determined by receiver operating characteristics for both ^{99m}Tc-MDP and ^{99m}Tc-PSMA, and their 95% confidence interval (CI) were calculated binomial exact. Comparisons of AUC were performed by using the DeLong method.[29] Data analysis was performed using Stata IC 15 (Stata Statistical Software Release 15; StataCorp LLC, College Station, TX).

RESULTS

A total of 41 patients were included in the study. Three patients were excluded from analysis due to having unquantifiable diffuse metastases (albeit matching). Table 1 shows a summary of selected patient-related characteristics of the 38 patients. The median age of the participants was 68.5 years (interquartile range [IQR], 11), and the median age at diagnosis was 67 years (IQR, 11). The stage of cancer diagnosis for most patients (n = 13, 36.11%) was 3A, and the median PSA was 28.95 ng/mL (IQR, 72) at the time of the study. On biopsy, 55.26% (n = 21) of the patients had a Gleason score of 7 (intermediate risk), whereas the 26.32% (n = 10) had a Gleason score of 8 to 10 (high risk). In addition, the mean time interval between the taking of PSA level and the first scan was 5.5 month (±5.41). The median time was 4 months (IQR, 5 months) with the maximum interval time being 20 months and the minimum being 1 month. On the other hand, the mean time between ^{99m}Tc-MDP and ^{99m}Tc-PSMA scans was 22 days (±20.8). The median time was 18 days (IQR, 10 days) with the maximum interval time being 96 days and the minimum being 4 days.

There were 38 patients assessed for bone metastases by ^{99m}Tc-MDP and ^{99m}Tc-PSMA. Of these, 13/38 (34.2%) patients were referred for primary staging, 16/38 (42.1%) for restaging, and 9/38 (23.6%) for biochemical progression after definitive therapy. Of the 9 patients referred for biochemical progression after definitive therapy, 8/25 had received a combination of pharmacotherapy, surgery, and radiotherapy, and only 1/25 reported having had a prostatectomy only. All the patients referred for restaging were on pharmacotherapy, and none of the patients received further therapy between the 2 scans. A cumulative total of 56 lesions were reported on BVC with ^{99m}Tc-MDP detecting 55/56 (98%) and ^{99m}Tc-PSMA detecting 52/56 (92%). On ^{99m}Tc-MDP, 4 lesions were classified as equivocal, and all these were reported as negative based on BVC. None of the equivocal MDP lesions was seen on ^{99m}Tc-PSMA, and there were no equivocal findings on ^{99m}Tc-PSMA at all. Based on the BVC, 11 patients (28.9%) were classified as having bone

TABLE 1. Selected Patient Characteristics

Patient Characteristics	Frequency (n)	%
Age category		
46–56 y	4	10.53
57–67 y	13	34.21
68–78 y	19	50
79–89 y	2	5.26
Age at diagnosis		
45–55 y	3	9.68
56–66 y	12	38.71
67–77 y	16	51.61
Stage of cancer at diagnosis		
1 (unspecified)	1	2.78
2 (unspecified)	1	2.78
2A	5	13.89
2B	5	13.89
2C	1	2.78
3 (unspecified)	2	5.56
3A	13	36.11
3B	2	5.56
4 (unspecified)	3	8.33
4A	1	2.78
4B	2	5.56
PSA level		
1 (0–9.9 ng/mL)	6	15.79
2 (10–20 ng/mL)	10	26.32
3 (>20 ng/mL)	22	57.89
Gleason score		
≤6 (low risk)	7	18.42
7 (intermediate risk	21	55.26
8–10 (high risk)	10	26.32

metastases, whereas 27 patients (71.1%) were classified as having no bone metastases. The mean number of lesions reported under BVC was 1.5 (±3.5). The maximum number of lesions was 16, whereas the minimum was zero. On ^{99m}Tc-MDP, 26.3% (n = 10) of the patients had bone metastases. The mean number of lesions observed on ^{99m}Tc-MDP was 1.45 (±3.4) (Table 2); the maximum was 15, whereas the minimum was zero. On the other hand, 23.68% (n = 9) of the patients had bone metastases under ^{99m}Tc-PSMA. The mean number of lesions observed under ^{99m}Tc-PSMA was 1.36 (±3.4).

In a univariate logistical analysis, the study showed a relationship ($P < 0.05$) among the presence of bone metastases on MDP with cancer stage, PSA level, and no relationship ($P > 0.05$) with age and Gleason score. There was a relationship among bone metastases seen on ^{99m}Tc-PSMA with cancer stage, PSA level, and Gleason score. In a bivariate analysis, the study showed that there was no relationship ($P > 0.05$) among Gleason score, PSA level, age category, and age category at diagnosis with the number of soft tissue metastases on ^{99m}Tc-PSMA. However, further analysis in a zero-inflated negative binomial regression showed that Gleason score (coefficient, 1.81; 95% CI, 0.48–3.15), age at diagnosis (coefficient, 0.84; 95% CI, 0.17–1.52), and stage of the cancer (coefficient, 0.48; 95% CI, 0.20–0.76) had a positive influence on the number of soft tissue metastases on ^{99m}Tc-PSMA. Furthermore, the study showed that ^{99m}Tc-PSMA uptake in the prostate gland was influenced by the form of interventions used (OR, 0.28; 95% CI, 0.12–0.63). The study showed that the odds of ^{99m}Tc-PSMA uptake in the prostate gland among those who had mixed interventions (OR, 0.027; 95% CI, 0.002–0.371) were lower than those who had no intervention. On the other hand, there were no statistical differences in the ^{99m}Tc-PSMA uptake between those who had no intervention and those who had medical intervention (OR, 0.361; 95% CI, 0.032–3.962). The Hosmer-Lemeshow test used to assess the goodness-of-fit showed that the model was sufficiently specified ($P = 0.831$). There was no statistical difference in the rate of detection of bone lesions between ^{99m}Tc-MDP and ^{99m}Tc-PSMA based the different stages ($P = 0.23$) and risk as defined by Gleason score ($P = 0.27$) and PSA value ($P = 0.42$), with both scans detecting the most lesions in stage 4 disease, intermediate- and high-risk Gleason score group, and high-risk PSA group (Table 3). The rate of detection of bone lesions between the 2 methods was comparable regardless of the indication, that is, staging/restaging and biochemical progression after radical therapy ($P = 0.66$) (Table 3).

TABLE 2. Number of Lesions and Number of Patients With or Without Lesions Observed Under ^{99m}Tc-MDP and ^{99m}Tc-MDP

	No. Lesions		No. Patients		
	Mean	SD	With Lesions	No Lesions	Equivocal
BVC	1.5	3.5	11 (28.95%)	27 (71.05%)	0
^{99m}Tc-PSMA	1.36	3.4	9 (76.32%)	29 (76.32%)	0
^{99m}Tc-MDP	1.45	3.4	10 (26.32%)	28 (73.68)	4

Correlation Between ^{99m}Tc-MDP and ^{99m}Tc-PSMA

A Wilcoxon matched pairs signed rank test between mean number of lesions observed under ^{99m}Tc-MDP and ^{99m}Tc-PSMA

TABLE 3. Number of Bone Lesions According to Patient Characteristics and Indications

Patient Characteristics and Indications	No. Bone Lesions Seen on ^{99m}Tc-MDP Scan	No. Bone Lesions Seen ^{99m}Tc-PSMA Scan	Paired *t* test *P*
Initial stage			
Stage 1–2	3	3	
Stage 3	9	7	
Stage 4	43	42	
			0.225
Gleason score			
≤6 (low risk)	1	0	
7 (intermediate risk	44	41	
8–10 (high risk)	11	11	
			0.27
PSA			
1 (0–9.9 ng/mL)	0	0	
2 (10–20 ng/mL)	1	1	
3 (>20 ng/mL)	54	51	
			0.42
Indication			
Primary staging/restaging	32	28	
Biochemical progression after radical therapy	23	24	
			0.66

showed no statistical difference ($z = 1.63$, $P = 0.103$). Based on the BVC as a standard of reference, there was no significant difference ($P = 0.317$) in sensitivity between ^{99m}Tc-MDP (90.91%, SE = 4.5%) and ^{99m}Tc-PSMA (81.82%, SE = 6.1%) in the detection of bone lesions.

Sensitivity and Specificity Analysis

In 38 patients involved in the overall bone lesion assessment by BVC, 27 patients (64%) were correctly classified as having no lesions, whereas 10 patients (24%) were also classified as having lesions under ^{99m}Tc-MDP. On the other hand, 1 patient classified as having bone lesions on BVC was not classified as such under ^{99m}Tc-MDP resulting in a detection of 10/11. Furthermore, analysis showed that, of the 27 patients classified as having no lesions under BVC, 4 patients were classified as equivocal under ^{99m}Tc-MDP. The sensitivity of ^{99m}Tc-MDP SPECT/CT was 90.91%, and the specificity was 100%. Receiver operating characteristics analysis revealed an accuracy measured as AUC of 0.95% (95% CI, 0.86%–1%) for ^{99m}Tc-MDP (Table 3). Of the 11 patients classified as having bone metastases under BVC, 9 (23.6%) were correctly assigned as having bone metastases under ^{99m}Tc-PSMA scan. There were no equivocal findings under ^{99m}Tc-PSMA. The sensitivity of ^{99m}Tc-PSMA SPECT/CT was 81.82%, and the specificity was 100%. Receiver operating characteristics analysis revealed an accuracy measured as AUC of 0.90.0% (95% CI, 0.79%–1%) (Table 4). The time interval among the scans that were negative on ^{99m}Tc-PSMA but positive on ^{99m}Tc-MDP was 9 days and 11 days, respectively.

DISCUSSION

When correlating the mean number of bone lesions detected by ^{99m}Tc-MDP bone scan with that of ^{99m}Tc-PSMA scan in detection of bone metastases in PCa patients, it was determined that there was no statistically significant difference between the 2 tracers ($z = 1.63$, $P = 0.103$). ^{99m}Tc-PSMA detected 52/55 (94.5%) of the lesions seen on ^{99m}Tc-MDP bone scan. The discordance seen in the 3/55 lesions not picked up on ^{99m}Tc-PSMA but reported on Tc-MDP bone scan is unusual. Possible reasons considered for this discordance include false-positive report on ^{99m}Tc-MDP considering that it is noted to have low specificity with uptake seen in benign pathology,[30–32] the possibility that these lesions were in the healing phase as ^{99m}Tc-MDP is known to remain positive for a as long as 6 months after resolution of skeletal metastases,[33,34] or else a PSMA-negative tumor phenotype could be an alternative explanation.[35,36] Based on the BVC as a standard of reference, the study still demonstrated no significant difference ($P = 0.317$) in sensitivity between ^{99m}Tc-MDP and ^{99m}Tc-PSMA in the detection of bone lesions, with ^{99m}Tc-PSMA demonstrated a sensitivity of 81.82% and specificity of 100% compared with ^{99m}Tc-MDP bone scan with a sensitivity of 90.9% and specificity of 100%. The time interval among the scans, which were negative on ^{99m}Tc-PSMA but positive on ^{99m}Tc-MDP, was 9 days and 11 days, respectively. A study done by Rathke et al[8] reported superior detection of bone metastases on ^{99m}Tc-PSMA with a sensitivity and specificity of 92% and 90% compared with ^{99m}Tc-MDP at 76% and 86%, respectively. The difference between this and our study could be due to the smaller sample size in our study and the nonstandardization of the BVC. The specificity of bone scan reported in this study is unusually high, and this was thought due to the small sample size with only 11 patients having metastases that were analyzed; then, the final interpretation of the scan involved the use of SPECT/CT in any foci that did not demonstrate typical findings resulting in the elimination of potential false-positives (Fig. 1).[37] As observed in other studies,[8] some ^{99m}Tc-MDP scans demonstrated equivocal findings, especially in areas more commonly associated with degenerative change while none were observed on the ^{99m}Tc-PSMA scan (Fig. 2).

Many studies comparing PSMA to ^{99m}Tc-MDP have used PMSA-labeled PET tracers such as ^{18}F-DCFPyL PET/CT[38] and ^{68}Ga.[25,39] These studies also reported a higher sensitivity in PSMA-labeled PET tracers compared with ^{99m}Tc-MDP, with sensitivity ranging from 96% to 100% and that of MDP being as low as 73%. One of the limitations of comparing our study to the above is the use of different imaging modalities with different resolutions (superior resolution on PET/CT[27,28]). However, the good detection rate of bone metastases by ^{99m}Tc-PSMA reported by this study and Rathke et al[8] makes a good argument for the use of ^{99m}Tc-PSMA in areas that have no access to PET scan. Further to this, studies comparing ^{99m}Tc-PSMA SPECT/CT to ^{68}Ga-PSMA PET/CT have demonstrated how ^{99m}Tc-PSMA SPECT/CT could be a potential substitute for ^{68}Ga-PSMA PET/CT.[9,40]

A similar study comparing the 2 tracers focused on patients with known bone metastases,[8] whereas our study included both new patients and patients being followed up. The risk profile in our study included low-, intermediate-, and high-risk patients. Although the use of ^{99m}Tc-PSMA is mostly reserved for detection of occult disease in patients with low PSA[41,42] and primary staging of high-risk patients[43,44] and bone scan to intermediate- to high-risk patients,[12] we were also interested in seeing how ^{99m}Tc-PSMA performs in patients across the risk spectrum, including patients typically reserved for staging bone scan.[6] Thomsen et al[45] reported a correlation between advanced disease stage and high PSA with bone metastases, and we report similar findings with patients having advanced disease stage and a high PSA more likely to have metastases on both ^{99m}Tc-PSMA and ^{99m}Tc-MDP scans and with the 2 methods having no statistically significant difference in detection rate (Table 3). In a study involving 106 PCa patients, Al-Ghazo et al[46] reported that PSA level >20 ng/mL and Gleason score >7 were independently predictive of positive bone scan. In our study, 98% of the bone lesions were observed in patients with PSA level >20 ng/mL and Gleason score >7. Of the patients referred for staging or restaging, only those with intermediate to high PSA levels demonstrated bone lesions. Interestingly, patients referred for biochemical progression after radical therapy had intermediate to high PSA and demonstrated comparable number of lesions on both scans (Table 3).

According to a report by Bechis et al,[47] with increasing age, men were significantly more likely to have high-risk PCa, this study demonstrated that age at diagnosis had a positive influence on the presence of soft tissue metastases on ^{99m}Tc-PSMA with a mean age at diagnosis of 69.2.

^{99m}Tc-PSMA scan detected soft tissue metastases to the lymph nodes in 7 patients; of these, 3 patients also had bone metastases and the ^{99m}Tc-PSMA scan detected the same number of bone lesions as ^{99m}Tc-MDP bone scan. This is an important finding as it demonstrates the ability of ^{99m}Tc-PSMA to give extra information on soft tissue disease without compromising on the bone findings. Uptake of ^{99m}Tc-PSMA in the prostate was seen in 28 patients. This was an important finding in 2 of these patients referred for

TABLE 4. Patient-Based Analysis of Lesions on ^{99m}Tc-MDP SPECT/CT and ^{99m}Tc-PSMA SPECT/CT

	^{99m}Tc-MDP	^{99m}Tc-PSMA
Sensitivity	90.91%	81.82%
Specificity	100%	100%
AUC	0.955	0.909
SE	0.045	0.061
95% CI	0.865–1	0.789–1

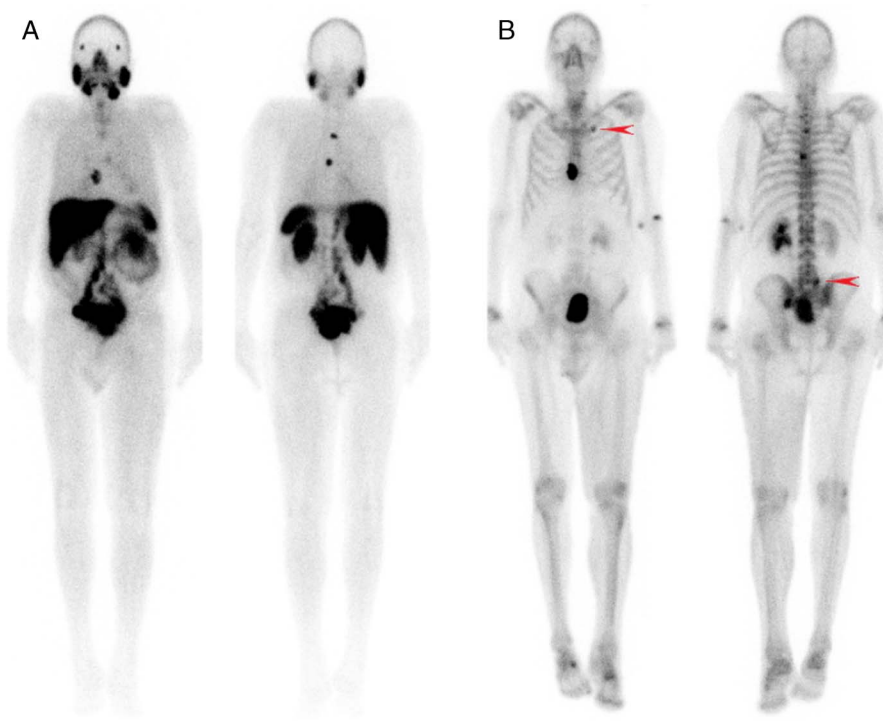

FIGURE 1. Planar ^{99m}Tc-PSMA (**A**) and ^{99m}Tc-MDP (**B**) demonstrating 2 matching typical bone lesions in the thoracic spine and sternum. However, ^{99m}Tc-MDP (**B**) also demonstrates uptake in areas of degenerative changes (arrowhead), requiring SPECT/CT to increase specificity.

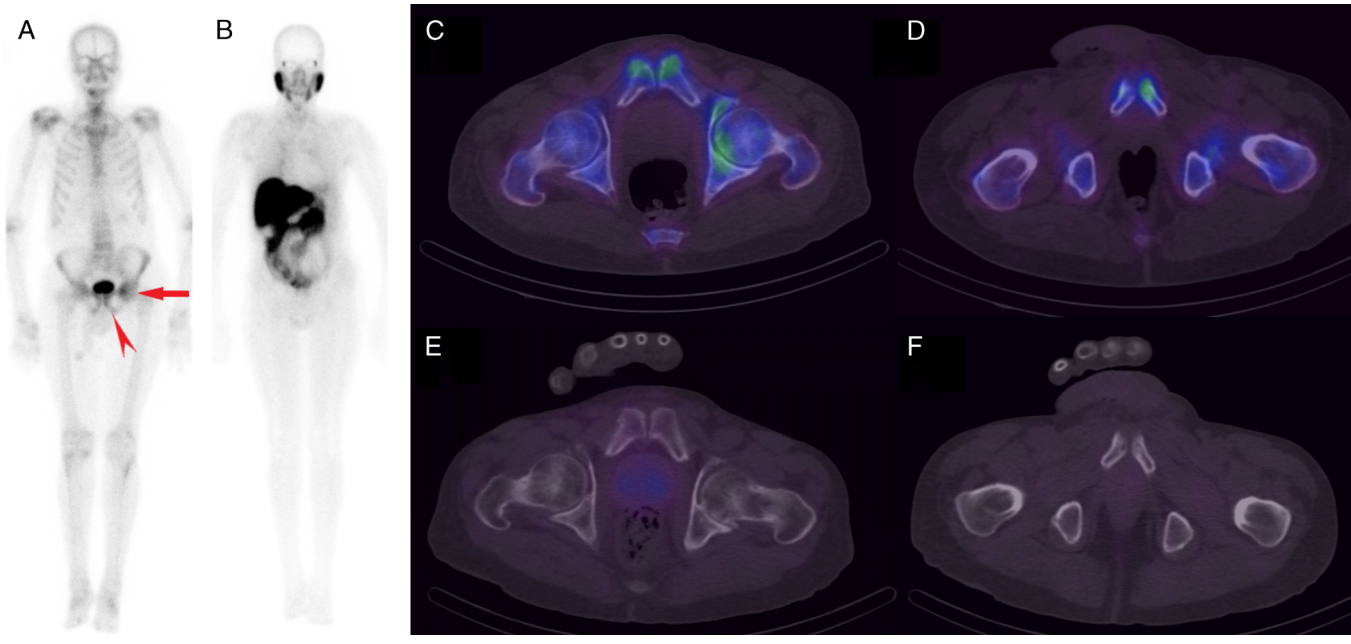

FIGURE 2. Whole-body ^{99m}Tc-MDP scan (**A**) showing asymmetrically increased uptake in the left pubis (arrowhead) and iliac region (arrow), whereas no obvious increased uptake is seen in the corresponding areas on ^{99m}Tc-PSMA scan (**B**). SPECT/CT through 2 different slices highlighting the above changes localizes the iliac findings to the left femoroacetabular joint region (**C**) in keeping with degenerative change. The focal uptake seen in the left pubis (**D**) localizes to an area of sclerosis adjacent to the pubic symphysis. This was of concern for metastasis; however, degenerative change was also a consideration due to the proximity to the joint (rendering the finding equivocal). On ^{99m}Tc-PSMA SPECT/CT scans (**E** and **F**), there was no pathological uptake in the corresponding areas to suggest osseous metastases.

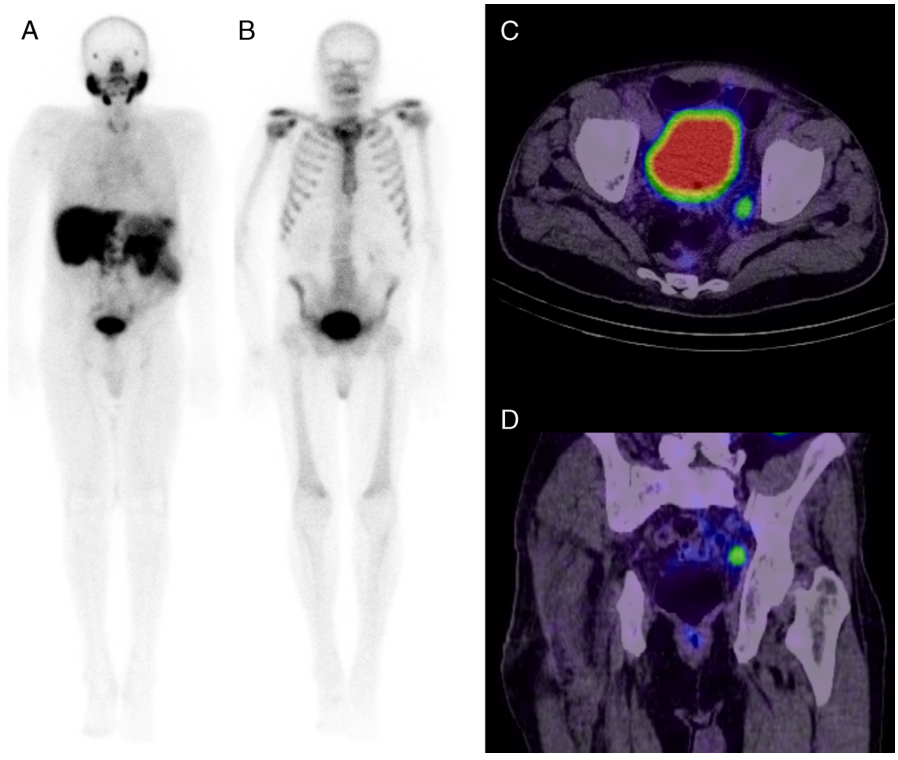

FIGURE 3. Whole-body planar ^{99m}Tc-PSMA (**A**) and ^{99m}Tc-MDP (**B**) images negative for bone metastases in a patient with a raised PSA. ^{99m}Tc-PSMA pelvic axial (**C**) and coronal (**D**) SPECT/CT demonstrate increased uptake in a left internal iliac lymph node in keeping with metastasis.

biochemical progression after radical therapy as these findings represent either residual disease or recurrence and thus explained the nonresolving PSA (Fig. 3). In 26/28 patients, the uptake in the prostate was nonspecific because they did not have a history of prostatectomy. The lack of specificity is due to the normal uptake of ^{99m}Tc-PSMA expected even in nonmalignant prostate glands. ^{99m}Tc-PSMA also demonstrated superiority in determining the significance of equivocal findings seen on bone scan.

Some studies reported a mean interval between the 2 scans from as few as 10 days[8] and others as many as 80 days.[48] Our target interval was a maximum of 28 days, and we achieved a mean of 21 days. Our decision for this method was due to the impracticality of shorter intervals and the concern for disease change in longer intervals. It is interesting to note that, despite the differences in the mean interval between this study and that reported by investigators with fewer days,[8] the findings are comparable.

The findings in our study make a good argument for the use of ^{99m}Tc-PMSA as an alternative to ^{99m}Tc-MDP for both staging and follow-up in patients who are not for palliative radioligand bone therapy. Therefore, in resource-limited situations where a patient can only get a single scan (such as our setup where patients who live far from the center may not afford to travel for multiple scans), it would be more beneficial if that scan was a ^{99m}Tc-PSMA regardless of the stage.

Among the limitations of this study was a lack of bone histology as the criterion standard. This has the potential of having some false-positive results on both scans. The smaller sample size has the potential to shift results away from what is expected in the represented population. The 3 patients who demonstrated diffuse disease were analyzed separately because their lesions were not quantifiable due to their diffuse extent. The findings in diffuse bone disease were comparable between the 2 tracers. The detection of ^{99m}Tc-PSMA–avid disease resulted in recommending ^{177}Lu-PSMA radioligand therapy in a case of failed chemotherapy.

When taken beyond the context of staging and assessment of the therapy response, the uptake seen on both scans does not always represent the same thing, especially when it comes to radioligand therapy where both still have a role in planning. Patients demonstrating intense ^{99m}Tc-PSMA uptake are good candidates for PSMA radioligand therapy such as ^{177}Lu-PSMA,[3,49] whereas those demonstrating reduced ^{99m}Tc-PSMA uptake, but increased MDP uptake, may benefit from radioligand palliative bone therapy.[50] In these cases, the 2 scans cannot replace each other.

CONCLUSIONS

Our preliminary results show that the ability of ^{99m}Tc-PSMA to detect bone metastases in PCa is comparable to that of ^{99m}Tc-MDP but with the additional benefit of providing information on soft tissue disease in both early and advanced disease. Therefore, in patients who can only afford a single scan, ^{99m}Tc-PSMA scan would be a better choice. With regards to therapy, ^{99m}Tc-PMSA scan might have utility to select candidates for PSMA radioligand therapy such as ^{177}Lu-PSMA, whereas ^{99m}Tc-bone scan may have similar utility in palliative radioligand bone therapy with bisphosphonates.

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