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Comparative Study of 18-F Sodium Fluoride PET/CT and Bone Scan in Determining Bone Lesions in Newly Diagnosed Prostate Cancer Patients

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ABSTRACT

Objective: To compare the diagnostic performance of bone scintigraphy and 18F-NaF-PET/CT in detection of bone metastasis in newly diagnosed high-grade prostate cancer patients.
Study Design: Comparative cross-sectional study.
Place and Duration of Study: Nuclear Medical Centre, Armed Forces Institute of Pathology and Armed Forces Institute of Radiology and Imaging, Rawalpindi Pakistan, from Jul 2020 to Dec 2022.
Methodology: Newly diagnosed high-grade prostate cancer patients with Gleason score ≥8 who underwent bone scintigraphy followed by 18F-NaF-PET/CT (Sodium Fluoride-Positron Emission Tomography/Computerized Tomography) for staging during study duration were included. We compared the diagnostic accuracy of both imaging modalities in detecting bone metastasis using two-point scale scoring system i.e., metastasis present or not present on per patient basis.
Results: A total of 45 patients with mean age 69.66±9.38 years and mean Prostatic Surface Antigen level 36.21±65.07 ng/ml were included. 18F-NaF-PET/CT detected bone metastasis in all 25 patients with bone metastasis (100%) compared to 20(80%) by bone scan. 4 patients had false-positive bone scan while 2 had false-positive 18F-NaF-PET/CT scan. Overall 18F-NaF-PET/CT demonstrated a higher sensitivity, specificity, positive predictive value, negative predictive value and accuracy compared to bone scan (100% vs 80%, 90% vs 80%, 92.59% vs 83.33%, 100% vs 76.19%, 95.56% vs 80% respectively).
Conclusion: 18F-NaF-PET/CT has better diagnostic performance than bone scintigraphy for the detection of bone metastasis in newly diagnosed high-grade prostate cancer patients.

Keywords: Bone scintigraphy, Prostate cancer, Radionuclide imaging, 18F-NaF-PET/CT.

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INTRODUCTION

Prostate cancer (PCa) is the second most frequently reported cancer worldwide with an estimated 248, 530 new cases and 34,130 cancer related deaths a year.[1] With recent advances in diagnostics and therapeutics, a significant improvement in overall survival and prognosis is observed.[2,3] Still, in developing and resource poor countries it contributes to significant cancer related mortality and morbidity due to limited access to health care facilities.[4]

Majority of the patients with advance PCa develop bony metastasis with approximately 90% of the patients having skeletal metastasis who died of prostate cancer.[5] Bony metastasis is the major prognostic factor and contributes to a substantial mortality and morbidity.

The planar whole-body skeletal scintigraphy or bone scan (BS) has been used conventionally to assess the presence and burden of disease.[6] Due to its sensitivity, affordability and accessibility it remains a prime diagnostic tool for disease assessment in prostate cancer patients with bone metastasis. However, despite its higher sensitivity, it is limited by low specificity due to radiotracer uptake in degenerative, traumatic and infectious lesions resulting in false positive results. The low specificity of planar imaging is addressed by hybrid imaging technique, single photon emission computed tomography fused with computed tomography (SPECT/CT). More than 90% of indeterminate bone lesions on planar imaging can be defined by SPECT/CT thus improving the diagnostic confidence.[7]

Positron Emission Tomography/Computed Tomography (PET/CT) is new hybrid molecular imaging modality that allows diagnosis, staging, treatment response monitoring, prognosis and surveillance. Royal Colleges of Physicians and Radiology (RCP, RCR), British Nuclear Medicine

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Society (BNMS) and European Association of Nuclear Medicine (EANM) recommend the use of 18F-NaF PET/CT for evaluation of benign and malignant bone etiologies.[8,9] Recently a number of studies have been done that document the superiority of 18F NaF PET/CT over bone scintigraphy in terms of better specificity and decreased incidence of false positive findings.[10]

Given the limited data in our population and clinical set up, we conducted this study comparing the role of both imaging modalities in detection of bone lesions in patients with newly diagnosed high grade Prostate Cancer.

METHODOLOGY

The comparative cross-sectional comparative study was conducted at Nuclear Medicine Centre, Armed Forces Institute of Pathology (AFIP) and Armed Forces Institute of Radiology Rawalpindi Pakistan, (AFIRI) from July 2020 to December 2022 after approval from Institutional Review Board (IRB certificate no. FC-NMC 19-11/READ-IRB/19/364).

Inclusion Criteria: Newly diagnosed prostate cancer patients with Gleason score ≥8 on histopathology and underwent Bone Scintigraphy (BS) followed by 18F-NaF-PET/CT were included.

Exclusion Criteria: Patients with prior history of malignancy or those with second malignancy or patients who had received therapy for PCa were excluded.

All patients meeting the inclusion criteria who reported to our center during study duration for staging work-up and underwent BS followed by 18F-NaF PET/CT imaging were included in our study (n=45). They were recruited using non-probability consecutive sampling and informed consent was obtained from all patients.

BS was done using dual-head gamma camera (Symbia T6) equipped with low energy high resolution (LEHR) parallel hole collimator (20% energy window set at peak of 140 keV using 256 x 256 matrix size). Tc-99m MDP was injected according to patient weight (550-740 MBq) followed by imaging 2.5 hours after injection. Anterior and posterior whole-body images followed by SPECT/CT of the required region was done. All images were processed using syngo workstation software (v. 2013, Siemens).

18F-NaF-PET/CT was done according to standard protocol using GE Discovery MI DR PET/CT scanner within 14 days after BS. Imaging was done 60 min after intravenous injection of NaF according to patient weight (296-444 MBq). First low-dose CT was acquired (140 kVP, 70-80 mA, 0.8 sec / CT rotation, pitch of 6 and table speed 22.5 m/sec) followed by PET scan (5-9 bed positions for 3 min each from skull to mid-thigh). CT acquisition data was used for attenuation correction while PET images were reconstructed using ordered-subsets expectation maximization algorithm. All scans were processed using GE AW server 3.2 ext 3.4.

BS images were interpreted as per consensus of two nuclear physicians while PET/CT as per consensus reading of a radiologist and a nuclear physician. For each patient, BS and PET/CT were interpreted using two scale scoring system i.e., metastasis present or not present. Clinical and imaging (BS, 18F-NaF-PET/CT, MRI, CT) follow-up for at least 12 months was used as reference standard in cases of discordant findings between both modalities. The diagnostic parameters of BS and PET/CT were calculated in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy by comparing with reference standard.

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 26. Qualitative data was presented as frequency and percentages while quantitative data was expressed as mean±standard deviation. Two-sample t-test was used to compare age and serum PSA levels with skeletal metastasis detection while Chi-square was used for Gleason score and clinical stage. Sensitivity, specificity, PPV, NPV and diagnostic accuracy were calculated using 2x2 table.

RESULTS

A total of 45 patients with newly diagnosed high grade PCa were included with mean age of 69.66±9.38 years and mean PSA level 36.21±65.07 ng/ml. Baseline clinicopathological characteristics of patients are shown in Table-I. Skeletal metastasis was confirmed in 25(55.6%) patients. Detection of skeletal metastasis is significantly associated with older age, raised serum PSA levels, Gleason score and clinical stage as shown in Table-II. All the patients without skeletal metastasis remained clinically and radiologically free from bone metastasis for at least 6 months after initial staging. Table-III shows concordance between bone scan and 18F-NaF-PET/CT for detection of metastatic lesions. Of 5 patients with false-negative bone scan and positive 18F-NaF-

PET/CT scan, 3 had progressive disease with rising PSA levels and positive scan findings at 6 months follow-up while 2 had confirmatory metastatic lesions on MRI. For the 4 patients with false positive scan findings, clinical, radiological and bone scan follow-up did not reveal any evidence of disease. Similarly, 2 patients with false-positive 18F-NaF-PET/CT scan had no metastatic disease on follow-up scan.

Table-IV summarizes sensitivity, specificity, PPV, NPV and overall accuracy of bone scintigraphy and 18F-NaF-PET/CT for detection of skeletal metastasis.

Table-I: Clinicopathological Characteristics of Patients (n=45)

Characteristics	Values
Age (years), Mean±SD	69.66±9.38
PSA level (ng/ml), Mean±SD	36.21±65.07
Gleason Score, n(%)	
8	22(48.9%)
9	19(42.2%)
10	4(8.9%)
Clinical Stage, n(%)	
1-2	31(68.9%)
3-4	14(31.1%)

Table-II: Patient Stratification Based on the Presence of Skeletal Metastasis (n=45)

Characteristics	Skeletal Metastasis (+)	Skeletal Metastasis (-)	*p*-value
Patients, n(%)	25(55.6%)	20(44.4%)	
Age (years), Mean±SD	72.60±6.44	66±11.22	0.005
PSA level (ng/ml), Mean±SD	58.28±80.83	8.62±10.53	0.007
Gleason Score, n(%)			
8 9-10	8 (32%) 17 (68%)	14 (70%) 6 (30%)	0.021
Clinical Stage, n(%)			
1-2 3-4	14(56%) 11(44%)	17(85%) 3(15%)	0.029

Table-III: Concordance between Bone Scintigraphy and 18F-NaF PET/CT for Detection of Skeletal Metastasis (n=45)

	Bone Scintigraphy (+)	Bone Scintigraphy (-)	Total
18F NaF PET/CT (+)	20	7	27
18F NaF PET/CT (-)	4	14	18
Total	24	21	45

DISCUSSION

In current prospective study we compare the diagnostic performance of Tc-99m MDP BS and 18F-NaF-PET/CT in detecting bone metastasis in newly diagnosed PCa with Gleason score ≥8. Out of total 45 patients bone metastasis were detected in 25(55.6%) patients. Other similar studies to ascertain the diagnostic accuracy of various imaging modality in newly diagnosed high-grade PCa patients and found skeletal metastasis in 52% patients.[11,12] Similarly, in a cross-sectional observational study conducted in Beijing China, 44.1% patients had bone metastasis at diagnosis.[13]

In the present study, we have found that detection of bone metastasis is significantly associated with serum PSA level, age, Gleason score and clinical stage of cancer. Otis *et al*. also have similar findings in their study.[14] A number of studies have been done in this regard with consistent findings that these parameters are associated with higher prevalence of bone metastasis and ultimately poor prognosis.[15,16]

In our study, we found that 18F-NaF-PET/CT was more accurate than BS in detecting skeletal metastatic lesion with better sensitivity and specificity. Our calculated sensitivity, specificity, PPV, NPV and accuracy for 18F-NaF-PET/CT were 100%, 90%, 92.59%, 100% and 95.56% respectively while for BS they were 80%, 80%, 83.33%, 76.19% and 80% respectively. Even-Sapir *et al*. prospectively compare the diagnostic performance of BS and 18F-NaF-PET/CT in 44 newly diagnosed high-grade PCa patients.[17] They reported a sensitivity, specificity, PPV and NPV of 57%, 57%, 59% and 55% respectively for BS while 100%, 82%, 87% and 100% for 18F-NaF-PET/CT. Jambor *et al*. conducted a prospective comparison of diagnostic performance of BS and 18F-NaF-PET/CT in high-grade PCa patients, concluding that 18F-NaF-PET/CT exhibited better sensitivity when compared to BS (89% vs 78%).[18] Fonager *et al*. prospectively compared the BS and 18F-NaF-PET/CT in detecting bone lesions in 37 newly diagnosed PCa patients.[19] The sensitivity, specificity, PPV and NPV were 78%, 90%, 96% and 60% respectively for BS while 89%, 90%, 96% and 75% respectively for 18F-NaF-

Table-IV: Diagnostics Parameters of Bone Scintigraphy and 18F-NaF PET/CT (n=45)

	Bone Scintigraphy	18F-NaF PET/CT
Sensitivity	80%(59.30-93.17)	100%(86.28-100)
Specificity	80%(56.34-94.27%)	90%(68.30-98.77)
Positive Predictive Value	83.33%(67.07-92.47)	92.59%(77.05-97.9)
Negative Predictive Value	76.19%(58.64-87.84)	100%(N/A)
Accuracy	80%(65.40-90.42%)	95.56%(84.85-99.46)

PET/CT. Recently a number of studies have been done in this regard which advocate superiority of 18F-NaF-PET/CT compared to BS for localization of bone metastasis in patients with PCa.[20,21]

LIMITATIONS OF STUDY

Our study was limited by the fact that we did not have histological confirmation of the discordant skeletal metastatic lesions as bone biopsies are very painful, challenging and not routinely performed in any center. This lack of gold standard can contribute toward false-positive and false-negative outcome for both modalities and may affect sensitivity and specificity.

CONCLUSION

18F-NaF-PET/CT has better diagnostic performance than Bone Scintigraphy for the detection of bone metastasis in newly diagnosed high-grade prostate cancer patients and can be utilized as potential primary staging imaging modality in such patients.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MUI & FH: Data acquisition, critical review, approval of the final version to be published.

MA & SZD: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MA & MIB: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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