Original Article

Comparison of Diagnostic Value between ^{99m}Technetium-Methylene Diphosphate Bone Scan and ^{99m}Technetium-Prostate-specific Membrane Antigen Scan in Patients with Prostate Cancer with Osseous Metastases

Mohsen Alemi, Farshad Banouei, Reyhaneh Ahmadi[1]

Urology and Nephrology Research Center, Hamedan University of Medical Sciences, [1]Department of Nuclear Medicine, School of Medicine, Hamedan University of Medical Sciences, Hamedan, Iran

Abstract

Background: Prostate cancer (PCa) ranks as the second most prevalent cancer among men globally. The utilization of efficient and cost-effective diagnostic and therapeutic approaches holds paramount importance in the diagnosis and treatment of these patients, significantly impacting treatment outcomes. This study focuses on the investigation and comparison of two commonly employed scans within the treatment process for these patients. **Methods:** In this prospective study, which spanned over 2 years, 40 patients diagnosed with PCa underwent examination using two scans: ^{99m} Technetium-Prostate-specific Membrane Antigen (^{99m}TC-PSMA) Scan and between Technetium-Methylene Diphosphate (^{99m}TC-MDP) Bone Scan. The findings of these scans were then compared with each other, as well as with the results obtained from magnetic resonance imaging and the prostate-specific antigen level. The analysis of the results was conducted utilizing SPSS 22 software, and descriptive statistical methods were employed to present the findings. **Results:** In this prospective study, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the ^{99m}TC-MDP Bone Scan were found to be 88.2%, 83.3%, 96.7%, 55.5%, and 87.5%, respectively. Similarly, for the ^{99m}TC-PSMA Scan, the corresponding values were 94.1%, 83.3%, 96.4%, 83.3%, and 92.5%, respectively. **Conclusions:** Based on the findings of this study, it can be concluded that the diagnostic accuracy of the ^{99m}TC-PSMA Scan is marginally higher compared to the ^{99m}TC-MDP Bone Scan. Therefore, for patients who are limited to only one scan, the ^{99m}TC-PSMA Scan appears to be the preferable choice.

Keywords: *^{99m}Technetium-methylene diphosphate bone scan, ^{99m}technetium-prostate-specific membrane antigen scan, prostate cancer*

Introduction

The prostate gland is a gland derived from the early embryonic endoderm.[1] In the male embryo, the prostate grows from the tail to the bladder neck, achieved through epithelial buds that derive from the endodermal sinus.[2] The dimensions of a normal prostate gland are 3 cm × 3 cm × 5 cm, and its volume is 25 mL. The human prostate is divided into three zones based on its histological features: the peripheral zone (PZ), the transition zone (TZ), and the central zone (CZ).[3] Seventy percent of all prostate cancer (PCa) occur in the PZ, 20% in the TZ, and 10% in the CZ.[4] Neurovascular bundles are bilaterally stretched along the posterolateral axis of the prostate and serve as the chosen route for tumors to spread to other areas. The prostate is typically the size and shape of a walnut or a golf ball. When this gland enlarges, it can potentially obstruct the flow of urine from the bladder through the urethra. Prostate enlargement occurs in almost all men with aging.[5]

Among U.S men, PCa is the second leading cause of cancer-related death.[6] Statistics published by the International Agency for Research on Cancer reveal that PCa is the second-most common cancer in males worldwide, with an incidence rate of 29.3 and a death rate of 7.6 per 100,000 individuals.[7] Lung and colon cancers rank first and third, respectively. Typically, the size of the prostate gland increases with age, thereby increasing the risk of PCa. This type of cancer is uncommon in men under the age of 50.[8]

Detecting PCa in its early stages, before it spreads to other parts of the body, is one of the most significant benefits of screening. This facilitates a smoother and shorter

How to cite this article: Alemi M, Banouei F, Ahmadi R. Comparison of diagnostic value between ^{99m}technetium-methylene diphosphate bone scan and ^{99m}technetium-prostate-specific membrane antigen scan in patients with prostate cancer with osseous metastases. Indian J Nucl Med 2023;38:340-9.

Address for correspondence:
Dr. Farshad Banouei, Urology and Nephrology Research Center, Hamedan University of Medical Sciences, Hamedan, Iran.
E-mail: farshadbanouei90@gmail.com

Received: 16-04-2023
Revised: 10-08-2023
Accepted: 25-09-2023
Published: 20-12-2023

Access this article online

Website: www.ijnm.in

DOI: 10.4103/ijnm.ijnm_52_23

Quick Response Code:

treatment process.[9] However, early detection of PCa may not necessarily result in improved health or increased life expectancy for patients. Some PCas are asymptomatic or pose no life-threatening risks. Nevertheless, if detected through screening tests, this may lead to unnecessary treatment procedures, and it is still unclear whether treating these cancers is effective.[10] The impact on life expectancy for these patients remains uncertain. Certain PCa treatments, including extensive prostate surgery and radiation therapy, can have long-term side effects in many men. The most common side effects are erectile dysfunction and urinary incontinence. In addition, these patients face a higher risk of mortality from cardiovascular diseases or suicide.[11]

Today, the management of advanced PCa has undergone significant changes with the introduction of several new and effective treatments. These treatments have resulted in improved patient survival. Moreover, the availability of more accurate imaging techniques has enabled physicians to make better treatment decisions for these patients. This, in turn, leads to enhanced patient care. The development of modern imaging methods has been driven by multiple factors, including more accurate staging and earlier detection of metastatic disease, precise identification of oligometastatic disease, and optimal assessment of treatment response. Advanced imaging modalities such as whole-body magnetic resonance imaging (MRI) and molecular imaging using combined positron emission tomography (PET) and computer tomography (CT) imaging, as well as combined PET and MRI utilizing new radiopharmaceuticals, offer novel opportunities for imaging that support and refine management approaches in patients with advanced PCa.[12]

Given the widespread prevalence of PCa and the significant costs incurred by patients and the healthcare system during diagnosis and treatment, the utilization of effective and cost-efficient diagnostic and treatment approaches holds great importance. Consequently, current efforts are focused on maximizing efficiency in the diagnosis and treatment process for these patients through the adoption of new technologies and advanced imaging methods. One of the most effective approaches in this regard is the utilization of traditional whole-body imaging and prostate-specific membrane antigen (PSMA) scanning.

Whole-body scintigraphy is a widely utilized imaging modality with high sensitivity for assessing bone metastasis in PCa. Its availability and low cost have made it a longstanding option. However, the accumulation of the radiopharmaceutical in degenerative, traumatic, and inflammatory lesions limits its comparability. In addition, this method is employed for treatment response monitoring and prognostic prediction in patients.[13]

The PSMA scan is a novel technique employed in nuclear medicine centers for the diagnosis and treatment of PCa. This scan encompasses various diagnostic and therapeutic approaches that utilize specific radioligands to target the PSMA protein found on the cell membrane. Initially discovered on prostate tumors, this protein is referred to as PSMA or folate hydrolase. The excessive accumulation of PSMA protein in cancer cells triggers assimilation, leading to tumor growth, proliferation, and metastasis. In addition, radioligand therapy, utilizing a chemical substance with a urea backbone that binds to cancer cells, can be utilized to eliminate other tumors. The intravenous injection method in PSMA treatment, which involves targeting radioligands, is well-tolerated by the patient's body and can be repeated multiple times. Statistics demonstrate that the positive impact of PSMA treatment is notable, even in advanced stages of cancer and in over 80% of affected patients.[14]

The Partin tables are validated predictive tools that utilize information from the digital rectal exam, serum prostate-specific antigen (PSA), and Gleason score to estimate the stage of PCa. These tables assess the risk of extracapsular extension (ECE), but they do not provide specific details regarding the location or extent of ECE, which is crucial for optimizing further treatment decisions. Prostate MRI has demonstrated its value in predicting ECE across all risk groups, with the most significant additional benefit observed in high-risk patients.[15] Furthermore, MRI has been shown to enhance other risk stratification tools and nomograms, such as the Kattan nomograms and the D'Amico classification, improving their accuracy in assessing PCa risk.[16]

Due to the limited availability of diagnostic and treatment resources in many developing countries, our study aimed to compare two specific scans based on the facilities accessible in these regions. For instance, while the comparison between ^{99m}Technetium (TC)-PSMA scan and ^{99m}TC-methylene diphosphate (MDP) scan with PSMA PET CT scan would provide more valuable insights, we refrained from including PSMA PET CT scan in this study due to its limited accessibility in many regions of these countries. Instead, we made an effort to design the study utilizing the simplest and most accessible facilities available in these regions.

Methods

The present study is a prospective study conducted from March 2021 to January 2023. It included 40 patients with previously diagnosed PCa through biopsy and other clinical investigations.

To ensure a more precise examination of the patients and facilitate result analysis, the entire body was divided into 11 distinct areas. Each zone was examined as a separate area, as outlined below:

- Area 1: Skull
- Area 2: Clavicle
- Area 3: sternum
- Area 4: Thorax including the ribs
- Area 5: Scapula

- Area 6: forearm, wrist, and fingers of the upper limb
- Area 7: Humerus
- Area 8: Vertebral column, sacrum and pelvis
- Area 9: Femur
- Area 10: Knee
- Area 11: tibia and fibula and wrist and fingers of the lower limb.

Inclusion criteria

- Willingness of patients to perform scans and participate in the study
- Availability of ^{99m}TC-PSMA bone scan and ^{99m}TC-MDP bone scan and MRI and having at least one of the following:
  - PSA >2 after radiotherapy
  - PSA >1 after radical prostatectomy
  - Pain in the bone
  - Stage T_1+ PSA >20
  - Stage T_2+ PSA >10
  - Gleason score 8–10
  - Stage T_{2c}
  - High alkaline phosphatase level.

Exclusion criteria

- Lack of satisfaction of patients to scan
- Receiving any radiopharmaceuticals within 10 days before the study
- History of previous sensitivity to radiopharmaceuticals

First, laboratory tests were conducted for the patients, including measurement of PSA and alkaline phosphatase levels. Subsequently, the patients underwent ^{99m}TC-MDP scan using the following procedure: 4 h after the injection of 20 milicurie (mCi) of TC MDP, whole-body scintigraphy was performed on both anterior and posterior projections, followed by single photon emission CT (SPECT) acquisition.

Subsequently, with a 10-day interval to ensure the elimination of the radiopharmaceutical from the body, the patients underwent ^{99m}TC-PSMA scan. The procedure involved the intravenous injection of 20 mCi TC-HYNC-PSMA, followed by whole-body imaging in the anterior and posterior projections at 30 and 240 min postinjection. In addition, SPECT images of the pelvic and chest regions were obtained 4 h postinjection.

Following the completion of these two scans, conducted 10 days apart, the patients underwent whole-body diffusion-weighted imaging MRI. The results of these examinations were summarized and interpreted by three nuclear medicine specialists and three radiologists. In cases where all three experts did not reach a consensus, the respective sample was excluded from the study.

Both scans were then compared and analyzed using the results from the MRI scans as a reference. To collect data for the study, a questionnaire was utilized. The questionnaire included information about the Gleason score of the disease, the serum alkaline phosphatase levels, and the location of detected metastasis in different types of scans. The collected data were analyzed using SPSS22 software that manufactured by International Business Machines Corporation that is an American multinational technology corporation headquartered in Armonk, New York. Analytical information was presented in the form of tables, ratios, and percentages. A 2 × 2 table was created in SPSS, and to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of Bone Scan ^{99m}TC-PSMA and ^{99m}TC-MDP Bone Scan compared to MRI, manual calculations were performed using the standard formulas.

Sensitivity was calculated by dividing the number of true positives by the total number of patients diagnosed with the scans, while specificity was calculated by dividing the number of true negatives by the total number of healthy individuals. Diagnostic accuracy was determined by dividing the sum of true negative and true positive cases by the total number of patients and healthy individuals.

To measure the positive and NPVs, the PPV was calculated by dividing the number of true positives by the sum of true positives and false positives, while the NPV was calculated by dividing the number of true negatives by the sum of true negatives and false negatives.

Results

In the statistical analysis conducted on the data obtained from this study, MRI was considered as the reference, and the results of both scans were compared. In this comparison, the sensitivity of ^{99m}TC-MDP scan was found to be 88.2%, while the sensitivity of ^{99m}TC-PSMA scan was 94.1%. This difference was determined to be statistically significant ($P < 0.007$).

The specificity of both ^{99m}TC-MDP scan and ^{99m}TC-PSMA scan was 83.3%, and no significant difference was observed ($P < 0.013$).

Regarding the PPV, both ^{99m}TC-MDP scan and ^{99m}TC-PSMA scan showed values of 96.7% and 96.9% respectively, indicating their similarity.

The NPV of ^{99m}TC-MDP scan was 55.5%, whereas the NPV of ^{99m}TC-PSMA scan was 83.3%. This difference was found to be statistically significant ($P < 0.003$).

The diagnostic accuracy of ^{99m}TC-MDP scan was determined to be 87.5%, while the accuracy of ^{99m}TC-PSMA scan was 92.5%. This difference was also statistically significant [$P < 0.01$, Table 1].

In the next stage, the patients' PSA levels were categorized into two groups: PSA levels <10 ng/dL as negative PSA and PSA levels >10 ng/dL as positive PSA. Among the patients, 3 individuals (7.5%) had PSA levels <10 ng/dL, while 37 patients (92.5%) had PSA levels >10 ng/dL.

Subsequently, the results of both scans were compared in relation to the positive or negative PSA groups, and the findings were as follows:

The sensitivity of ^{99m}TC-MDP scan was 91.8%, while the sensitivity of ^{99m}TC-PSMA scan was slightly higher at 94.5%. However, this difference was not statistically significant ($P < 0.006$).

The specificity of ^{99m}TC-MDP scan was 33.3%, whereas the specificity of ^{99m}TC-PSMA scan was 66.6%. This difference was found to be statistically significant ($P < 0.008$).

The PPV of ^{99m}TC-MDP scan was 94.4%, and the NPV of ^{99m}TC-PSMA scan was 97.2%. The difference between these values was not statistically significant ($P < 0.0017$).

The NPV of ^{99m}TC-MDP scan was 25%, while the NPV of ^{99m}TC-PSMA scan was 50%. This difference was statistically significant ($P < 0.009$).

The diagnostic accuracy of ^{99m}TC-MDP scan was 87.5%, and the diagnostic accuracy of ^{99m}TC-PSMA scan was 92.5%. This difference was also statistically significant ($P < 0.05$).

In the next step, the data obtained from this study were further examined and evaluated in detail. Each of the 11 areas of the body underwent individual ^{99m}TC-MDP scan, ^{99m}TC-PSMA scan, and MRI, resulting in a total of 440 areas being assessed.

The patients were then divided into two age groups: those who were <60 years old and those who were more than 60 years old. Among the patients, 9 individuals (22.5%) were <60 years old, while 31 patients (77.5%) were more than 60 years old. The results of both scans were compared based on age, and in the group of patients <60 years old, a total of 3 areas (3%) showed false results in ^{99m}TC-PSMA scan, and 5 areas (5%) showed false results in ^{99m}TC-MDP scan. However, the difference between these results was not statistically significant [$P < 0.01$, Table 2].

In the age group of more than 60 years, a total of 6 areas (1.8%) showed false results in ^{99m}TC-PSMA scan, while a total of 12 areas (3.6%) showed false results in ^{99m}TC-MDP scan. This difference was found to be statistically significant [$P < 0.01$, Table 3].

In the subsequent stage, the patients were categorized into five groups based on their Gleason score. Among the patients, 3 individuals (7.5%) had a Gleason score of 6 or less, 15 patients (37.5%) had a Gleason score of 7 (3+4 or 4+3), 7 patients (17.5%) had a Gleason score

Table 1: Comparison of the diagnostic value of ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan

Scan type	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
^{99m}TC-PSMA scan	94.1	83.3	96.9	83.3	92.5
^{99m}TC-MDP scan	88.2	83.3	96.7	55.5	87.5

PPV: Positive predictive value, NPV: Negative predictive value

Table 2: Comparison of the diagnostic value of ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan according to age in patients <60 years old with prostate cancer with bone metastases

Scan type	The results of the scans	The results of the scans separately (%)
^{99m}TC-PSMA scan	27 positive areas	25 true-positive areas (25.3)
Number of 9 patients and a total of 99 areas		2 false-positive areas (2)
	72 negative areas	71 true-negative areas (71.7)
		1 false-negative areas (1)
^{99m}TC-MDP scan	25 positive areas	23 true-positive areas (23.3)
Number of 9 patients and a total of 99 areas		2 false-positive areas (2)
	74 negative areas	71 true-negative areas (71.7)
		3 false-negative areas (3)

Table 3: Comparison of the diagnostic value of ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan according to age in patients over 60 years old with prostate cancer with bone metastases

Scan type	The results of the scans	The results of the scans separately (%)
^{99m}TC-PSMA scan	53 positive areas	49 true-positive areas (14.4)
The number of 31 patients and a total of 341 areas		4 false-positive areas (1.2)
	288 negative areas	286 true-negative areas (83.8)
		2 false-negative areas (0.6)
^{99m}TC-MDP scan	53 positive areas	46 true-positive areas (13.6)
The number of 31 patients and a total of 341 areas		7 false-positive areas (2)
	288 negative areas	283 true-negative areas (82.8)
		5 false-negative areas (1.6)

of 8, 11 patients (27.5%) had a Gleason score of 9, and 4 patients (10%) had a Gleason score of 10. The results of the scans were then compared separately for each group.

In the first group, no false results were observed for both ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan (0%) [Table 4].

In the second Group, 2 areas (1.2%) showed false results in ^{99m}TC-PSMA scan, while 6 areas (3.6%) showed false results in ^{99m}TC-MDP scan [Table 5].

In the third group, 3 areas (3.9%) yielded false results in ^{99m}TC-PSMA scan, while 1 area (1.3%) showed false results in ^{99m}TC-MDP scan [Table 6].

In the fourth group, 4 areas (3.3%) showed false results in both ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan [Table 7].

In the fifth group, 2 areas (4.4%) showed false results in both ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan, and these differences were not statistically significant [Table 8].

In the subsequent stage, the patients were categorized into three groups based on their serum PSA levels. Among the patients, 3 individuals (7.5%) had PSA levels <10, 3 patients (7.5%) had PSA levels between 10 and 20, and 36 patients (85%) had PSA levels >20.

In the first group, no false results were observed in ^{99m}TC-PSMA scan (0%), while 1 area (3.1%) showed false results in ^{99m}TC-MDP scan [Table 9].

In the second group, no false-positive results were observed for both ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan [Table 10].

In the third group, 9 areas (2.2%) showed false results in ^{99m}TC-PSMA scan, while 16 areas (4.2%) showed false results in ^{99m}TC-MDP scan [Table 11].

In the subsequent stage, the patients were divided into two groups based on their serum alkaline phosphatase levels.

Table 4: Comparison of diagnostic value of ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan according to Gleason score in patients with Gleason score 6 or less with prostate cancer with bone metastases

Scan type	The results of the scans	The results of the scans separately (%)
^{99m}TC-PSMA scan	0 positive areas	0 true-positive areas (0)
The number of 3 patients and a total of 33 areas	33 negative areas	0 false-positive areas (0) 33 true-negative areas (100) 0 false-negative areas (0)
^{99m}TC-MDP scan	0 positive areas	0 true-positive areas (0)
The number of 3 patients and a total of 33 areas	33 negative areas	0 false-negative areas (0) 33 true-negative areas (100) 0 false-positive areas (0)

Table 5: Comparison of diagnostic value of ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan according to Gleason score in patients with Gleason score 7 with prostate cancer with bone metastases

Scan type	The results of the scans	The results of the scans separately (%)
^{99m}TC-PSMA scan	18 positive areas	18 true-positive areas (10.9)
The number of 15 patients and a total of 165 areas	147 negative areas	0 false-positive areas (0) 145 true-negative areas (87.9) 2 false-negative areas (1.2)
^{99m}TC-MDP scan	22 positive areas	18 true-positive areas (10.9)
The number of 15 patients and a total of 165 areas	143 negative areas	4 false-positive areas (2.4) 141 true-negative areas (85.5) 2 false-negative areas (1.2)

Table 6: Comparison of diagnostic value of ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan according to Gleason score in patients with Gleason score 8 with prostate cancer with bone metastases

Scan type	The results of the scans	The results of the scans separately (%)
^{99m}TC-PSMA scan	12 positive areas	10 true-positive areas (12.9)
The number of 7 patients and a total of 77 areas	65 negative areas	2 false-positive areas (2.6) 64 true-negative areas (83.2) 1 false-negative areas (1.3)
^{99m}TC-MDP scan	9 positive areas	9 true-positive areas (11.7)
The number of 7 patients and a total of 77 areas	68 negative areas	0 false-positive areas (0) 67 true-negative areas (87) 1 false-negative areas (1.3)

Table 7: Comparison of diagnostic value of ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan according to Gleason score in patients with Gleason score 9 with prostate cancer with bone metastases

Scan type	The results of the scans	The results of the scans separately (%)
^{99m}TC-PSMA scan	21 positive areas	17 true-positive areas (14)
The number of 11 patients and a total of 121 areas		4 false-positive areas (3.3)
	100 negative areas	100 true-negative areas (82.7)
		0 false-negative areas (0)
^{99m}TC-MDP scan	19 positive areas	16 true-positive areas (13.2)
The number of 11 patients and a total of 121 areas		3 false-positive areas (2.4)
	102 negative areas	101 true-negative areas (83.4)
		1 false-negative areas (1.2)

Table 8: Comparison of diagnostic value of ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan according to Gleason score in patients with Gleason score 10 with prostate cancer with bone metastases

Scan type	The results of the scans	The results of the scans separately (%)
^{99m}TC-PSMA scan	13 positive areas	11 true-positive areas (25)
The number of 4 patients and a total of 44 areas		2 false-positive areas (4.4)
	31 negative areas	31 true-negative areas (70.6)
		0 false-negative areas (0)
^{99m}TC-MDP scan	11 positive areas	10 true-positive areas (22.8)
The number of 4 patients and a total of 44 areas		1 false-positive areas (2.2)
	33 negative areas	32 true-negative areas (72.8)
		1 false-negative areas (2.2)

Table 9: Comparison of diagnostic value of ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan according to serum prostate-specific antigen in patients with serum prostate-specific antigen level <10 and prostate cancer with bone metastases

Scan type	The results of the scans	The results of the scans separately (%)
^{99m}TC-PSMA scan	1 positive areas	1 true-positive areas (3.1)
The number of 3 patients and a total of 33 areas		0 false-positive areas (0)
	32 negative areas	32 true-negative areas (96.9)
		0 false-negative areas (0)
^{99m}TC-MDP scan	2 positive areas	1 true-positive areas (3.1)
The number of 3 patients and a total of 33 areas		1 false-positive areas (3.1)
	31 negative areas	31 true-negative areas (93.8)
		0 false-negative areas (0)

Table 10: Comparison of diagnostic value of ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan according to serum prostate-specific antigen level in patients with serum prostate-specific antigen level 10–20 with prostate cancer with bone metastases

Scan type	The results of the scans	The results of the scans separately (%)
^{99m}TC-PSMA scan	4 positive areas	4 true-positive areas (12.1)
The number of 3 patients and a total of 33 areas		0 false-positive areas (0)
	29 negative areas	29 true-negative areas (87.9)
		0 false-negative areas (0)
^{99m}TC-MDP scan	4 positive areas	4 true-positive areas (12.1)
The number of 3 patients and a total of 33 areas		0 false-positive areas (0)
	29 negative areas	29 true-negative areas (87.9)
		0 false-negative areas (0)

Among the patients, 12 individuals (30%) had normal alkaline phosphatase levels, while 28 patients (70%) had elevated alkaline phosphatase levels.

In the first group, false results were observed in 2 areas (1.6%) for ^{99m}TC-PSMA scan and 4 areas (3.2%) for ^{99m}TC-MDP scan [Table 12].

In the second group, false results were observed in 7 areas (2.2%) for ^{99m}TC-PSMA scan and in 13 areas (4.2%) for ^{99m}TC-MDP scan [Table 13].

Discussion

A bone scan, which is the most commonly used imaging technique for assessing bone metastasis, is known for its high sensitivity. However, it is also characterized by low specificity. MDP bone scan reveals reactive bone deposition rather than directly detecting the presence of cancer cells. This means that benign conditions can sometimes resemble tumors, and early-stage therapeutic changes may not be discernible. Moreover, the scan cannot differentiate between regression and progression. As a result, the practical application of MDP is somewhat restricted in today's clinical practice.[17]

In the study conducted by Fallah *et al*., which aimed to review and compare scans using 68Ga-PSMA PET/CT and ^{99m}Tc-PSMA SPECT/CT, it was observed that the diagnostic accuracy for detecting prostate bed lesions was slightly higher in 68Ga-PSMA PET/CT compared to ^{99m}Tc-PSMA SPECT/CT. However, when it came to lesions outside the prostate, both scans showed comparable diagnostic accuracy. Therefore, it appears that ^{99m}Tc-PSMA SPECT/CT could serve as a suitable alternative to 68Ga-PSMA PET/CT.[18]

The study conducted by Singh *et al*. concluded that the combination of whole-body ^{99m}Tc-PSMA with regional SPECT/CT shows promise as a potential alternative to 68Ga-PSMA PET in detecting advanced-stage metastatic PCa and evaluating the response to PSMA-based targeted therapies.[19]

Currently, numerous studies are being conducted to overcome obstacles, enhance diagnostic accuracy, and evaluate the strengths and limitations of the aforementioned

Table 11: Comparison of diagnostic value of ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan according to serum prostate-specific antigen in patients with serum prostate-specific antigen level >20 in patients with prostate cancer with bone metastases

Scan type	The results of the scans	The results of the scans separately (%)
^{99m}TC-PSMA scan	56 positive areas	52 true-positive areas (14)
The number of 34 patients and a total of 374 areas		4 false-positive areas (1)
	318 negative areas	313 true-negative areas (83.8)
		5 false-negative areas (1.2)
^{99m}TC-MDP scan	57 positive areas	49 true-positive areas (13.2)
The number of 34 patients and a total of 374 areas		8 false-positive areas (2.1)
	317 negative areas	309 true-negative areas (82.6)
		8 false-negative areas (2.1)

Table 12: Comparison of the diagnostic value of ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan according to the level of serum alkaline phosphatase in patients with alkaline phosphatase <160 with prostate cancer with bone metastases

Scan type	The results of the scans	The results of the scans separately (%)
^{99m}TC-PSMA scan	13 positive areas	11 true-positive areas (8.3)
The number of 12 patients and a total of 132 areas		2 false-positive areas (1.6)
	119 negative areas	119 true-negative areas (90.1)
		0 false-negative areas (0)
^{99m}TC-MDP scan	13 positive areas	10 true-positive areas (7.5)
The number of 12 patients and a total of 132 areas		3 false-positive areas (2.4)
	119 negative areas	118 true-negative areas (89.3)
		1 false-negative areas (0.8)

Table 13: Comparison of the diagnostic value of ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan according to the level of serum alkaline phosphatase in patients with alkaline phosphatase >160 with prostate cancer with bone metastases

Scan type	The results of the scans	The results of the scans separately (%)
^{99m}TC-PSMA scan	50 positive areas	47 true-positive areas (15.3)
The number of 28 patients and a total of 308 areas		3 false-positive areas (0.9)
	258 negative areas	254 true-negative areas (82.5)
		4 false-negative areas (1.3)
^{99m}TC-MDP scan	50 positive areas	44 true-positive areas (14.3)
The number of 28 patients and a total of 308 areas		6 false-positive areas (1.9)
	258 negative areas	251 true-negative areas (81.5)
		7 false-negative areas (2.3)

scans. These studies aim to combine the findings of these scans with other imaging modalities such as MRI and CT scan. The outcomes of these studies have revealed a diverse range of advantages and disadvantages, along with improvements in sensitivity, specificity, and positive and NPVs associated with these scans.

The investigation of SPECT tracers in the management of PCa is gaining momentum. This is primarily due to the limitations on accessing PET and the comparatively higher costs associated with instrumentation and radionuclides used in PET, which are prevalent in many countries.[20-23]

While the utilization of imaging modalities such as SPECT/CT can be highly beneficial for detecting suspicious lesions in ^{99m}TC-MDP scan and ^{99m}TC-PSMA scan, the limitations in terms of facilities and access to these modalities have resulted in their restricted use in developing countries. In such cases, alternative methods that are more accessible, such as MRI or a combination of clinical symptoms, should be considered.

In the present study, the sensitivity of ^{99m}TC-MDP scan was 88.2%, while the sensitivity of ^{99m}TC-PSMA scan was 94.1%. These values were relatively higher compared to those reported in other studies.[24]

Regarding specificity, ^{99m}TC-MDP scan exhibited a specificity of 83.3%, while ^{99m}TC-PSMA scan showed the same specificity value. However, these values were slightly lower compared to the reported values of 94% and 92%, respectively, in other studies.[25]

The PPV of ^{99m}TC-MDP scan was 96.7%, while the PPV of ^{99m}TC-PSMA scan was 96.9%. These values were slightly lower than the range of 88%–94% reported in other studies.[26]

For the NPV, ^{99m}TC-MDP scan had a value of 55.5%, and ^{99m}TC-PSMA scan had a value of 83.3%. These values were somewhat lower compared to the reported range of 80%–89% for both scans in other studies.[27]

In terms of accuracy, ^{99m}TC-MDP scan had an accuracy of 87.5%, while ^{99m}TC-PSMA scan had an accuracy of 92.5%. These values were slightly higher compared to the reported values of approximately 72% for ^{99m}TC-PSMA scan and 83% for ^{99m}TC-MDP scan in other studies.[28,29]

A study conducted by Zhao and Ji revealed that on an individual patient basis, 68Ga-PSMA-11 PET/CT demonstrates superior diagnostic performance compared to ^{99m}Tc-MDP BS for the detection of bone metastases in PCa. The findings suggest that the use of 68Ga-PSMA-11 PET/CT is more effective in identifying bone metastases in PCa patients.

In addition, the study highlights that when 68Ga-PSMA-11 PET/CT yields negative results, the utilization of ^{99m}Tc-MDP BS offers limited additional information. This suggests that in cases where 68Ga-PSMA-11 PET/CT provides negative findings, the use of ^{99m}Tc-MDP BS may not significantly contribute to further diagnostic insights in relation to bone metastases detection.[30]

In this study, 97% of the results obtained from the examination of organs using ^{99m}TC-PSMA scan were reported as true, while 3% were reported as false. Similarly, for the examination conducted using ^{99m}TC-MDP scan, 95% of the results were true, and 5% were false. In the age group over 60 years, 98.2% of the examinations performed with ^{99m}TC-PSMA scan were reported as true, with 1.8% being false. In the same age range, 96.5% were true for ^{99m}TC-MDP scan, and 3.5% were false. These findings indicate the higher accuracy of ^{99m}TC-PSMA scan in both age groups examined. It is worth noting that a similar investigation focusing on age has not been conducted in similar studies to date.

In the present study, when examining patients based on their Gleason score, it was observed that there was no significant difference in the diagnostic value between ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan. However, in cases with lower Gleason scores, the scan appeared to have a slightly higher diagnostic value compared to those with higher Gleason scores. This observation may be attributed to the smaller sample size in the lower Gleason score group, although it was not statistically significant.

In the investigations conducted on the samples based on the serum PSA level in these patients, it was observed that the diagnostic value of ^{99m}TC-PSMA scan was slightly higher compared to ^{99m}TC-MDP scan across three ranges of PSA levels: <10, 10–20, and more than 20. Among these ranges, in the group with PSA values > 20, which represented the majority of the samples, ^{99m}TC-PSMA scan yielded 97.8% true results and 2.3% false results, while ^{99m}TC-MDP scan showed 95.8% true results and 4.2% false results. These findings were consistent with similar studies conducted elsewhere.[31]

Furthermore, based on the serum alkaline phosphatase level, the patients were divided into two categories: those with alkaline phosphatase levels <160 and those with levels higher than 160. In the study focusing on this factor, the diagnostic value of ^{99m}TC-PSMA scan was slightly higher compared to ^{99m}TC-MDP scan. Specifically, in the group with alkaline phosphatase levels <160, 98.5% of the results from ^{99m}TC-PSMA scan were true, with 1.5% being false. For ^{99m}TC-MDP scan, the values were 96.9% true and 3.1% false. In the group with alkaline phosphatase levels above 160, ^{99m}TC-PSMA scan yielded 97.8% true results and 2.2% false results, while ^{99m}TC-MDP scan showed 95.8% true results and 4.2% false results. Although these values did not reach statistical significance, they indicate that the detection value of ^{99m}TC-PSMA scan was higher compared to ^{99m}TC-MDP scan.

This study was conducted in a developing country with limited treatment facilities. Due to the lack of access to numerous diagnostic and treatment resources in these countries, the objective of this study was to compare the diagnostic accuracy of these scans based on the available facilities. Although a more precise imaging method such as PSMA PET CT scan should ideally be used for the comparison between ^{99m}TC-PSMA scan and ^{99m}TC-MDP scan, the unavailability of this scan in many regions of these countries made it necessary to compare the scans based on the accessible facilities.

In addition, considering the limited treatment budget and restricted access to these two scans in these countries, this study aimed to assess the comparative advantages of each scan, allowing doctors to make more confident choices.

The results obtained from this study demonstrate the significant ability of both scans to detect PCa metastases. However, ^{99m}TC-PSMA scan holds the advantage of detecting metastases in both soft tissue and bone tissue. When it comes to detecting bone metastases, ^{99m}TC-PSMA scan showed comparable performance to ^{99m}TC-MDP scan. In a resource-limited setting like ours, ^{99m}TC-PSMA scan may serve as a preferable alternative to ^{99m}TC-MDP scan for staging and evaluating patients with biochemical progression after treatment. Additionally, it can assist in identifying patients eligible for radiolabeled ligand therapy, particularly those utilizing PSMA.

In general, based on the results obtained from this study and similar studies, it appears that for patients who can only undergo one scan, the utilization of PSMA scan is recommended due to its treatment role and usability. It serves as a superior choice, especially in ligand therapy such as 177 LU PSMA.

It is hopeful that conducting and publishing studies of this nature will contribute to the enhancement of healthcare in these underserved countries.

Conclusions

Nowadays, due to the numerous limitations present in developing countries and the escalating prevalence of PCa within these regions, the utilization of affordable and accessible diagnostic and treatment methods holds significant importance. In this context, the selection of the most suitable scan type for these patients carries great value, considering these constraints. Therefore, we anticipate that by conducting studies akin to this research, a pivotal stride can be taken toward enhancing the healthcare of patients in these countries.

Acknowledgments

I am grateful to all of those with whom I have had the pleasure to work during this and other related projects.

Authors contributions

Farshad Banouei (the corresponding author) is responsible for ensuring that the descriptions are accurate and agreed by all authors. All authors had made substantial contributions to all of the following: (1) the conception and design of the radiological work, (2) the measurement, analysis, and interpretation of data; (3) drafting the work and revising it; (4) conduction of revision and corrections as per reviewers' comments. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. All authors approved the revised version. All authors read and approved the final manuscript.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author.

Ethics approval and consent to participate

The medical ethics were considered and respected. The study was approved by the Institutional Ethics Committee in Hamedan University of Medical Sciences.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Cuomo D, Porreca I, Cobellis G, Tarallo R, Nassa G, Falco G, *et al.* Carcinogenic risk and Bisphenol A exposure: A focus on molecular aspects in endoderm derived glands. Mol Cell Endocrinol 2017;457:20-34.
2. Grieshammer U, Agarwal P, Martin GR. A Cre transgene active in developing endodermal organs, heart, limb, and extra-ocular muscle. Genesis 2008;46:69-73.
3. Ali A, Du Feu A, Oliveira P, Choudhury A, Bristow RG, Baena E. Prostate zones and cancer: Lost in transition? Nat Rev Urol 2022;19:101-15.
4. De Visschere P, Oosterlinck W, De Meerleer G, Villeirs G. Clinical and imaging tools in the early diagnosis of prostate cancer, a review. JBR BTR 2010;93:62-70.
5. Hammerich KH, Ayala GE, Wheeler TM. Anatomy of the prostate gland and surgical pathology of prostate cancer. In: Prostate Cancer, Published by Cambridge University Press. Cambridge: Cambridge University; 2009. p. 1-10.
6. Gupta N, Patel HD, Taylor J, Borin JF, Jacobsohn K, Kenfield SA, *et al.* Systematic review of the impact of a plant-based diet on prostate cancer incidence and outcomes. Prostate Cancer Prostatic Dis 2022;25:444-52.
7. Howe HL, Wingo PA, Thun MJ, Ries LA, Rosenberg HM, Feigal EG, *et al.* Annual report to the nation on the status of cancer (1973 through 1998), featuring cancers with recent increasing trends. J Natl Cancer Inst 2001;93:824-42.

8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
9. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, *et al.* EAU guidelines on prostate cancer. Part 1: Screening, diagnosis, and treatment of clinically localised disease. Eur Urol 2011;59:61-71.
10. Kramer BS, Brown ML, Prorok PC, Potosky AL, Gohagan JK. Prostate cancer screening: What we know and what we need to know. Ann Intern Med 1993;119:914-23.
11. Catalona WJ. Prostate cancer screening. Med Clin North Am 2018;102:199-214.
12. Perez-Lopez R, Tunariu N, Padhani AR, Oyen WJ, Fanti S, Vargas HA, *et al.* Imaging diagnosis and follow-up of advanced prostate cancer: Clinical perspectives and state of the art. Radiology 2019;292:273-86.
13. Langsteger W, Rezaee A, Pirich C, Beheshti M. (18) F-NaF-PET/CT and (99m) Tc-MDP bone scintigraphy in the detection of bone metastases in prostate cancer. Semin Nucl Med 2016;46:491-501.
14. Maurer T, Eiber M, Schwaiger M, Gschwend JE. Current use of PSMA-PET in prostate cancer management. Nat Rev Urol 2016;13:226-35.
15. Wang L, Hricak H, Kattan MW, Chen HN, Scardino PT, Kuroiwa K. Prediction of organ-confined prostate cancer: Incremental value of MR imaging and MR spectroscopic imaging to staging nomograms. Radiology 2006;238:597-603.
16. Murphy G, Haider M, Ghai S, Sreeharsha B. The expanding role of MRI in prostate cancer. AJR Am J Roentgenol 2013;201:1229-38.
17. Pandit-Taskar N, O'Donoghue JA, Durack JC, Lyashchenko SK, Cheal SM, Beylergil V, *et al*. A phase I/II study for analytic validation of 89Zr-J591 ImmunoPET as a molecular imaging agent for metastatic prostate cancer. Clin Cancer Res 2015;21:5277-85.
18. Fallahi B, Khademi N, Karamzade-Ziarati N, Fard-Esfahani A, Emami-Ardekani A, Farzanefar S, *et al.* 99mTc-PSMA SPECT/CT versus 68Ga-PSMA PET/CT in the evaluation of metastatic prostate cancer. Clin Nucl Med 2021;46:e68-74.
19. Singh B, Sharma S, Bansal P, Hooda M, Singh H, Parihar AS, *et al.* Comparison of the diagnostic utility of 99mTc-PSMA scintigraphy versus 68Ga-PSMA-11 PET/CT in the detection of metastatic prostate cancer and dosimetry analysis: A gamma-camera-based alternate prostate-specific membrane antigen imaging modality. Nucl Med Commun 2021;42:482-9.
20. Hicks RJ, Hofman MS. Is there still a role for SPECT-CT in oncology in the PET-CT era? Nat Rev Clin Oncol 2012;9:712-20.
21. Schmidkonz C, Hollweg C, Beck M, Reinfelder J, Goetz TI, Sanders JC, *et al.* (99m) Tc-MIP-1404-SPECT/CT for the detection of PSMA-positive lesions in 225 patients with biochemical recurrence of prostate cancer. Prostate 2018;78:54-63.
22. Rauscher I, Maurer T, Souvatzoglou M, Beer AJ, Vag T, Wirtz M, *et al.* Intrapatient comparison of 111In-PSMA I and T SPECT/CT and hybrid 68Ga-HBED-CC PSMA PET in patients with early recurrent prostate cancer. Clin Nucl Med 2016;41:e397-402.
23. Su HC, Zhu Y, Ling GW, Hu SL, Xu XP, Dai B, *et al.* Evaluation of 99mTc-labeled PSMA-SPECT/CT imaging in prostate cancer patients who have undergone biochemical relapse. Asian J Androl 2017;19:267-71.
24. Jain H, Sood R, Faridi MS, Goel H, Sharma U. Role of 68Ga-PSMA-PET/CT for the detection of primary prostate cancer prior to biopsy: A prospective study. Cent European J Urol 2021;74:315-20.
25. Bravaccini S, Puccetti M, Bocchini M, Ravaioli S, Celli M, Scarpi E, *et al.* PSMA expression: A potential ally for the pathologist in prostate cancer diagnosis. Sci Rep 2018;8:4254.
26. van Leeuwen PJ, Emmett L, Ho B, Delprado W, Ting F, Nguyen Q, *et al.* Prospective evaluation of 68Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer. BJU Int 2017;119:209-15.
27. Stabile A, Pellegrino A, Mazzone E, Cannoletta D, de Angelis M, Barletta F, *et al*. Can negative prostate-specific membrane antigen positron emission tomography/computed tomography avoid the need for pelvic lymph node dissection in newly diagnosed prostate cancer patients? A systematic review and meta-analysis with backup histology as reference standard. Eur Urol Oncol 2022;5:1-17.
28. Fendler WP, Schmidt DF, Wenter V, Thierfelder KM, Zach C, Stief C, *et al.* 68Ga-PSMA PET/CT detects the location and extent of primary prostate cancer. J Nucl Med 2016;57:1720-5.
29. Drakopoulos M, Vejdani K, Osman M. Comparison of diagnostic certainty and accuracy of 18F-NaF PET/CT and planar 99mTc-MDP bone scan in patients with prostate cancer. Journal of Nuclear Medicine 2014;55.
30. Zhao G, Ji B. Head-to-head comparison of (68) Ga-PSMA-11 PET/CT and (99m) Tc-MDP bone scintigraphy for the detection of bone metastases in patients with prostate cancer: A meta-analysis. AJR Am J Roentgenol 2022;219:386-95.
31. Pomykala KL, Czernin J, Grogan TR, Armstrong WR, Williams J, Calais J. Total-body (68) Ga-PSMA-11 PET/CT for bone metastasis detection in prostate cancer patients: Potential impact on bone scan guidelines. J Nucl Med 2020;61:405-11.