Bone metastases in prostate cancer - Gallium-68-labeled prostate-specific membrane antigen or Fluorine 18 sodium fluoride PET/computed tomography - the better tracer?

Original article

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Bone metastases in prostate cancer – Gallium-68–labeled prostate-specific membrane antigen or Fluorine 18 sodium fluoride PET/computed tomography – the better tracer?

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Objective **The objective was to assess the roles of ^{68}Ga-PSMA PET/CT and ^{18}F-NaF PET/CT in evaluation of skeletal metastatic lesions in prostate cancer.**

Methods **Two hundred consecutive prostate cancer patients who had undergone ^{68}Ga-PSMA PET/CT and ^{18}F-NaF PET/CT at baseline evaluation ($n = 80$) and following suspected recurrence or disease progression (restaging) ($n = 120$) were analyzed retrospectively.**

Results **PSMA and NAF scans were positive for skeletal metastatic lesions in 67% (134 patients) and negative in 33% (66 patients). The scans were concordant in 80% (160 patients: 66 negative and 94 positive) and discordant in 20% (40 patients). Among 40 discordant results, 14 were baseline and 26 were restaging studies. PSMA detected more number of lesions in 11 (nine baseline and two restaging). These were true positive marrow or lytic metastatic lesions. NaF revealed more number of lesions in 29 (5 initial and 24 restaging). These were false positive on follow-up imaging. No statistical difference (*P* value = 0.7 by McNemar test) between the two scans for identifying absence or presence of at least one skeletal lesion was noted at baseline staging.**

Conclusion **Though, both ^{18}F-NaF and ^{68}Ga-PSMA are excellent tracers for evaluation of skeletal metastases in prostate cancer, there is a distinct advantage of ^{68}Ga-PSMA PET/CT due to detection of additional skeletal lesions and absence of false positive lesions. In addition, absence of PSMA avidity in healed metastases in the restaging setting opens up new avenue for assessment of response of skeletal metastases. *Nucl Med Commun* 43: 1225–1232**

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Keywords: metastasis, prostate cancer, PSMA, skeletal

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Introduction

Prostate cancer has a strong predilection for developing metastases to the bone with an incidence of 65–75% in advanced prostate cancer [1,2]. The commonest appearance of bone metastases from prostate cancer is increased osteoblastic activity on CT and radiographs and is also the cause of accumulation of bone-specific tracers like ^{99m}Tc-methylene diphosphonate (MDP) and Fluorine-18 sodium fluoride (^{18}F-NaF). This is an advantage and, thus, the high sensitivity of these tracers for detection of osteoblastic skeletal metastases. Conventional imaging modalities (CIM) like radiographs and CT are relatively less sensitive for the detection of skeletal metastases. CIM are also not very effective in detection of marrow lesions. The bone-specific tracers, ^{99m}Tc-MDP and ^{18}F-NaF though highly sensitive for detection of osteoblastic metastases, fail in detecting and underestimating skeletal metastases that are not osteoblastic, that is lytic and marrow skeletal lesions. Moreover, while estimating the response to hormonal or chemotherapy drugs, it is very difficult to assess the response for skeletal lesions. This is because the healing in bone lesions occurs by sclerosis and these tracers fail to differentiate between a sclerotic healing change or an increase in osteoblastic reaction or appearance of a new lesion [3]. To add to the problems, the response assessment criteria, such as RECIST 1.1 (response evaluation criteria in solid tumors), do not provide criteria for assessment of bone response more so in osteoblastic disease, which is the commonest manifestation in prostate cancer [4].

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In the past few years, gallium-68–labeled prostate-specific membrane antigen (^{68}Ga-PSMA) [Glu-NH-CON H-Lys-(Ahx)-^{68}Ga(HBED-CC)] has been developed as a novel tracer for detection of recurrent prostate cancer at low levels of serum PSA. Recent studies have shown moderate sensitivity and a high specificity for detection of lymph nodal metastases in initial staging of intermediate and high-risk prostate cancer [5]. PSMA can also detect visceral and skeletal metastases and serves as one-stop shop for metastatic work-up of a patient with prostate cancer. Few recent studies have shown that ^{68}Ga-PSMA PET/CT detects skeletal disease burden reducing the need for additional imaging modalities [6,7]. It also has low false positive detection as compared to ^{99m}Tc-MDP bone scan. Lytic and marrow metastases are present in 13.6 and 19.5% of patients with prostate cancer, which might be missed on CIM [8].

In our institute, prior to the availability of PSMA, skeletal metastases work-up was done using either ^{18}F-NaF PET/CT scan or ^{99m}Tc-MDP bone scan. In the initial days of starting PSMA PET/CT, there was a period when we did PSMA for nodal staging and NaF for skeletal metastases work-up of prostate cancer. The aim of this study was to compare the role of ^{68}Ga-PSMA PET/CT with ^{18}F-NaF PET/CT in evaluation of skeletal metastases.

Materials and methods

Patient population

Two hundred consecutive men diagnosed with carcinoma prostate between October 2014 and December 2015, who underwent both ^{68}Ga-PSMA PET/CT and ^{18}F-NaF at baseline/initial staging (n = 80) and following suspected recurrence or disease progression (restaging group) (n = 120), within 7 days of each other, were retrospectively analyzed. The indications for doing the PET/CT studies in the restaging setting were either biochemical recurrence after curative treatment or suspicion of disease progression based on serum PSA or clinical evaluation. All patients were followed up for a period of 12 months. This was a retrospective observational study. It was approved by the institutional review board (IRB no. 900668), with waiver of informed consent as per institutional policy for retrospective studies. Patient demographics are shown in Table 1.

Table 1 Patient demographics

Variable	Frequency
Age	Mean: 66.41 (range: 44–87)
Gleason score	Range: 6–10
S. PSA	Median: 31 ng/ml
S. PSA (initial staging)	Range: 6–11632 ng/ml
S. PSA (restaging)	Range: 0.04–4768 ng/ml

Gallium-68–labeled prostate-specific membrane antigen synthesis and quality control

All chemicals were procured from ABX advanced biochemical compounds, Germany. All radioactivity measurements were done with CapintecCRC 25 PET dose calibrator. The entire labeling process was carried out by wet chemistry through the good manufacturing practice compliant iQS Ga-68 fluidic labeling module. Radiochemical purity of formulation (^{68}Ga-PSMA-HBED-CC) was determined by thin layer chromatography (TLC) using 0.1 mol/l Tri-sodium citrate buffer as mobile phase (Solvent) and ITLCSG strips as solid phase. The ratio of fronts (Rf) value of ^{68}Ga-PSMA-HBED-CC was less than 0.3 and the Rf value of $^{68}GaCl_3$ was more than 0.9.

Gallium-68–labeled prostate-specific membrane antigen PET/computed tomography protocol

Contrast-enhanced PET/CT imaging was performed 1 h after injecting 111–148 MBq (3–4 mCi) of ^{68}Ga-PSMA-HBED-CC. Imaging was performed on Philips Gemini TF (Philips, The Netherlands) at 512 × 512 matrix for CT at 300 mAs and 120 kV and for 2 min/bed position at 144 × 144 matrix for PET. The images were acquired from base of skull to mid-thigh. The images are reconstructed using RAMLA reconstruction algorithm.

Fluorine-18 sodium fluoride PET/computed tomography scan protocol

PET/CT imaging was performed 60 min after injecting 5 MBq/Kg ^{18}F-NaF, intravenously. Imaging was performed on Philips Gemini TF (Philips, The Netherlands) PET/CT scanner. PET emission images were obtained in a 3-dimensional mode at 2 min/bed position at 144 × 144 matrix. The CT was acquired at 300 mAs and 120 kV and reconstructed in a 512 × 512 matrix with a thickness of 3.75 mm. The images are reconstructed using RAMLA reconstruction algorithm. Thin reconstruction in bone algorithm was done as and when needed. PET-CT and fusion images were reviewed on an Extended Brilliance Workspace (EBW) Philips workstation, version V4.5.3.40140.

Image interpretation and analysis

The PET-CT studies were retrospectively and independently reviewed by two nuclear medicine physicians with more than 15 years of experience. All studies were retrieved from picture archiving and communication system database and reviewed on EBW Philips workstation. Any disagreements were resolved by consensus reading.

Qualitative visual analysis

The scans were interpreted visually. Skeletal lesions on ^{68}Ga-PSMA with significantly higher activity than the background were considered positive for metastasis. The mediastinal blood pool was taken as the background activity. Increased tracer uptake on ^{18}F-NaF with characteristic findings of metastasis on CT was used to consider them as positive lesions. Lytic or sclerotic lesions with no associated degenerative or benign changes as seen

morphologically were considered metastatic. Clear-cut degenerative and benign/traumatic lesions on CT component with increased uptake were excluded. Lesions with increased uptake with no definite morphological characteristics to consider as benign or malignant were labeled as equivocal. At least one metastatic site was biopsied to establish metastatic involvement. For equivocal lesions, on the basis of the follow-up data, patients were labeled as metastatic disease or no metastatic disease, and this was used to assess the diagnostic accuracy of PET/CT studies. Patients who were metastatic and responded to treatment were considered positive and lesions with no change in the follow-up studies were considered benign. No semiquantitative analysis or standardized uptake value (SUV) cutoffs were used in the analysis.

Statistical analysis

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of PSMA and NaF for detection of skeletal metastases were calculated. Differences between the two studies were compared by the McNemar test. McNemar test is used on paired nominal data. *P* value of less than 0.05 was considered statistically significant.

Results

The mean age of the population was 66.41 years, median serum PSA was 31 ng/ml. PSMA and NAF scans were positive for skeletal metastatic lesions in 67% (134 patients) and negative in 33% (66 patients). The scans were concordant in 80% (160 patients: 66 negative and 94 positive) and discordant in 20% (40 patients) (Table 2). The sites of the disease location are mentioned in Table 3.

Among the scans that were positive and concordant, two patients showed fracture sites in the ribs, which were positive on both NAF and PSMA PET-CT. One patient showed a clear fracture site on the CT images and was, thus, labeled as benign; in the other patient, there was no abnormal PSMA uptake or lesion in the follow-up imaging.

Among the discordant result, 14 were baseline evaluation and 26 were in the restaging group. PSMA detected more number of lesions in 11 patients, nine patients in the initial staging group and two patients in the restaging group. All these lesions were true positive based on follow-up imaging. Though NaF revealed more skeletal lesions in 29 patients (5 initial and 24 restaging), all were false positive on follow-up imaging.

Discordant lesions in baseline evaluation

Fourteen patients had discordant results out of a total of 80 patients at baseline evaluation (Table 4). Nine out of the 14 patients showed more number of lesions on PSMA PET/CT. Three out of these nine patients were exclusively positive only on PSMA PET/CT. Out of these three patients, lytic metastasis was seen in one and marrow metastases in two patients (Fig. 1). Rest of the 6/9 patients showed more number of skeletal lesions in terms of marrow metastases, which were not evident in NAF PET/CT. These were all true positives.

Table 2 Flow chart of results

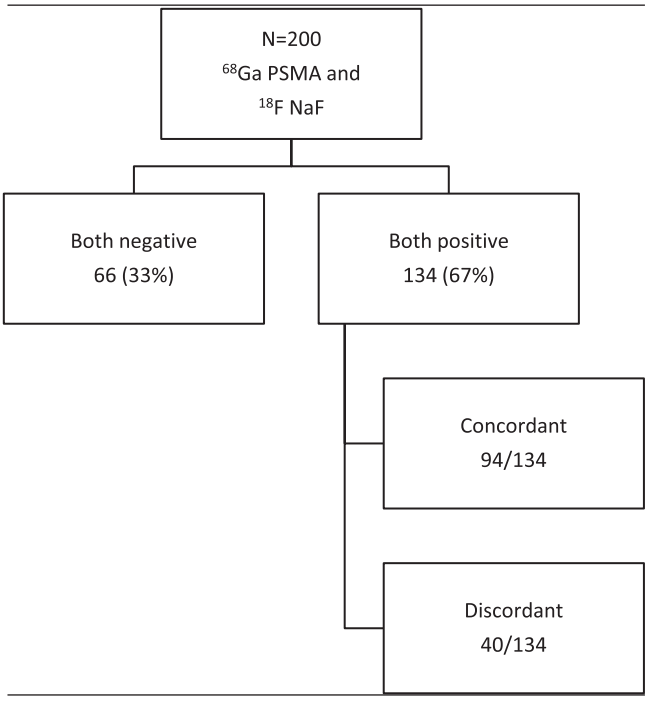


Table 3 Showing sites of skeletal lesions

Number of lesions	*N*	Sites
>10	87	Extensive involving most of the axial and appendicular skeleton
<10	47	Mainly involving pelvic bones and vertebrae, followed by ribs, skull, femur, sternum, scapula, clavicle and humerus.

Five out of the 14 patients showed more number of lesions on NaF PET/CT. These lesions were rounded sclerotic lesions and were equivocal. On follow-up imaging, all these lesions remained unchanged were categorized as benign. These were false positive lesions (Fig. 2).

No statistically significant difference (*P* value = 0.7 by McNemar test) between the two scans for identifying absence or presence of at least one skeletal lesion was noted.

Discordant lesions in restaging evaluation

Twenty-six patients had discordant results out of a total of 120 patients in the posttreatment setting (Table 4). Twenty-four out of the 26 patients showed more number of lesions on ^{18}F-NaF PET-CT, which were negative on PSMA PET/CT. These lesions remained static on follow-up imaging at 12 months. These were old sclerotic metastatic lesions, which continued to show uptake on NaF scan. These were

due to posttreatment healing changes seen on NaF PET/CT (Fig. 3). These lesions were false positive on NaF study in the restaging setting. Two patients showed more lesions on ^{68}Ga-PSMA PET-CT. These were early marrow metastases that were picked up only on PSMA study and were missed on NaF study.

The overall sensitivity, specificity, PPV, NPV and accuracy of ^{68}Ga-PSMA PET/CT was 100, 98.50, 99.05, 100 and 99.42%, respectively.

Table 4 Details of discordant result in gallium-68–labeled prostate-specific membrane antigen and Fluorine 18 sodium fluoride PET/computed tomography in baseline and restaging evaluation

Discordant lesions	PSMA lesions > NaF lesions	NaF lesions > PSMA lesions
Discordant lesions on baseline study	9 (all TP)	5 (all FP)
Discordant lesions in restaging setting	2 (both TP)	24 (all were FP)

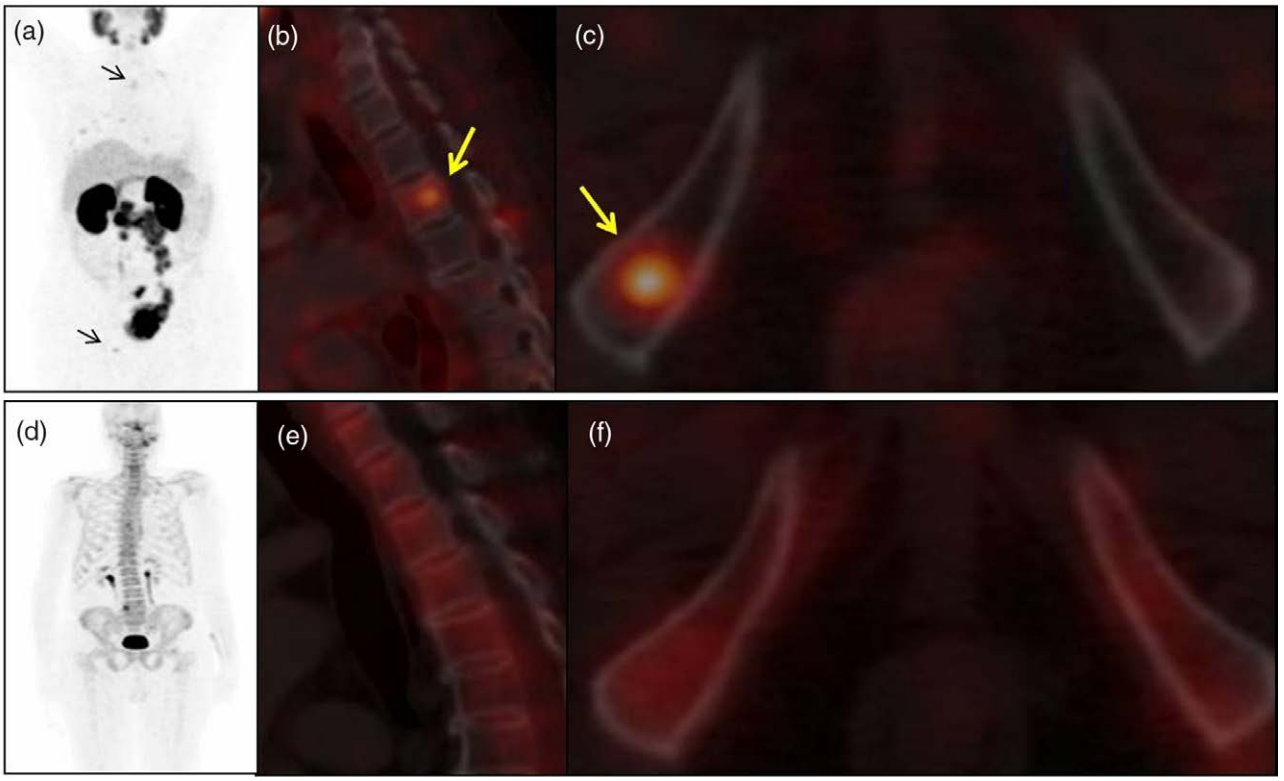
FP, false positive; NaF, sodium fluoride; PSMA, prostate-specific membrane antigen; TP, true positive.

The overall sensitivity, specificity, PPV, NPV and accuracy of ^{18}F-NaF PET/CT was 96.84, 69.47, 76.03, 95.65 and 83.16%, respectively (Table 5).

Discussion

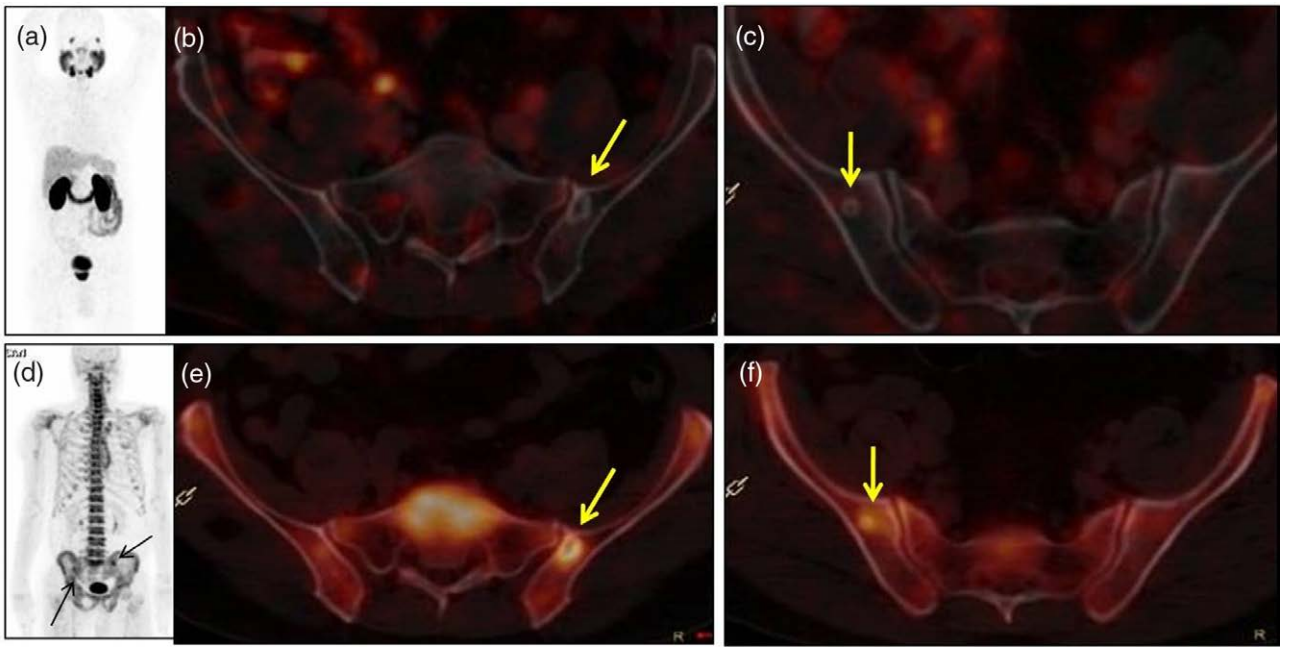
Bone metastases are the most common cause of mortality in prostate cancer and approximately 80% of prostate cancer patients die due to this. This mandates early detection of skeletal involvement, which can improve the 5-year survival of these patients [9,10]. Cortical bone and bone marrow are common sites of metastatic involvement in prostate cancer. ^{99m}Tc-MDP bone scan has been the standard imaging modality for detection of osteoblastic skeletal metastases. The advantages of bone scan are whole-body imaging and high sensitivity for detection of osteoblastic lesions. The only disadvantage of bone scan is that it lacks the specificity to identify true negative lesions. It detects all lesions that have increased bone turnover; be it benign or malignant and cannot differentiate between infection, trauma, degenerative changes, bone tumors and metastases [11,12]. CT scan is not very sensitive for detection of marrow lesions. These become

Fig. 1



Marrow metastases seen on ^{68}Ga-PSMA PET/CT, missed on ^{18}F-NaF PET/CT. Seventy-six years old, case of adenocarcinoma prostate with Gleason's score 5 + 3 = 8, serum PSA 33 ng/ml for baseline evaluation. PSMA PET/CT shows marrow metastases in upper dorsal vertebra and right ischium (arrows in a–c). These lesions are not seen on the NaF PET/CT (d–f). Focal increased uptake in right L4-5 vertebral level is degenerative on NaF scan. ^{18}F-NaF, Fluorine 18 sodium fluoride; ^{68}Ga-PSMA, gallium-68–labeled prostate-specific membrane antigen; CT, computed tomography.

Fig. 2



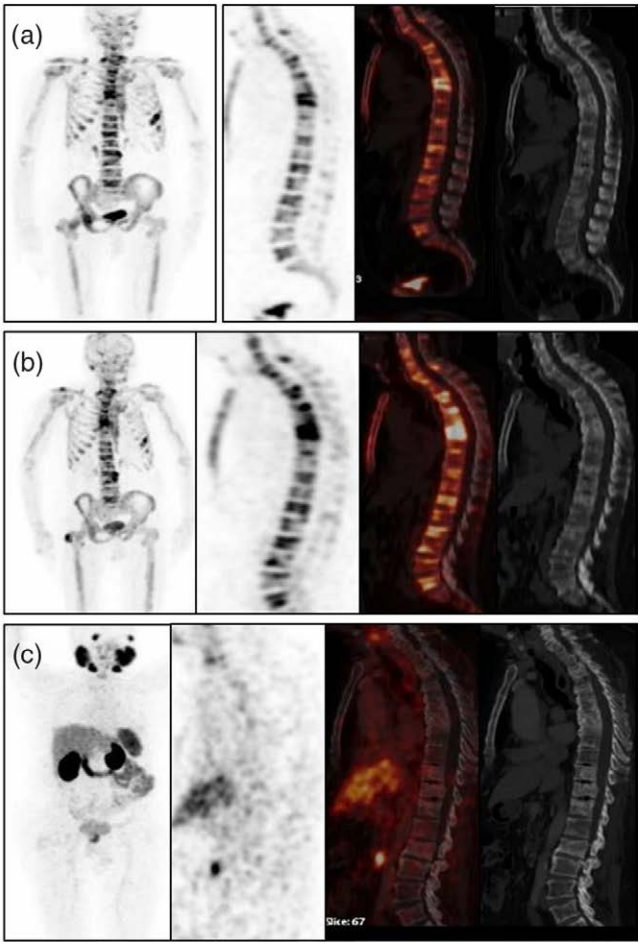
Benign skeletal lesions show no uptake on ^{68}Ga-PSMA PET/CT but are false positive of ^{18}F-NaF PET/CT. Sixty years old, a case of adenocarcinoma prostate, serum PSA 24 ng/ml, for initial evaluation. PSMA PET/CT shows localized disease in the prostate (a), with no nodal or bony metastases. NaF PET-CT shows increased uptake in well-corticated, central lucent lesions in the pelvis (arrows in d–f). These lesions have remained the same on subsequent imaging, confirming the benignity of these lesions. ^{18}F-NaF, Fluorine 18 sodium fluoride; ^{68}Ga-PSMA, gallium-68–labeled prostate-specific membrane antigen; CT, computed tomography.

visible only when there is progressive sclerosis or a reactive marrow response. Thus, there is definitely a need for a better tracer to identify the true burden of metastatic skeletal involvement in prostate cancer. This lacuna was partially filled by ^{18}F-NaF PET/CT. The advantages being whole-body imaging, high sensitivity and high specificity, better image quality and better spatial resolution as compared with bone scintigraphy. NaF has better pharmacokinetics, higher bone uptake and lower radiation burden than MDP [13,14]. The high specificity is due to morphological characterization of the lesions, which show increased uptake because of the combined CT with PET. It also has the ability to detect small lesions as compared with bone scan due to the increased resolution of a PET scanner as compared with a gamma camera, on which a bone scan is done [10,11,15,16]. A meta-analysis comparing the diagnostic performance of ^{18}F-NaF PET/CT and ^{99m}Tc-MDP scans has shown better sensitivity and specificity of 96 and 91% for NaF PET/CT compared with 88 and 80% for MDP bone scan [17].

The aim of our study was to compare PSMA and NaF in detection of metastatic skeletal lesions in both the settings of initial evaluation and in restaging. We compared the accuracy of both these tracers in evaluation of bony metastatic lesions in prostate cancer. This study was aimed at giving us an insight as to which tracer would be the best for initial staging and restaging in detection of bone metastases. Our results showed that the overall sensitivity, specificity, PPV, NPV and accuracy of PSMA was better than NaF. The values were 100, 98.5, 99.05, 100 and 99.42%, respectively, for PSMA as compared with 96.84, 69.47, 76.03, 95.65 and 83.16%, respectively, for NaF. There was a small difference between the sensitivity for both. But the specificity, PPV and NPV of PSMA were 100% or close to 100%, which was much higher than that of NaF PET/CT, leading to an overall higher accuracy of PSMA PET/CT. In the meta-analysis by Zhou *et al.* [18]., the patient-based sensitivity and specificity for PSMA were 97 and 100% and for NaF were 96 and 97%. Our results for sensitivity and specificity for PSMA are the same. However, though the sensitivity of NaF in our study is similar to theirs; there is a wide difference in the specificity of the NAF PET/CT (97% vs. 67%), this could be due to the healing response seen in sclerotic lesions on NaF PET/CT, which continued to show increased uptake; despite the lesions being treated and the false positive uptakes in benign lesions in baseline setting.

In the initial staging setting of prostate cancer, there was statistically significant difference in detection of skeletal metastases between the PSMA and NaF PET/CT scans.

Fig. 3



Healed sclerotic lesions show no uptake in ^{68}Ga-PSMA PET/CT, but show intense uptake on ^{18}F-NaF PET/CT. Seventy-three years old, a case of metastatic castrate-resistant prostate cancer, on second-line chemotherapy – Cabazitaxel. NaF PET-CT done in February 2014 (a), shows increased tracer uptake in extensive sclerotic lesions throughout the axial and appendicular skeleton. The PSA was 0.87 ng/ml. NaF PET-CT was repeated in July 2015, serum PSA was 1.2 ng/ml, NaF scan (b) continues to show increased tracer uptake in extensive sclerotic lesions. PSMA PET-CT done in July 2015, shows healed sclerotic skeletal lesions with no increased uptake which indicates that these lesions are healed, dormant lesions. ^{18}F-NaF, Fluorine 18 sodium fluoride; ^{68}Ga-PSMA, gallium-68–labeled prostate-specific membrane antigen; CT, computed tomography.

Exclusively lytic and marrow metastases were seen in three patients on PSMA PET/CT, which were missed on NaF PET/CT. Additional marrow lesions were also seen on PSMA PET-CT. NaF PET-CT had more false positive benign lesions.

Uprimny *et al.* [19], in their study, comparing PSMA and NaF PET/CT in 16 patients, prior to radionuclide therapy showed that more number of lesions were detected on NaF as compared with PSMA PET/CT. This is not in concordance with our study; this is probably due to the late stage at which the bone metastases were assessed in their study. At this stage, that is prior to radionuclide therapy, most patients had received androgen deprivation therapy (ADT) and chemotherapy and the disease was advanced. It is well known that advanced, metastatic castrate-resistant and very aggressive disease may show less number of lesions on PSMA PET/CT. In a recent prospective study comparing ^{68}Ga-PSMA PET/CT, ^{18}F-NaF PET/CT and WB MRI, in initial staging of prostate cancer patients in 60 individuals, Dyrberg *et al.* [20] found 100% sensitivity, specificity and accuracy with PSMA PET/CT and 95, 97 and 96% with NaF PET/CT. These results are very similar to that seen in our study.

Apart from initial staging, there is a void in assessing response to treatment in evaluation of skeletal metastases. Bone metastases heal by sclerosis. Thus neither a bone scan nor NaF PET/CT is accurate in evaluation of response to treatment as these scans continue to show increased tracer uptake in the sclerotic bone lesions, even after the lesion has responded to treatment. Assessment of

Table 5 Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of Fluorine 18 sodium fluoride and gallium-68–labeled prostate-specific membrane antigen PET/computed tomography

	SN (%)	SP (%)	PPV (%)	NPV (%)	Accuracy (%)
PSMA	100	98.50	99.05	100	99.42
NaF	96.84	69.47	76.03	95.65	83.16

NaF, sodium fluoride; NPV, negative predictive value; PPV, positive predictive value; PSMA, prostate-specific membrane antigen; SN, sensitivity: SP, specificity.

response in bone metastases is important as bone metastases significantly contribute to disease-related mortality and morbidity. Few studies have looked at assessment of response in bone metastases using NaF PET/CT with encouraging results [21]. But these need quantitative and semiquantitative methods of evaluation using various SUVs; which are cumbersome and time-consuming in day-to-day assessment of these studies. Moreover, additional problems associated with therapy-induced flare phenomenon may occur during response assessment of skeletal lesions, which may lead to increased uptake and, thus, increase in the SUV values [22]. The national oncology PET registry reported a change in management in 40% of patients with NaF PET/CT in treatment assessment of skeletal metastases [23]. But this change in management was mainly due to appearance of a new lesion and disease progression. Identification of a new lesion and, thus, disease progression can easily be identified on NaF PET/CT. Most studies assessing treatment response in skeletal metastases report either progressive disease or nonprogressive disease [24–26]. Assessment of partial response and complete response may be difficult and time-consuming if using SUVs for assessment. Additional discrepancies with serum PSA values may arise when a marrow lesion, not visible on NaF PET/CT on previous imaging; heals by sclerosis and is visualized on response assessment NaF PET/CT. This may lead to incorrect labeling it as a new lesion and, hence, disease progression. On the other hand, few studies assessing treatment response with ^{68}Ga-PSMA PET/CT and ^{18}F-Choline PET/CT have shown promising results [27,28].

In the restaging cohort in our study, more number of lesions were seen on NaF than on PSMA PET/CT in 24 patients, which were all healed lesions as assessed by follow-up and serial PSA values. In two patients, marrow metastases were seen only on PSMA PET/CT and missed on NAF PET/CT. Thus, clearly for restaging, ^{68}Ga-PSMA PET/CT is a better agent compared with ^{18}F-NaF PET/CT.

The limitations of our study are retrospective nature, heterogenous patient population in the restaging setting post-ADT, docetaxel, cabazitaxel and mixed population of metastatic castrate sensitive prostate cancer (CSPC) and castrate-resistant prostate cancer (CRPC). Despite the different tumor biology and different treatment protocols, both mCSPC and mCRPC were analyzed as a group. Also, histopathological correlation for all metastatic lesions was not possible, nor was it ethical to have histopathological correlation for all lesions. The detected lesions were assumed positive or negative based on follow-up imaging. The strengths of our article include a good number of patients, 80 in the baseline setting and 120 in the restaging setting. Head-to-head comparison was done with both the agents in both cohorts.

PSMA PET/CT and NaF PET/CT are both excellent imaging agents for the detection of bone metastases in the staging of prostate cancer. However, both in initial staging and restaging settings, PSMA is a better agent than NaF. This is because of detection of additional marrow and lytic lesions by PSMA PET/CT and correct identification of a healed metastatic lesion in the post-treatment setting.

Conclusion

Though both ^{18}F-NaF and ^{68}Ga-PSMA are excellent tracers for evaluation of skeletal metastases in prostate cancer, there is a distinct advantage of ^{68}Ga-PSMA PET/CT due to detection of additional skeletal lesions. Absence of PSMA avidity in healed metastases in the restaging setting opens up new avenue for assessment of response of skeletal metastases.

Acknowledgements

Ethics approval: approved by Institutional Ethics Committee. IRB No 900668. Retrospective studies have a waiver of consent.

Conflicts of interest

There are no conflicts of interest.

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