How to Cite:
Badr, S. A., Moustafa, H., Omar, W., Siddiq, I., & Elahmadawy, M. A. (2022). Diagnostic & prognostic impact of 18F-NaF PET/CT versus 99mTc-MDP bone scan in detection of bone metastases: Initial and follow up assessment. *International Journal of Health Sciences*, *6*(S9), 2795–2812.
https://doi.org/10.53730/ijhs.v6nS9.13075

Diagnostic & prognostic impact of 18F-NaF PET/CT versus 99mTc-MDP bone scan in detection of bone metastases: Initial and follow up assessment

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***Abstract*---**Purpose: To assess the role of ^{18}F-NaF PET/CT in the detection of metastatic bone disease compared to ^{99m}Tc-MDP bone scan (+/-SPECT/CT). Methods: 64 adult patients with locally advanced primary tumor were enrolled in this study. All patients underwent pretherapy ^{18}F-NaF PET/CT and ^{99m}Tc-MDP bone scan. Results: Among the 64 patients ^{18}F-NaF PET/CT revealed positive bone metastases in 26 patients, only 19 of them have positive results in ^{99m}Tc-MDP bone scan, while the remaining 7 patients were falsely negative in ^{99m}Tc-MDP bone scan. On the other hand ^{18}F-NaF PET/CT diagnosed 38 patients free of osseous metastases, 5 patients of them were falsely diagnosed having osseous metastases by ^{99m}Tc-MDP bone scan. None of patient has positive bone metastases by ^{99m}Tc-MDP & negative ^{18}F-NaF PET/CT for bone metastases in our study group. The overall results revealed significant higher sensitivity for ^{18}F-NaF PET/CT (100%) compared to ^{99m}Tc-MDP bone scan (73.08%) ($P<0.05$)

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
Manuscript submitted: 9 May 2022, Manuscript revised: 18 July 2022, Accepted for publication: 27 August 2022

as well as higher specificity for ^{18}F-NaF PET/CT (100%) compared to ^{99m}Tc-MDP bone scan (86.8%) ($P<0.05$). Conclusion: 18F-NaF PET/CT is a high-quality skeletal imaging with convenient diagnostic performance in either lytic or sclerotic bone lesions surpassing that of Tc99m MDP, with lower equivocal interpretations.

***Keywords*---**Naf PET/CT, Bone metastases, ^{99m}Tc-MDP bone scans.

Introduction

Metastasis of malignant neoplasms to bone is not uncommon, osseous metastasis being far more prevalent than primary bone malignancies. For hematogenous malignant cells spread, bone is considered the third preferable site after liver and lungs. Cancers that are preferably associated with bone metastases include those of the prostate and breast (65-75% of patients) and those affecting the lung (30-40%) and kidney (20-32%). Early detection of skeletal metastasis is critical for accurate staging and optimal treatment; allowing implementation of treatment strategies to reduce the risk of complications and improve quality of life [1].

^{99m}Tc-methylene diphosphonate (MDP) planar bone scan or single-photon emission computed tomography (SPECT) is widely used as noninvasive methods for detecting osseous metastases. However, these methods cannot obtain cross-sectional images of all the lesions, and they have lower resolution than other imaging techniques, such as positron emission tomography/computed tomography (PET/CT) [2].

^{18}F-Sodium fluoride (^{18}F-NaF) is a PET tracer for bone imaging which was initially approved for the clinical use by the U.S FDA in 1972. It has been proven to be an excellent bone-seeking agent. It has high image quality, spatial resolution and greater sensitivity than conventional ^{99m}Tc-MDP bone scintigraphy, due to its rapid bone uptake, minimal serum protein binding, rapid first-pass extraction and faster blood clearance. Many studies support the clinical utility of ^{18}F-NaF-PET/CT in assessing the extent of metastatic bone disease in oncologic patient [3]. In addition to high diagnostic performance , ^{18}F-NaF-PET/ CT was shown to impact the patient management and provides prognostic information in multiple clinical scenarios [4].

There is still no clear estimate if 18F-NaF-PET/CT can replace the routinely used ^{99m}Tc-MDP bone scan in the detection of osseous metastases especially in patients with high clinical suspicion of osseous metastases. The aim of this study was to assess the value of ^{18}F-NaF PET/CT in evaluation of osseous metastases in patients with locally advanced primary tumors in respect to:- Its role in diagnosis of osseous metastases compared to planner ^{99m}Tc-MDP bone scan and/or SPECT/CT in initial assessment of patients with locally advanced primary tumors. Influence of osseous metastases detected by ^{18}F-NaF PET/CT on therapy outcome.

Patients and Methods

This prospective study was performed in National Cancer Institute (NCI) Egypt at the period between first June 2018 and 1st October 2019. Sodium Fluoride fluorine-18 was produced at children cancer hospital Egypt (CCHE) specifically for this research. Sixty four patients with histopathologically proven locally advanced malignancy in the initial pre-therapy phase were recruited in this study. All patients scheduled for planner 99mTc-MDP bone scan with SPECT/CT and 18F-NaF PET/CT within a period of maximum one week apart. Follow up 18F-NaF PET/CT scan was performed within a period of 6-12 months from the specific treatment.

All patients were informed about details of the study. The ethical committee of NEMROCK and the radiation safety committee at NCI had given approval for study design. Patients with different primary tumors were categorized into 3 groups: Tumors that have tendency to give osteoblastic osseous metastases (prostate cancer), Tumors that have tendency to give lytic osseous metastases (lung and HCC). Tumors that have tendency to give mixed osteoblastic and lytic osseous metastases (breast, mesothelioma, urinary bladder, pancreas, ovary and nasopharyngeal tumors).

Imaging and related procedures

Planar whole-body bone scan (+/- SPECT/CT), and ^{18}F-NaF PET/ CT were performed within a timeframe of seven days.

^{18}F-NaF PET/CT

Patient preparation: patients were instructed to be well-hydrated between the time of radiopharmaceutical injection and the time of imaging, and to empty their bladder frequently between the injection and delayed imaging, including immediately before the scan.

Acquisition: ^{18}F-NaF PET/CT scans were performed using Discovery PET-CT scanner (GE Medical System, USA). All scans were performed 60 min after the intravenous administration of approximately 370–555MBq (10–15mCi) of ^{18}F-NaF in 3D mode from the vertex to foot, encompassing 12-14 bed positions (120 s per bed position). The non-contrast-enhanced low-dose CT was acquired using the following parameters: 140 kV, 80 mA, PITCH: 1.375, slice thickness: 3.75 mm. No CT contrast agents were administered. Both PET and CT scans were performed for patients under normal tidal breathing.

Processing: From the raw emission data collected, the image was reconstructed by iterative reconstruction with CT-derived attenuation correction using the ordered subsets expectation maximization algorithm. The spatial resolution of the reconstructed PET image was 3.75 mm.

Image interpretation: ^{18}F-NaF PET-CT images for each patient were examined in axial, coronal, and sagittal planes. Both CT and fused PET-CT images were used for better lesion localization. **Data Analysis per patient and per lesion was performed depending on the following criteria:** The skeletal system was

divided into five regions: Skull bones, rib cage (including ribs, sternum, scapulae and clavicles), spine, pelvis and long bones. The interpretation of bone scan and bone PET was performed based on the criteria described by Krasnow et al. [22]. Abnormal uptake located at joints, increased uptake on the edge of vertebral bodies adjacent to disk spaces, or typical linear uptake were interpreted as arthritis, osteophytes, or benign compression fractures, respectively [23]. A lesion with a central cold defect was considered malignant [22]. Qualitative (Visual) and semi-quantitative assessment (using the maximum standardized uptake values (SUV max) for the most active osseous lesion in each region of the skeleton were done.

For each patient, the presence or absence of skeletal metastasis was determined by combining his/her clinical, imaging, and follow up data. Metastatic bone lesion was confirmed if any of the following criteria were present: Other radiographic confirmation (MRI or CT); Progression of bony lesion on subsequent radiographic or nuclear medicine studies (CT, MRI, bone scan or 18F-NaF PET/CT & 18F-FDG-PET/CT). A lesion was considered to be benign if: Other radiographic study (MRI or CT) showed it to be benign, or it was resolved or stationary on follow-up imaging without any active treatment.

Follow up: Follow up data for patients are collected retrieved from their medical records at the NCI hospital where clinical and radiological data were obtained to evaluate patients' response to therapy till the last visit as well as survival data. Follow up 18F-NaF PET/CT study is then performed at time scale ranging from 6 to 16 months from the initial study for 58 patients (who survived till the time of the follow up and agreed to do follow up study). Whereas 6 patients lost follow up. The follow up was done to 35 patients using 18F-NaF PET/CT scan while the remaining 23 patients were followed up by reviewing their clinical data and skeletal imaging. The follow up data was used together with the other radiological modalities and clinical data as a reference standard to differentiate between the false positive results of 18F-NaF PET/CT and false negative results of bone scan regarding bone metastases.

Statistical analysis

Data was analyzed using SPSS win statistical package version 21 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using either student t-test or Mann-Whitney test (non-parametric t-test) as appropriate. A p-value ≤ 0.05 was considered significant. Receiver operator characteristic (ROC) curve analysis used to find the best cut off value for SUV max to discriminate between benign and malignant osseous lesions, with the highest sensitivity & specificity. The cut off value for SUV max was correlated with pathological types & presence or absence of osseous deposits using Chi-square test. A p-value ≤ 0.05 was considered significant. Kaplan-Meier method calculated all survival estimates. Other predictor and prognostic variables were related to survival using log rank test. P value was set significant at 0.05 levels.

Results

This prospective study was conducted on 64 adult patients with a biopsy proven high grade (locally advanced) primary tumor at their pre-therapy phase. Median age of our group was 56 years (range 30-83) with male: female ration 1:1.8. Within the study group, the predominating primary malignancy was breast cancer representing 57.8 % followed by lung cancer representing 12.5%; the rest of primary pathological types represent the remaining 29.7 %.

According to pattern of bone metastases, patients were grouped into three groups; those with primary tumors have tendency to give sclerotic osseous deposits, those give lytic bone lesions or otherwise mixed lytic & sclerotic lesions. The most frequent was the tumors that have tendency to give mixed pattern of bone metastases (breast, mesothelioma, urinary bladder, pancreas, ovary and nasopharyngeal tumors) representing 73% of our patients, followed by those that give lytic pattern of osseous metastases (lung and HCC) (19% of our patients) while the least is the tumors that have purely sclerotic osseous metastases (prostate cancer) (8% of our patients).

^{99m}Tc-MDP SPECT/CT bone scan

Based on clinico-laboratory, radiological and follow up data results, 26 patients out 64 were proven to have bone metastases. ^{99m}Tc-MDP bone scan with SPECT/CT was able to detect true metastatic bone lesions in only 19 patients out of them, 7 patients had false negative results (5 of them had purely lytic metastatic osseous deposits and the remaining two patients had mixed lytic and sclerotic osseous deposits), 33 patients were true negative of osseous metastases, while 5 patients were falsely diagnosed to have osseous metastases (they had benign sclerotic lesions mostly in the spine region). Per patient analysis revealed sensitivity of 73.1%, specificity of 86.8%, NPV of 82.5% & overall accuracy of 81.2%.

Overall lesion-based analysis was done. Total number of 320 lesions were scintigraphically reported; 250 lesions were considered as benign lesions on scintigraphic basis. 23 out of the 250 lesions proved later to be false negative for metastases and the remaining 227 lesions proved to be true negative (70.9%). On the other hand, the 70 scintigraphically-reported positive metastatic lesions ,15 lesions of them proved later to be false positive and the remaining 55 lesions proved to be true positive (17.2%). Per lesion analysis revealed Sensitivity of 70.5%, specificity of 93.8 %, NPV of 90.8% and accuracy of 88.1%. No significant difference was noted when assessing diagnostic performance of ^{99m}Tc-MDP SPECT/CT bone scan on either patient or lesion-based analysis (P-value 0.96).

Detection of bone metastases using ^{18}F-NaF PET/CT imaging

By analyzing ^{18}F-NaF PET images only without being fused with CT images, 29 patients were recorded as being positive for metastatic bone lesions, 5 of them were falsely positive. While 35 patients were negative for osseous metastases; 2 of them were falsely negative. After fusing ^{18}F-NaF PET and CT images, number of patients that interpreted to have metastatic bone lesions declined to 26 patients

and the remaining 38 patients were free from true osseous metastases. There was no significant statistical difference between ^{18}F-NaF PET and ^{18}F-NaF PET/CT fused images in detection of osseous metastases (P value 0.87). However fused ^{18}F-NaF PET/CT images lead to better evaluation with no false positive or false negative results Table 1.

Table 1: Metastatic patients detected by ^{18}F-NaF PET versus that detected by fused ^{18}F-NaF PET/CT

	^{18}F-NaF PET		^{18}F-NaF PET/CT		P value
	N.	%	N.	%	
True Negative	33	51.6%	38	59.4%	0.87
True positive	24	37.5%	26	40.6%	
False negative	2	3.1%	0	0%	
False positive	5	7.8%	0	0%	
Total	64	100%	64	100%	

Similar to bone scan; the skeleton was also divided into 5 regions. Detection of bone metastases using ^{18}F-NaF PET/CT was assessed in each skeletal region separately. Apart from the skull region; that showed lower sensitivity and accuracy of 92% and 98.4% respectively; ^{18}F-NaF PET/CT showed high sensitivity, specificity and accuracy in the detection of metastatic osseous lesions in the rest of the skeletal regions mounting to 100%.

Bone metastases were detected in 26 out of 64 patients using ^{18}F-NaF PET/CT.

All patients with different primary malignancies were categorized according to tendency of their primary tumor to give sclerotic, lytic or mixed bone deposits. There was significant difference in the prevalence of metastatic osseous deposits among the different pathological categories (P value = 0.057). The primary tumors that have lytic osseous deposits have the highest prevalence of osseous metastases among their group (in 8 out of 12 patients) representing 66.7%. while the primary tumors that have mixed CT pattern of osseous metastases represent the majority of the metastatic patients in the whole studied groups (15 out of 26 metastatic patients) representing 57.7% of the metastatic patients (Table 2).

Table 2: prevalence of true bone deposits among 64 patients with different primary malignancies based on their predominating bone deposits nature

Patients	Sclerotic		Lytic		mixed		Total	P value
	N.	%	N.	%	N.	%		
Free	2	40%	4	33.3%	32	68.1%	38	0.057
metastatic	3	60%	8	66.7%	15	31.9%	26	
	5	100%	12	100%	47	100%	64	

The value of ^{18}F-NaF PET in the detection of the bone metastases was assessed; it showed higher sensitivity than that of ^{99m}Tc-MDP (92.3% compared to 73%). The sensitivity of ^{18}F-NaF PET in the detection of bone metastases increased after fusion with CT images reaching 100%. Specificity of ^{18}F-NaF PET in the detection

of bone metastases was similar to that of ^{99m}Tc-MDP bone scan; but it also increased after the hybrid technique from 86.8% to 100%. Also accuracy of detection of osseous metastases using ^{99m}Tc-MDP bone scan was 81.2% while it raised to reach 90% and 100% using ^{18}F-NaF PET and fused ^{18}F-NaF PET/CT images respectively (Table 3).

Table 3: ^{18}F-NaF PET/CT versus ^{18}F-NaF PET and ^{99m}Tc-MDP in the detection of osseous metastases in 64 patients with high grade primary tumors:

	^{99m}Tc- MDP	^{18}F-NaF PET	^{18}F-NaF PET/CT	P value
Sensitivity	73.08%	92.3%	100%	0.02
Specificity	86.8 %	86.8%	100%	
PPV	79.2 %	82.8%	100%	
NPV	82.5 %	94.3%	100%	
Accuracy	81.2%	90%	100%	

Lesion based analysis in ^{18}F-NaF PET/CT

Accuracy of ^{18}F-NaF PET/CT in the detection of osseous metastases was also assessed according to lesion-based analysis. There was 320 lesions detected; 77 lesions were true positive (24.1%), 242 lesion true negative (75.6%) and one lesion false negative with no false positive lesions while in ^{99m}Tc-MDP bone scan there was 23 lesions marked as false negative lesions and 15 lesions as false positive (Table 4).

Table 4: Lesions based analysis for the detection of osseous metastases using ^{18}F-NaF PET/CT versus ^{99m}Tc-MDP bone scan

	^{99m}Tc- MDP		^{18}F-NaF PET/CT		P value
True positive	55	17.2%	77	24.1%	0.00001
False positive	15	4.7%	0	0.0%	
True negative	227	70.9%	242	75.6%	
False negative	23	7.2%	1	0.3%	

According to this lesion-based analysis; there was significant difference in the sensitivity, specificity, and overall accuracy of ^{18}F-NaF PET/CT and ^{99m}Tc-MDP bone scan in the detection of osseous metastases among the enclosed patients; ^{18}F-NaF PET/CT showed higher sensitivity 98.7% compared to 70.5 % of ^{99m}Tc-MDP bone scan. Similarly, ^{18}F-NaF PET/CT showed higher specificity and overall accuracy (100% and 99.7% respectively compared to 93.8% and 88.1% of ^{99m}Tc-MDP bone scan) (Table 5).

Table 5: Detection of osseous metastases using ^{18}F-NaF PET/CT versus ^{99m}Tc-MDP according to lesion-based analyses

	^{99m}Tc-MDP	^{18}F-NaF PET/CT	P value
Sensitivity	70.5%	98.7%	<0.001
Specificity	93.8%	100.0 %	
PPV	78.5 %	100.0%	
NPV	90.8 %	99.5 %	
Accuracy	88.1%	99.6%	

Diagnostic value of ^{18}F-NaF PET/CT of bone metastases in terms of disease activity

Correlation between different values of SUV max of the osseous lesions and their nature; being metastatic or benign lesions were done. Cut off point is marked between the metastatic and benign osseous lesions using Receiver Operator Characteristic (ROC) Curve Analysis.

Receiver Operator Characteristic (ROC) Curve Analysis for SUV max diagnostic cut off point

ROC curve was used to mark a diagnostic SUV max cut off point that discriminate between metastatic and benign osseous lesions in the included patients with best compromise between sensitivity & specificity. ROC curve marked SUV max of 33.2 as a diagnostic cut-off discriminator between both groups with a sensitivity of 69.2%, and specificity of 73.1%. Figure 1

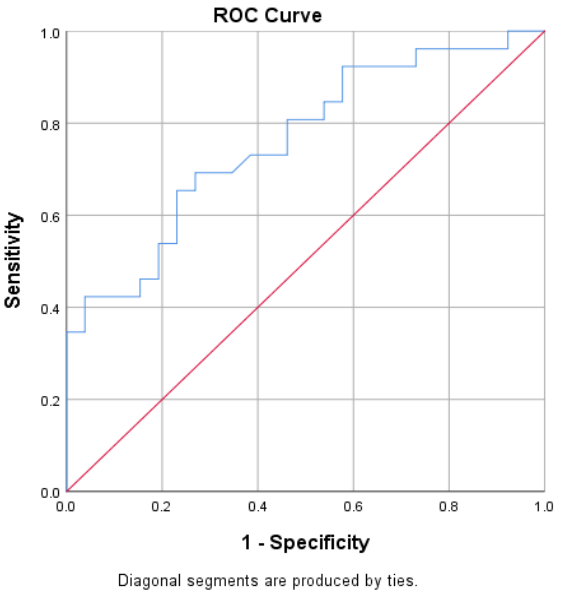


Figure 1: ROC Curve for SUV max of the metastatic osseous deposits

Correlation between this cut off SUV max of the osseous lesions and therapy response and overall survival in the included patients was done. In respect to therapy response the patients were divided into controlled (complete remission, partial remission & stationary) & Non-controlled (progression, relapse) groups. No significant difference in the average value of the initial SUV max could be detected among both groups. Table 6.

Table 6: Response of Patients with osseous lesions in correlation with SUVmax cutoff point

Cut-off SUVmax	Controlled NO.	%	Non-Controlled NO.	%	P value
<33.2	15	50%	10	55.6%	0.7
>33.2	15	50%	8	44.4%	

Predictive value of ^{18}F-NaF PET/CT in terms of Tumor burden

Correlation between prognosis and extent of osseous metastases was done. There was No significant difference in either therapy response or survival between patients that have metastatic osseous deposits in one region and those having osseous deposits in more than skeletal region. The magnitude of tumor burden in osseous metastatic group seems to have no significant impact in respect to prognosis.
Table 7

Table 7: Patients' response in relation to number of regions involved in metastatic patients detected by ^{18}F-NaF PET/CT

Response	No. of regions involved in metastatic patients detected by NaF					
	Mean	SD	Median	Minimum	Maximum	P value
Controlled	3.50	1.68	4.00	1.00	5.00	0.160
Non controlled	2.58	1.44	2.50	1.00	5.00	

Figure 2: 45 years old male presented with recently diagnosed pancreatic carcinoma at the pre-therapy stage, Fig.A: ^{99m}Tc-MDP bone scan negative for osseous metastases, Fig. B: ^{18}F-NaF PET/CT shows multiple ^{18}F-NaF avid lesions at right iliac crest, left iliac bone, multiple ribs bilaterally, DV6 and DV8 with subtle CT changes. Fig. C: 8 months Follow up after chemotherapy, ^{18}F-NaF PET/CT shows progression of the ^{18}F-NaF avid lesions with appearance of evident sclerosis in CT & Newly developed ^{18}F-NaF avid lesions at lumbar vertebrae.

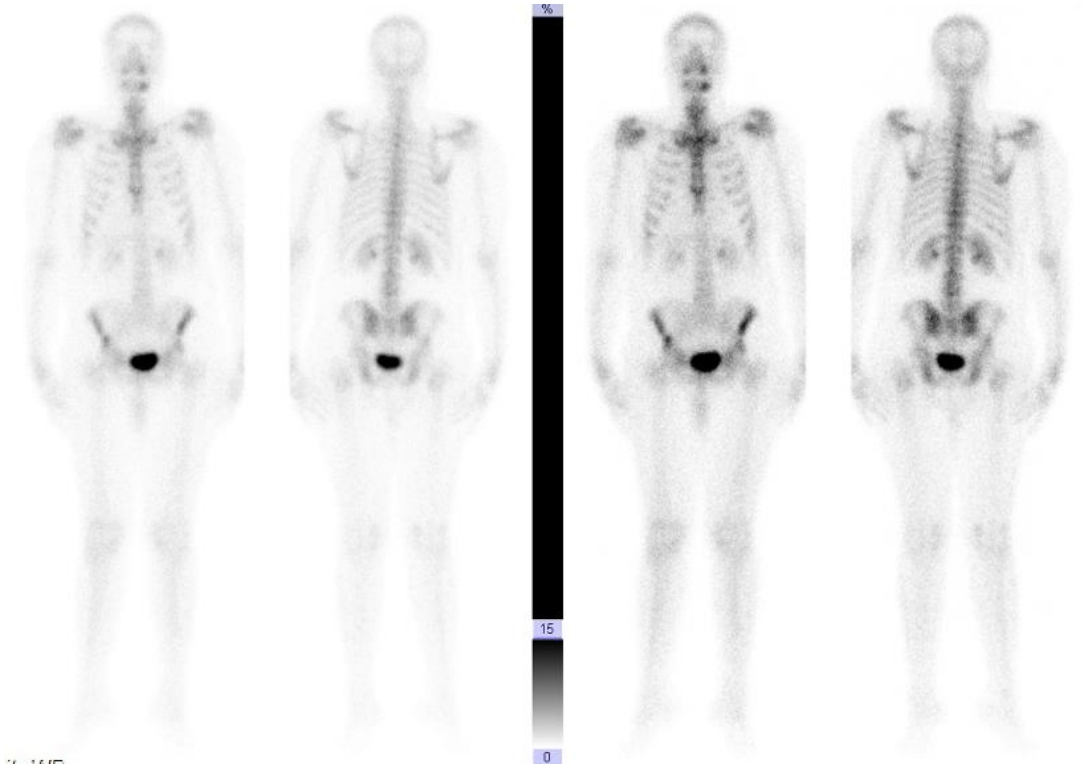


Figure 2A

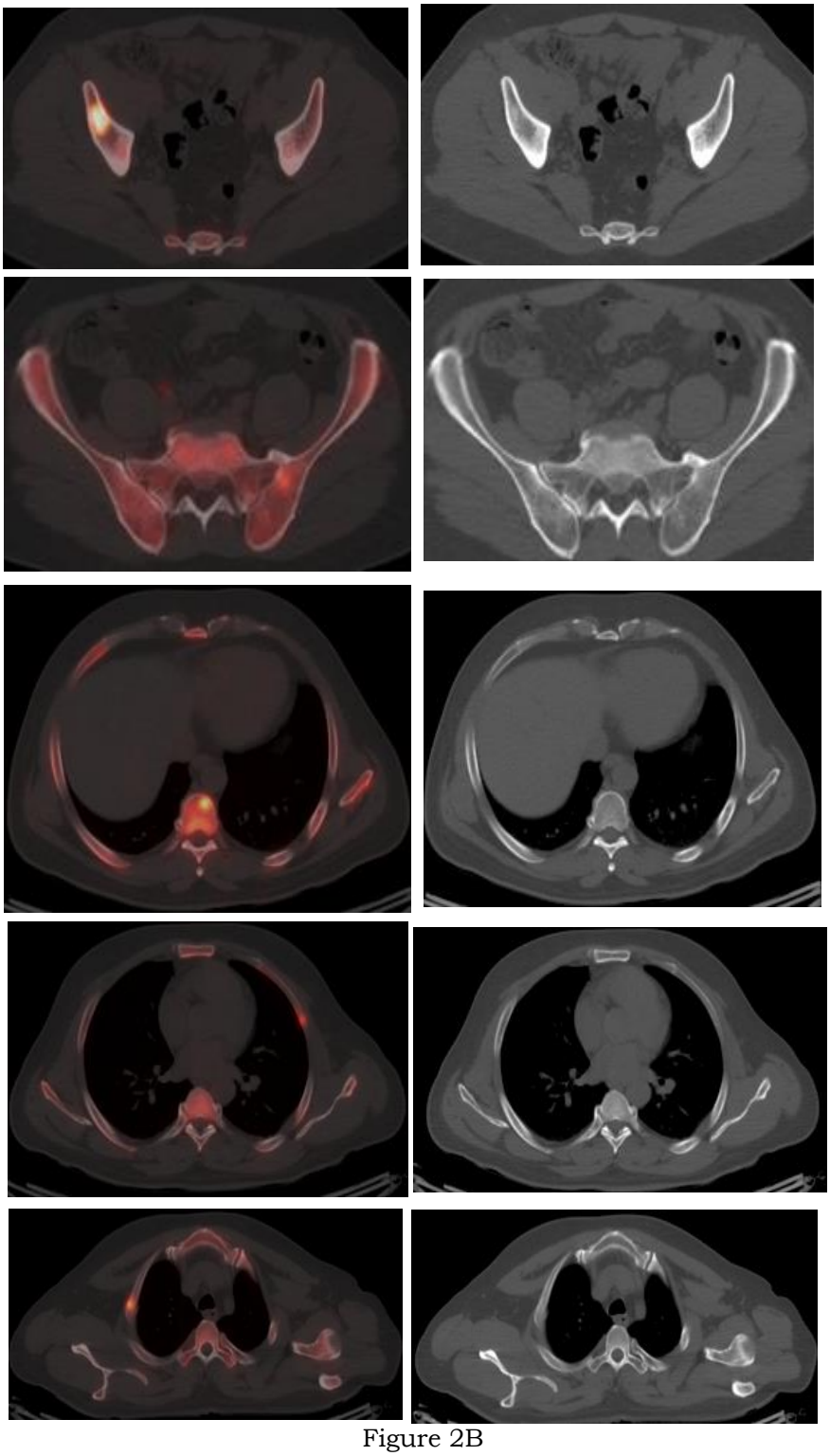


Figure 2B

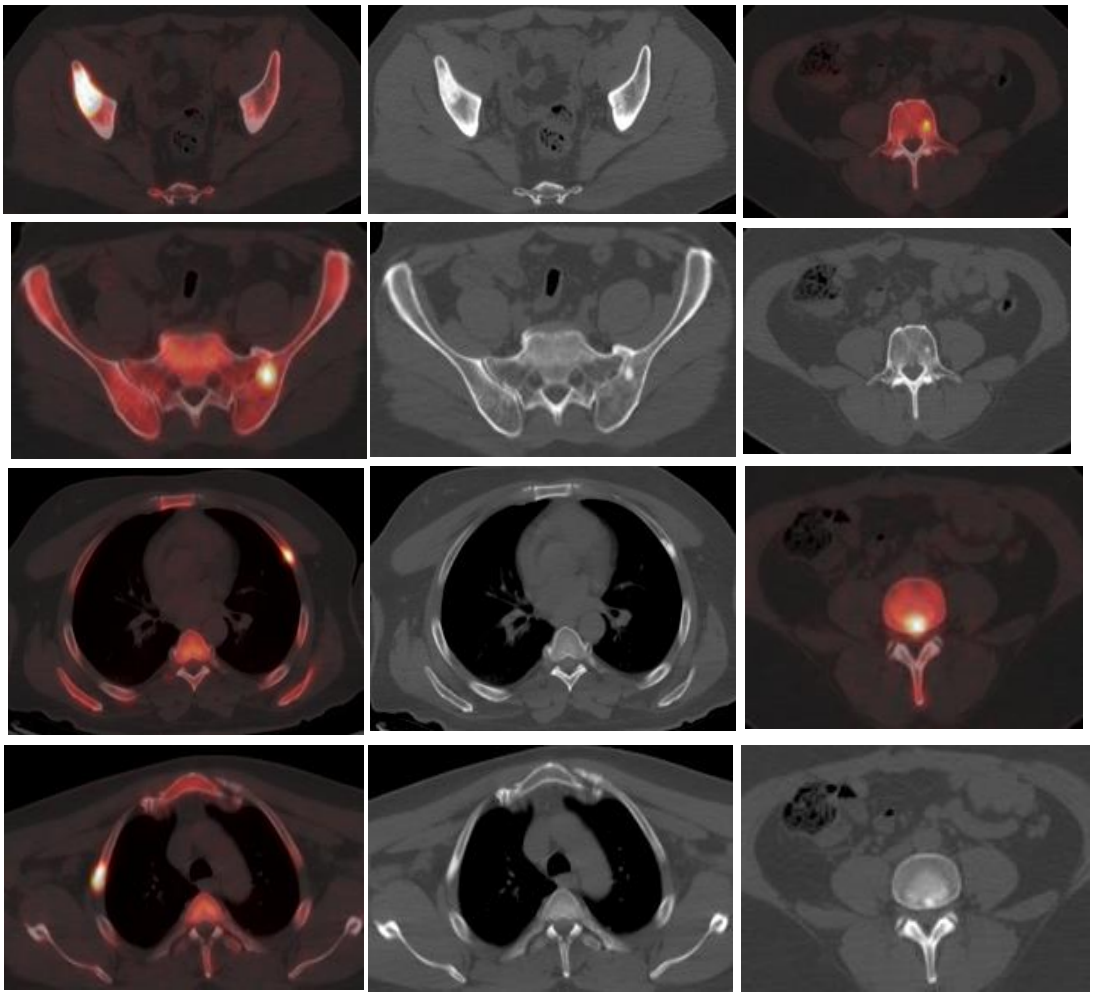


Figure 2C

Figure 3: 39 years old female patient presented with recently diagnosed locally advanced breast cancer (invasive duct carcinoma) at the pre-therapy stage. Fig. A: ^{99m}Tc-MDP bone scan; negative for metastases. Fig. B: ^{18}F-NaF PET/CT; negative for metastases. Then the patient received chemotherapy and 12 months-follow up assessment revealed, Fig. C: ^{18}F-NaF PET/CT shows newly developed fluorine avid metastatic osseous deposit at the sternal body while, Fig. D: ^{18}F-FDG PET/CT shows sclerotic lesion at the sternal body in CT cuts with no significant FDG uptake (False negative).

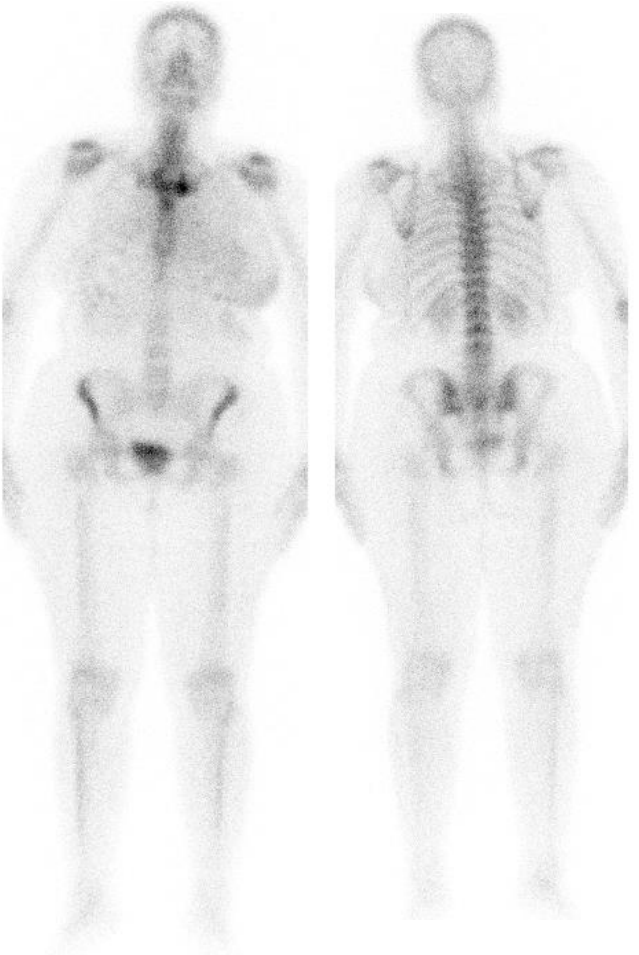
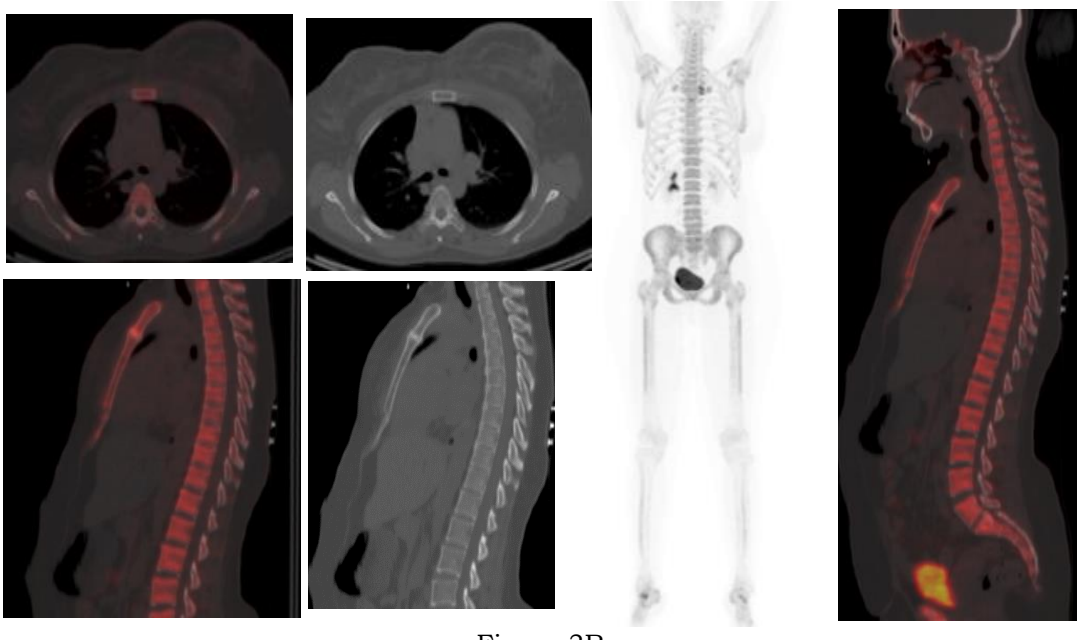


Figure 3 A



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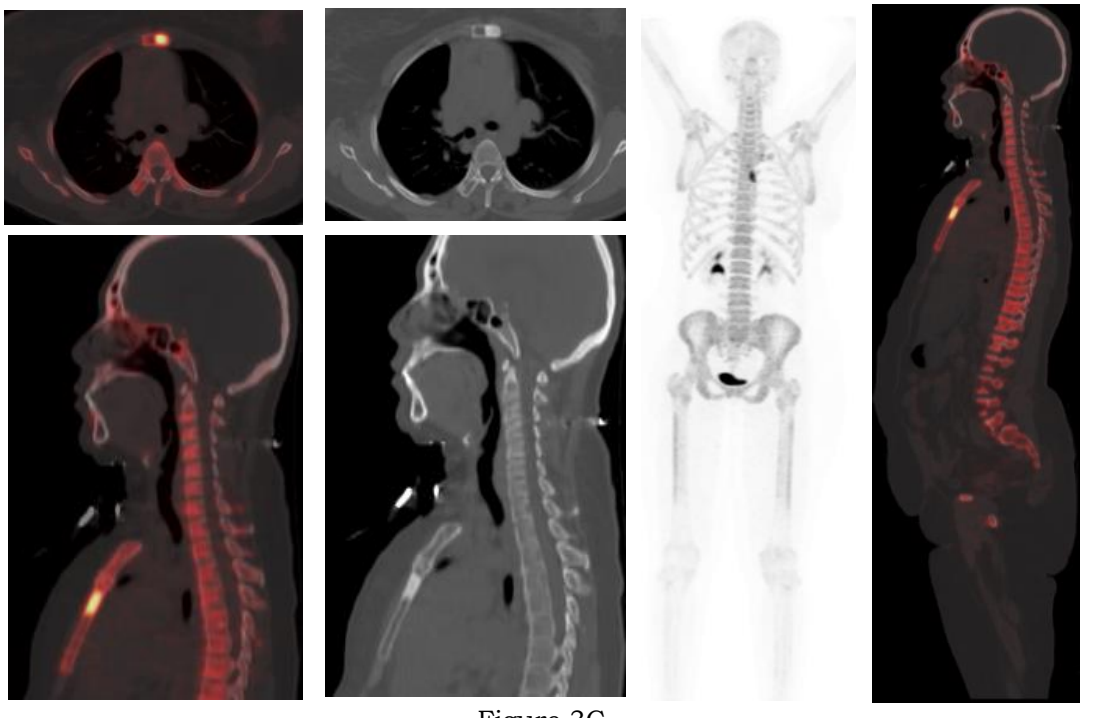

Figure 3C

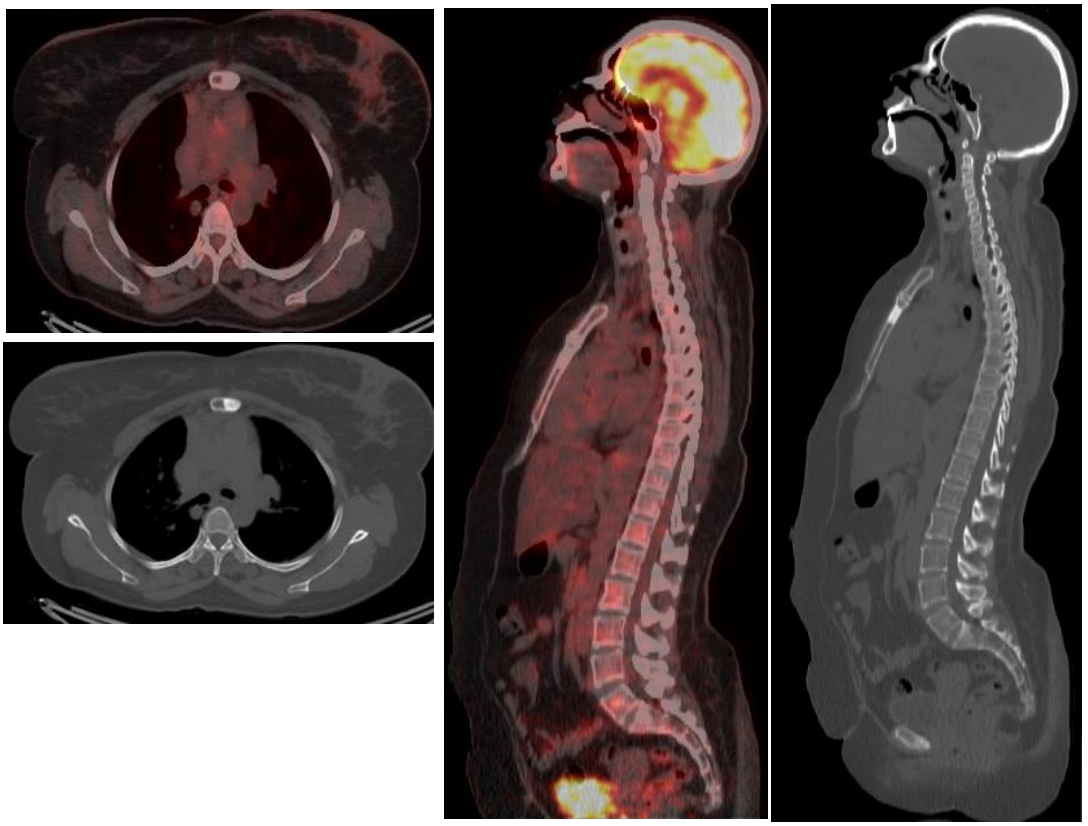

Figure 3D

Discussion

^{99m}Tc-MDP bone scan is a widely available technique that has been used for decades, with known high sensitivity that may be altered with dominantly lytic or marrow based bone lesions. ^{18}F- NaF is old tracer that was restricted in the past due to unavailability of PET/CT scanners; currently due to its high first pass extraction and availability of PET/CT scanners, many studies have been investigated the use of ^{18}F-NaF PET/CT in detection of bone metastases, yet no guidelines upfront its use in metastatic work up in neoplastic tumors [5]. However, both ^{99m}Tc-phosphonates and ^{18}F-NaF are non-specific bone radiotracers that can show areas of altered osteogenic activity; there were discrepancy in their performance in the detection of osseous metastases; this could be attributed to higher bone uptake and faster blood clearance of ^{18}F-NaF compared with ^{99m}Tc-phosphonate agents, combined with superior spatial resolution of PET that allow a more accurate diagnosis of bone metastases [6].

In the present study we assessed the accuracy of ^{18}F-NaF PET/CT in assessment of bone metastasis in patients with initially diagnosed high grade primary malignant neoplasms and compared to the traditionally used ^{99m}Tc-MDP bone scan. Our study included 64 patients with high grade primary tumors; 26 patients proved to have osseous metastases, while the remaining 38 patients were

free of osseous metastases using clinical and radoiological data as well as follow up studies as reference standard method.

By analyzing ^{18}F-NaF PET without CT component of the study; there was misdiagnosis in 7 patients, 5 patients diagnosed falsely to have metastatic deposits and another 2 falsely interpreted to be free of osseous metastases. The ^{18}F-NaF PET showed higher sensitivity in detecting osseous metastases than that of ^{99m}Tc MDP bone scans (92.3 % compared to 73% respectively) yet with similar specificity (86.8%) in both of them.

Using the hybrid technique improved both the sensitivity and specificity of ^{18}F-NaF in detection of osseous metastases. ^{18}F-NaF PET/CT identifies those patients with osseous metastases with no false negative ^{18}F-NaF PET/CT results giving high sensitivity indices (i.e. sensitivity & NPV) mounting to 100%. In contrast ^{99m}Tc-MDP bone scan identify 19 out of 26 bone metastatic patients with significantly lower sensitivity indices (sensitivity and NPV) of 73% and 84% respectively. Similarly, ^{18}F-NaF PET/CT also has higher specificity indices (specificity and PPV) than that of ^{99m}Tc-MDP bone scan (100% and 100% in ^{18}F-NaF PET/CT compared to 86.8% and 79.2% in ^{99m}Tc-MDP respectively). Our results are similar to that achieved by Even-Sapir in 2006, they studied 44 men with high-risk prostate cancer using ^{18}F-sodium fluoride PET/CT and ^{99m}Tc-diphosphonate. The sensitivity of ^{18}F-NaF PET/CT versus SPECT was 100% versus 92% & the specificity of ^{18}F-NaF PET/CT was 100% versus 82% of ^{99m}Tc-MDP bone SPECT. [7].

Also, Hetzel et al. in 2009 prospectively assessed ^{18}F-NaF PET for detection of bone metastases in lung cancer in 103 patients compared to planar bone scintigraphy, SPECT of the vertebral column. Sensitivity of ^{18}F-NaF PET/CT was 98.9% compared to 77.1% for bone scan and 87.5% for SPECT [8]. In the present study, analysis of the 18F-NaF PET/CT were also done respecting their primary tumor ; we divided the patients into 3 study groups according to the common CT pattern of osseous metastases that their primary tumors give into lytic , sclerotic or mixed osseous metastases. There was significant difference in the prevalence of osseous metastases among the three groups in our study being more common in those having primary tumor that give lytic osseous metastases. In our study, there was no significant difference in the sensitivity of 18F-NaF PET/CT in detection of osseous metastases among the 3 study groups (100 % in all groups).

Our results were similar to that of Damle et al. study conducted in 2013, they compared the role of 18F-fluoride PET/CT, FDG PET/CT and 99mTc-MDP bone scans in the detection of bone metastases in patients with lung, prostate and breast carcinoma representing pathologies that have tendency to give different types of osseous metastases . Sensitivity and negative predictive value (NPV) of 18F-fluoride PET/CT was 100 % in all three malignancies, while that of FDG PET/CT was 79 % and 73 % in NSCLC, 73 % and 80 % in breast cancer and 72 and 65 % in prostate cancer. As compared to the 99mTc-MDP bone scan, all parameters were superior for 18F-fluoride PET/CT in prostate and breast cancer, but sensitivity and NPV were equal in NSCLC [9].

In our study we analyzed 18F-NaF studies using lesion based analysis; high sensitivity and specificity are achieved in 18F-NaF PET/CT; 98.8 % and 100% respectively compared to 73.1% and 86.8% in 99mTc-MDP bone scan.

Our results are concordant with that achieved by Liu et al. In their study; on the patient basis, the pooled sensitivity and specificity of 18F-fluoride PET/CT were 96% and 93%. On the lesion basis, the pooled sensitivity and specificity were 94% and 95%. 18F-fluoride PET/CT showed both higher sensitivity ($p<0.005$) and specificity ($p<0.05$) [10]. The use of SUV is currently a routine in the oncological clinical practice of 18F-FDG PET/CT imaging. However there is no strong evidence that the use of SUV max as quantitation method is valid in 18F-NaF PET/CT study. Few studies tried to mark SUV max cutoff point to differentiate between benign and metastatic osseous lesions in 18F-NaF PET/CT study as trial for semi quantitative and quantitative assessment of 18F-NaF PET/CT scans. In the current study, SUVmax 33.2 was defined as a diagnostic cut off point to discriminate between the benign and malignant osseous lesions in 18F-NaF PET/CT studies.

Similarly Lapa et.al. marked SUVmax value 42 as a cutoff value above which the osseous lesion is more likely to be metastatic in 18F-NaF PET/CT study[11]. While Belal et.al. marked lower SUVmax as cut off point (SUVmax 15) to differentiate between benign and malignant osseous lesions in 18F-NaF PET/CT [12]. In the present study there was no significant difference demonstrated in therapy outcome or overall survival between patient with focal & extensive osseous infiltration. This finding can be explained on the heterogeneity of selected population, variation in risk scoring and therapy regimen. On the other hand, osseous metastases may follow all or none rule in respect to prognosis in patients i.e. Single focal metastatic osseous lesion may have similar outcome to extensive larger infiltration. However, further larger study with more homogenous group of patient may be required for clarifying such finding.

Conclusion

18F-NaF PET/CT is a high-quality skeletal imaging with convenient diagnostic performance in either lytic or sclerotic bone lesions surpassing that of Tc99m MDP, with lower equivocal interpretations, encouraging its re-adoption. Quantitative 18F-NaF PET may provide a more objective assessment for therapy response in metastatic bone disease.

References

1. V. Cuccurullo et al., “Bone metastases radiopharmaceuticals: an overview.,” Curr. Radiopharm., vol. 6, no. 1, pp. 41–47, Mar. 2013.
2. L. Zhang et al., “A comparative study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography and (99m)Tc-MDP whole-body bone scanning for imaging osteolytic bone metastases.,” BMC Med. Imaging, vol. 15, p. 7, Mar. 2015.
3. E. Dyrberg et al., “(68)Ga-PSMA-PET/CT in comparison with (18)F-fluoride-PET/CT and whole-body MRI for the detection of bone metastases in patients with prostate cancer: a prospective diagnostic accuracy study.,” Eur. Radiol., vol. 29, no. 3, pp. 1221–1230, Mar. 2019.
4. I. F. Gareen et al., “Hospice Admission and Survival After (18)F-Fluoride PET Performed for Evaluation of Osseous Metastatic Disease in the National Oncologic PET Registry,” J. Nucl. Med., vol. 59, no. 3, pp. 427–433, Mar. 2018.
5. U. Tateishi, S. Morita, and T. Inoue, “Diagnostic accuracy of 18F-fluoride PET and PET/CT in patients with bone metastases: a systematic review and meta-analysis update,” Clin. Transl. Imaging, vol. 1, no. 2, pp. 123–134, Apr. 2013.
6. R. Kumar Kulshrestha et al., “The Role of 18 F-Sodium Fluoride PET/CT Bone Scans in the Diagnosis of Metastatic Bone Disease from Breast and Prostate Cancer,” 2016.
7. E. Even-Sapir et al., “The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT.,” J. Nucl. Med., vol. 47, no. 2, pp. 287–97, Feb. 2006.
8. M. Hetzel et al., “F-18 NaF PET for Detection of Bone Metastases in Lung Cancer: Accuracy, Cost-Effectiveness, and Impact on Patient Management,” J. Bone Miner. Res., vol. 18, no. 12, pp. 2206–2214, Dec. 2003.
9. N. A. Damle et al., “The role of 18F-fluoride PET-CT in the detection of bone metastases in patients with breast, lung and prostate carcinoma: a comparison with FDG PET/CT and 99mTc-MDP bone scan.,” Jpn. J. Radiol., vol. 31, no. 4, pp. 262–269, Apr. 2013.
10. Y. Liu et al., “The diagnostic performance of 18F-fluoride PET/CT in bone metastases detection: a meta-analysis,” Clin. Radiol., vol. 74, no. 3, pp. 196–206, Mar. 2019.
11. P. Lapa et al., “The value of quantitative analysis in (18)F-NaF PET/CT.,” Rev. Esp. Med. Nucl. Imagen Mol., vol. 36, no. 2, pp. 78–84, Mar. 2017.
12. S. Lindgren Belal et al., “3D skeletal uptake of (18)F sodium fluoride in PET/CT images is associated with overall survival in patients with prostate cancer.,” EJNMMI Res., vol. 7, no. 1, p. 15, Dec. 2017.