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Prospective Study Evaluating $Na^{18}F$-Positron Emission Tomography/Computed Tomography (NaF-PET/CT) in Predicting Clinical Outcomes and Survival in Advanced Prostate Cancer

Running title:
NaF-PET/CT in Advanced Prostate Cancer

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ABSTRACT

This prospective pilot study evaluated the ability of sodium fluoride ($Na^{18}F$) positron emission tomography/computed tomography (NaF-PET/CT) to detect and monitor bone metastases over time and its correlation with clinical outcomes and survival in advanced prostate cancer. **Patients and Methods:** Sixty prostate cancer patients, including 30 with and 30 without known bone metastases by conventional imaging underwent NaF-PET/CT at baseline, 6, and 12 months. Positive lesions were verified on follow-up scans. Changes in standardized uptake values (SUV) and lesion number were correlated with prostate-specific antigen (PSA) change, clinical impression, and overall survival (OS). **Results:** Sixty patients underwent 170 NaF-PET/CT scans. Significant associations included SUV and PSA percent change at 6 ($P = 0.014$) and 12 months ($P = 0.0005$); SUV maximal percent change from baseline and clinical impression at 6 months ($P = 0.0147$) and 6–12 months ($P = 0.0053$); SUV change at 6 months and OS ($P = 0.018$); number of lesions on NaF-PET/CT and clinical impression at baseline ($P < 0.0001$), 6 ($P = 0.0078$), and 12 months ($P = 0.0029$); number of lesions on NaF-PET/CT per patient at baseline and OS ($P = 0.017$). In an exploratory analysis, paired ^{99m}Tc-MDP bone scans (TcBS) were available in 35 patients at baseline, 19 at 6 months, and 14 at 12 months ($n = 68$ scans). Malignant lesions on NaF-PET/CT ($n = 57$) were classified on TcBS as malignant 65%; indeterminate 25%; and negative 10%. Additionally 69% of paired scans showed more lesions on NaF-PET/CT than on TcBS. **Conclusion:** Baseline number of malignant lesions and changes in SUV on follow-up NaF-PET/CT significantly correlates with clinical impression and OS. NaF-PET/CT detects more bone metastases earlier than TcBS and enhances detection of new bone disease in high-risk patients.

INTRODUCTION

Prostate cancer is the most common noncutaneous malignancy in men in the United States, with an estimated 250,000 new cases and approximately 29,000 deaths annually (*1*). Although the majority of patients present with localized disease and have an excellent prognosis, a subgroup of patients will develop metastases (*2*). Also, despite initial response to chemical or surgical castration, many patients become resistant and recur or progress (*3*). Despite dramatic recent advances in the treatment of metastatic castration-resistant prostate cancer (mCRPC), and the approval by the U.S. Food and Drug Administration (FDA) of 5 systemic therapies since 2010, prostate cancer remains the second leading cause of cancer death in men in the U.S. (*4,5*).

Approximately 90% of patients with mCRPC have bone metastases (*6*), the primary cause of morbidity and mortality. ^{99m}Tc-methylene diphosphonate (MDP) bone scan (TcBS) is currently the most widely used method for detecting bone metastasis; however, sodium fluoride-18 (NaF) positron emission tomography combined with computed tomography (PET/CT) has higher sensitivity and specificity.

NaF-PET/CT provides rapid (within 1 hour), bone-specific uptake and blood clearance and excellent visualization of the axial skeleton. NaF-PET/CT's ability to detect skeletal metastases has been evaluated in various types of cancer, including prostate cancer, and a series of studies have reported improved sensitivity and specificity compared to TcBS (*7-13*). In 2011 the FDA approved a New Drug Application for NaF-PET/CT from the National Cancer Institute; however, its routine clinical use is not yet defined.

This pilot study assesses the ability of NaF-PET/CT to detect and monitor bone metastases over time in prostate cancer patients either on surveillance or on active therapy and correlates these data with

clinical markers and survival. We hypothesized that changes in NaF-PET/CT over time, and their overall trend, would predict clinical outcomes.

PATIENTS AND METHODS

Patients

This was a prospective, 2-arm, pilot study of prostate cancer patients from 11/2010 to 4/2013. Arm 1 accrued patients with known bone metastases on standard imaging modalities such as CT or TcBS any time prior to enrollment. Arm 2 accrued patients without known bone metastases but who were at high risk for metastases based on rising PSA (30 patients/arm; $n = 60$) (Table 1). All participants underwent a NaF-PET/CT at baseline, 6, and 12 months. Patients could be undergoing treatment at any time point or be under surveillance. Patients with both castration-sensitive and castration-resistant tumors were enrolled. Patients had to have a PSA of $\geq$ 10 ng/mL or a PSA doubling time of $<$ 6 months, and either no known bone metastases on standard imaging (TcBS, CT, etc.) or any PSA level and known bone metastases on standard imaging. All patients must have received primary definitive therapy. Patients with soft tissue-only metastases were excluded. Clinical study data included start and discontinuation dates of all antineoplastic therapy, concomitant medications, PSA at the time of each NaF-PET/CT scan, and results of clinical TcBS and anatomical imaging such as CT and magnetic resonance imaging. Patients receiving treatment were assessed for response using the Prostate Cancer Working Group 2 criteria (*14*); NaF-PET/CT scans did not guide clinical decisions.

This study was approved by the National Cancer Institute's Institutional Review Board at the Center for Cancer Research in Bethesda, Maryland. Written informed consent was obtained from each patient who participated in the study.

Imaging Techniques

Patients were injected with 111–185 MBq (3–5 mCi) of NaF. Two hours post-injection, imaging was performed on a Philips Gemini TF system (Philips Health Care, Cleveland, OH). TcBS and NaF-PET/CT were analyzed and reviewed separately by 3 experienced nuclear medicine physicians. Differences were resolved through consensus. Lesions on NaF-PET/CT were classified as benign, malignant, or indeterminate based on their location and accompanying CT features. Lesions were considered benign if located at a joint, if they were characteristic of degenerative changes, or if the patient had a history of trauma in that region. Lesions were classified as malignant if they had a characteristic osteoblastic appearance on CT. Lesions with focal radiotracer uptake but no correlative CT findings were considered indeterminate. Scan results were categorized as positive if any malignant lesion was present. Ground-glass bone lesions on CT were categorized as malignant. NaF-PET/CT scans were interpreted without knowledge of other imaging modalities.

Low-dose CT transmission scans were obtained (120 kVp, 60 mAs, 0.75-sec rotation time, 1.438 pitch, 5 mm axial slice thickness) for attenuation correction and localization. Emission PET images were obtained at 2 min/bed position with 22 slices in bed overlap. PET images were reconstructed using the Gemini TF's default reconstruction algorithm (BLOB-OS-TF, a 3D ordered subset iterative Time of Flight reconstruction technique using 3 iterations, 33 subsets, voxel size 4x4x4 mm^3). Imaging review and analysis was performed using software from MIM Software, Cleveland OH.

Data Analysis

NaF-PET/CT classification. At 6 and 12 months, scans were categorized as progressive disease (PD) if there were any new lesions; stable disease (SD) if there were no new lesions; and improved disease (ID) if there was resolution of previous lesions.

SUV. Per lesion, SUV was defined as the mean of the upper 20^{th} percentile of pixel values (80% threshold). Maximum SUV (out of all identified lesions) at baseline and maximal percent change of

SUV (out of all identified lesions between 2 consecutive visits) at follow-up were used to correlate with clinical outcomes.

Statistical Analysis

The primary objective of this study was to assess the reproducibility of bone uptake of NaF. The study required 60 patients (30 in each arm) to obtain the 95% confidence interval (CI) for the mean percent change of ± 3.7%. These results have been reported (*15*). The secondary objective of the study, as reported here, was to assess changes in NaF over time and their ability to predict clinical outcomes.

Magnitude of per-lesion change of serial SUV measures was assessed by the critical percent change, defined as $[\exp(Z_{0.975} \times \sqrt{2} \times \sigma) - 1] \times 100$, ($\sigma$ = standard deviation due to within-lesion variability of serial SUV); $Z_p = p$th quantile standard normal distribution.

Maximum SUV at baseline and maximal percent change of SUV, number of lesions, and PSA were compared with respect to clinical impression. Differences in the distribution of maximal percent change of SUV, number of lesions, and PSA percent change with respect to clinical outcome (PD/SD/ID) were tested by the nonparametric Kruskal-Wallis rank test. The association between PSA and SUV values used the Spearman's rank correlation coefficients. Receiver operating characteristic (ROC) analysis was performed and area under the curve (AUC) was estimated to assess the feasibility of using maximal percent change of SUV from baseline to 6 months to evaluate patients' progression status (PD vs. SD/ID).

The Cox proportional hazards model was used to determine the prognostic value of number of lesions and change in SUV on survival. ROC analysis evaluated the predictive value of SUV maximal percent change on 2-year survival post-6-month scan. Statistical analysis used R version 3.1.0 (*16*).

ROC analysis with binary outcome was implemented with the R package *ROCR* (*16*), and ROC analysis of survival outcome was implemented with the R package *survival ROC.*

RESULTS

We performed 170 NaF-PET/CT scans on 60 prostate cancer patients (60 at baseline, 58 at 6 months, and 52 at 12 months), 84% of which demonstrated bone lesions. At baseline NaF-PET/CT, 239 lesions were evaluable. Lesions per patient ranged from 0–52 at baseline, 0–65 at 6 months, and 0–59 at 12 months. Eight patients had superscans, defined as showing > 50 lesions. In this case one lesion was selected per anatomical site (5 lesions/superscan/patient). See Table 2 for distribution of malignant bone metastases on NaF-PET/CT.

Standardized Uptake Value

We recorded the SUV for each lesion. Maximal percent change in SUV from baseline to 6-month and 6- to 12-month scans correlated with clinical impression (mean maximal percent change 141%, $P = 0.0147$; mean maximal percent change 157%, $P = 0.0053$, respectively).

The ROC analysis of maximal percent change of SUV with respect to PD at 6 months yielded a 0.84 AUC (95% CI: 0.62, 0.98). The threshold of SUV maximal percent change was 57.1%, with sensitivity 75% (6/8), specificity 82.8% (24/29), positive predictive value 54.5% (6/11), and negative predictive value 92.3 (24/26). There was a significant increase in SUV between 6 and 12 months in patients who progressed at 12 months ($P = 0.005$).

Number of Lesions

The median and range of number of lesions with respect to clinical impression at each scan are shown in Table 3. The distributions of the number of lesions with respect to clinical impression were significantly different at 6 and 12 months ($P < 0.01$).

PSA

At baseline, patients with metastatic lesions had significantly higher PSA levels than those without metastases ($P = 0.016$). The correlation between change of PSA and SUV maximal percent change at 6 months ($R^2_s = 0.39$; $P = 0.014$) and 12 months ($R^2 = 0.58$; $P = 0.0005$) was also significant. Examples of NaF-PET/CT change with PSA are seen in Figures. 1A and 1B.

Survival

Median follow-up was 35 months (range, 17–45 months), during which 18 patients died. The Cox proportional hazards model estimated the effects of covariates on OS. The number of lesions at baseline NaF-PET/CT correlated significantly with OS ($P = 0.017$). Maximum SUV at baseline was not a significant predictor, but maximal percent change at 6 months correlated with survival ($P = 0.018$, hazard ratio: 1.23 for 50% maximal percent change). ROC analysis at 2 years post-6-month NaF-PET/CT had an AUC of 0.88 (95% CI: 0.76, 0.97). At the threshold of 50.4% change in SUV, sensitivity and specificity were 73% (11/15) and 78% (18/23), respectively. Eleven of 16 patients whose change in SUV exceeded the threshold died.

Longitudinal Observation

Arm 1, the metastatic group, had the largest number of deaths (14 vs. 4 in Arm 2); it also had 2 patients without definite bone lesions on all 3 NaF-PET/CTs. This calls into question the original classification based on prior TcBS. The metastatic group also had 11 patients with increasing numbers

of lesions at follow-up; 6 of these patients died. There were more deaths in patients with fluctuations in lesion number at follow-up than in those with stable lesion numbers at follow-up.

In Arm 2, the nonmetastatic group, 14/30 patients (baseline PSA: 0.06–190) had bone metastasis on baseline NaF-PET/CT (range, 1–7; average 3); 7 had no change in lesion number at the 2 follow-up scans; 3 died. The other half of this arm (n = 16) had no bone metastasis on baseline NaF-PET/CT and did not develop bone lesions on follow-up. This arm also had more patients (n = 22) with no change in lesion number on follow-up scans.

Ground-Glass Lesions on CT

Focal NaF uptake in bone lesions without an apparent CT correlate was noted in 26/60 patients. These 26 patients had an average of 17 lesions identified by NaF-PET/CT, of which approximately 4 lesions/patient (107 total) revealed a subtle CT ground-glass appearance on closer scrutiny. In 18 patients, the ground-glass lesions changed to dense lesions in 35/107 (33%) lesions and from dense to ground-glass in 6/107 (5%) lesions (in patients on hormonal therapy). In 8 patients, the majority of lesions (62%) remained unchanged. Patients whose ground-glass lesions became denser were 9.4 times more likely to progress at 12 months than patients without ground-glass lesions (P = 0.0152), potentially indicating an early opportunity for therapeutic intervention.

NaF-PET/CT vs. TcBS

A patient-based analysis of 68 paired NaF-PET/CT and TcBS images in 37 patients taken at baseline (n = 35), 6-month follow-up (n = 19), and 12-month follow-up (n = 14) (Figure. 2; Table 4) compared detection of bone metastases. Results demonstrated 66% (45/68) concordance between NaF-PET/CT and TcBS in terms of final impression (37 positive, 3 indeterminate, and 5 negative) (Table 4).

NaF-PET/CT detected more lesions in 47/68 (69%) paired scans (Figure. 2) (mean = 4 more lesions/patient). Figure 3 shows an example of lesions seen on NaF-PET/CT vs. TcBS.

Fibrous Dysplasia

Fibrous dysplasia, an incidental radiologic finding, is scar-like tissue that develops in place of normal bone. It is generally considered a pediatric condition and is usually asymptomatic (*17,18*). Monostotic fibrous dysplasia is more prevalent in craniofacial bones, where it is typically diagnosed radiographically by its characteristic radiolucency, resembling ground glass or heterogeneous sclerosis. We detected 8 incidental cases (13%) of fibrous dysplasia in the NaF-PET/CTs among the 60 patients on study, limited to the ethmoid (2/8), nasal (5/8), and sphenoid (1/8) bones of the skull (Figure. 4).

DISCUSSION

Prostate cancer progression is characterized by a variety of disease states, including clinically localized disease; rising PSA, noncastrate; rising PSA, castration-resistant; clinically metastatic, noncastrate; and clinically metastatic, castration-resistant (*19*). Bone metastases are a frequent manifestation, yet there is no accurate quantitative method for imaging prostate cancer metastases in bone (*20*). NaF-PET/CT has been studied mostly in the clinically metastatic, castration-resistant state, and its role in earlier disease states has not been established. Several studies have evaluated the ability of NaF-PET/CT to detect bone metastases compared to other nuclear and radiologic modalities, with highly favorable results for NaF-PET/CT (*7-13,21,22*). NaF-PET/CT demonstrated high reproducibility in a prospective study of dual baseline scans in patients with prostate cancer and multiple myeloma (*15*), supporting its clinical value in oncology practice. Still, many clinicians are reluctant to embrace NaF-PET/CT as it is unclear whether it is overly sensitive and thus does not accurately represent disease status.

Here, we longitudinally evaluated NaF-PET/CT in prostate cancer patients and compared results to clinical outcomes. In both arms of the study, most patients had stable NaF-PET/CTs over the course of a year. Patients with known bone metastasis who had increases in lesion number had shorter survival. NaF-PET/CT detected more bone lesions than TcBS in 69% of patients (Figure. 2). The number of lesions detected at baseline NaF-PET/CT significantly correlated with OS, and the distribution of lesions correlated with clinical impression (therapy received, PSA, TcBS, and CT and/or MRI results) at each time point (baseline, 6, and 12 months) (Table 3).

A number of quantitative measures on NaF-PET/CT appeared to correlate with clinical parameters. For instance, percent change in SUV at follow-up was associated with both clinical impression and 2-year OS. Patients with a larger increase in SUV at the 6-month scan tended to have shorter survival. A multicenter NaF-PET/CT study is underway in patients with mCRPC receiving either microtubule-directed chemotherapy or androgen-directed therapy (NCT01516866). Patients are scanned prior to initiating therapy and during treatment. This study will aid in determining the NaF-PET/CT SUV change that constitutes treatment response or failure.

Our longitudinal data analysis revealed that malignant lesions on NaF-PET/CT remained positive at 6 and 12 months unless the patient received effective therapy (Figures. 1A and 1B). While confounding factors such as uptake in benign bone lesions (i.e., fibrous dysplasia), urinary excretion potentially impeding visualization of the pelvis, and tumor flare (*23*) following therapy remain problematic, this study demonstrates the feasibility of monitoring the response of metastatic bone lesions simply by monitoring lesion count on NaF-PET/CT imaging. To our knowledge, this is the first report of follow-up NaF scans of prostate cancer patients over a one-year period correlated with survival.

In our study, the concordance of lesion number between NaF-PET/CT and TcBS was 66% (44/68), with NaF-PET/CT showing higher specificity in detecting early metastatic disease, consistent

with previous studies (*7-13,21*). Six patients with negative and 14 with indeterminate TcBS scans evidenced malignant bone disease on corresponding NaF-PET/CTs (Table 4). Among the 30 men enrolled in the nonmetastatic arm, 14 (40%) were found to have malignant bone lesions on baseline NaF-PET/CT (range, 1–7; average, 3), confirming prior studies suggesting NaF-PET/CT was more sensitive than TcBS in detecting early metastatic disease (*7-13,21*). In the evolving and complex therapeutic arena of prostate cancer, earlier detection of metastatic disease would be particularly helpful when counseling men on the role of definitive local therapy, which is generally not recommended in the setting of clinically demonstrable metastatic disease. Clinicians are concerned that detecting progressive disease on NaF-PET/CT may lead to premature discontinuation of an effective therapy, as all current therapies for prostate cancer were FDA-approved using TcBS as the standard metric.

Several prior studies have noted that focal NaF uptake is more sensitive than CT scans, which are often normal at the hot spot on PET (*9*). Upon closer inspection, areas with focal uptake may demonstrate subtle ground-glass opacity (*24*) on CT, a phenomenon seen in 26 (43%) of our patients. We noted distinctly different SUVs in ground-glass lesions versus dense sclerotic lesions at baseline evaluation. Our analysis did not reveal an association between ground-glass lesions, their SUVs, and clinical outcome, but did find that patients with ground-glass lesions that became more sclerotic had a higher risk of clinical progression than patients with no ground-glass lesions. The ability to identify bone metastases with functional NaF-PET/CT imaging prior to anatomic CT findings may help to change management strategies.

Falsely increased fluorodeoxyglucose activity in benign bone lesions such as fibrous dysplasia has often been reported. In this study, NaF-PET/CT detected 8 cases of fibrous dysplasia, all located in the skull, suggesting that it is more common than suspected and that NaF-PET/CT may be more sensitive for fibrous dysplasia than conventional TcBS. CT's ability to demonstrate the characteristic

appearance of fibrous dysplasia in bone was extremely helpful in properly diagnosing these cases as benign.

This pilot study was limited by a heterogeneous patient population that included patients with castration-resistant and hormone-responsive prostate cancer. A study involving a larger patient population may validate our conclusions. A further limitation was the difficulty of obtaining histopathologic confirmation of metastatic bone lesions. Finally, the study was not powered to compare NaF-PET/CT to TcBS. Many patients had paired NaF-PET/CT and TcBS at the 3 time points. Therefore, the number of lesions and the patient-based classification on both scans were only compared preliminarily.

CONCLUSION

NaF-PET/CT detects more bone metastases than TcBS and detects them earlier in the disease course. Over the 12 months of this trial, the number of lesions at baseline NaF-PET/CT and their SUV change were associated with clinical impression and OS. Patients with fewer bone lesions tended to have a better prognosis. Greater change in SUV at 6 and 12 months correlated with greater change in PSA. A larger percent increase in SUV was associated with clinical impression of PD and shorter survival.

In this study, patients who had an SUV change of $\geq 50.4\%$ had a significantly higher risk of death. We also found that subtle ground-glass opacities on CT, coincident with positive NaF uptake, are likely to represent early metastatic lesions. Additionally, the unexpectedly high rate of incidental detection of fibrous dysplasia suggests that this benign condition is more prevalent than previously suspected and is detected more frequently with NaF-PET/CT. Our analysis demonstrates that NaF-PET/CT may be a useful tool in the diagnosis, prognosis, and follow-up of prostate cancer patients at high risk for bone metastasis. This study provides preliminary data to accurately power larger studies

evaluating response to therapy. Further studies are warranted to assess whether castration sensitivity and type of therapy affect the ability of NaF-PET/CT to accurately identify response to treatment.

DISCLOSURE

The authors have no conflict of interest.

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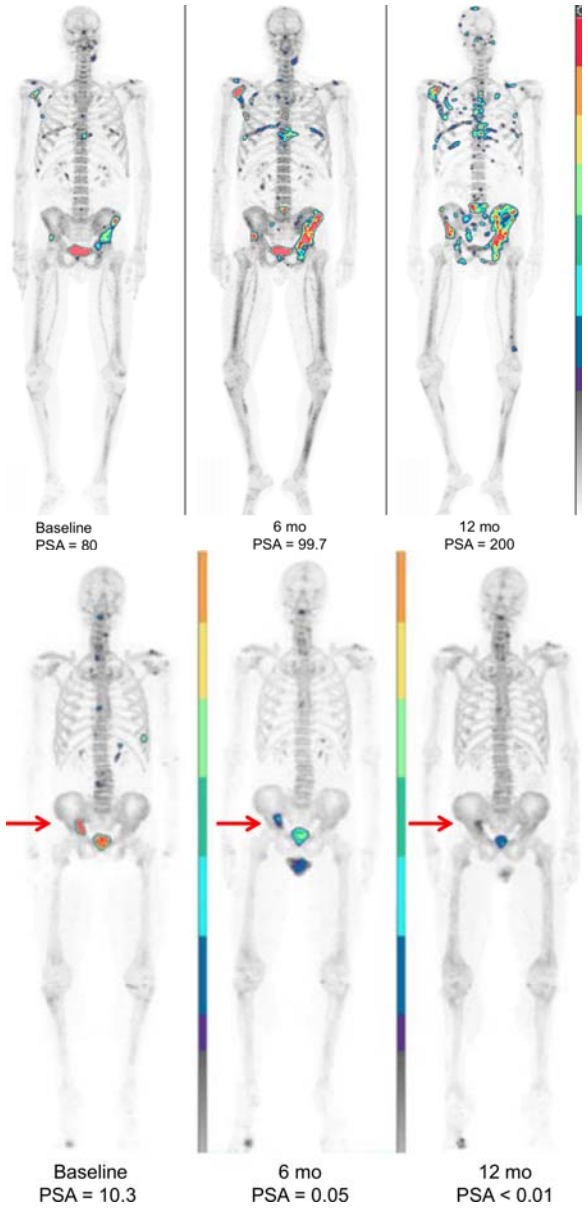
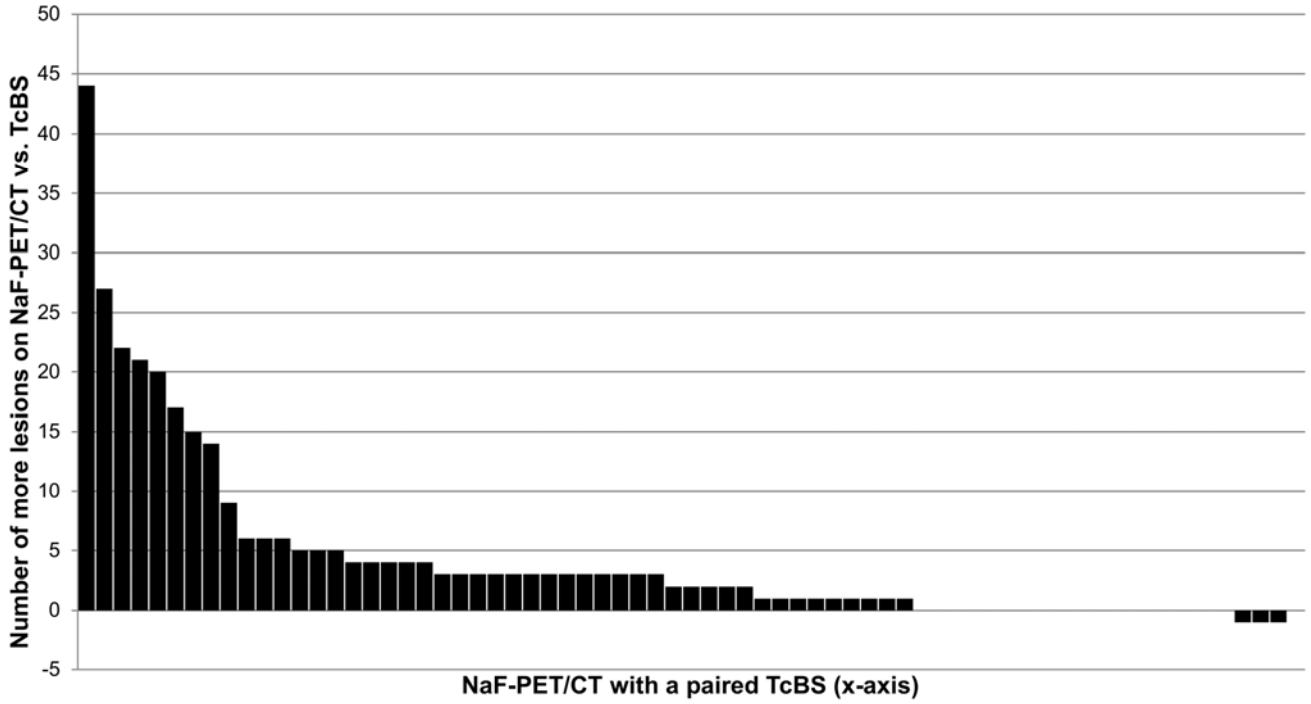


FIGURE 1. (A) Progressive disease on NaF-PET/CT in a 67-year-old male with post-docetaxel mCRPC whose PSA increased on treatment with abiraterone acetate (6 months) and cabazitaxel (12 months). Sequential NaF-PET/CT scans detected multiple new skeletal lesions. Image intensities were equally adjusted. (B) Improved disease on NaF-PET/CT in a 66-year-old male with mCRPC who had a PSA response to docetaxel chemotherapy. Sequential NaF-PET/CT scans showed a significant decrease in uptake in the right pelvic skeletal lesion. Image intensities were equally adjusted.



Lesion number on NaF-PET/CT vs. TcBS	*n* = 68 (%)
NaF-PET/CT > TcBS	47 (69%)
NaF-PET/CT = TcBS	18 (27%)
NaF-PET/CT < TcBS	3 (4%)

FIGURE 2. Number of lesions on NaF-PET/CT vs. TcBS.

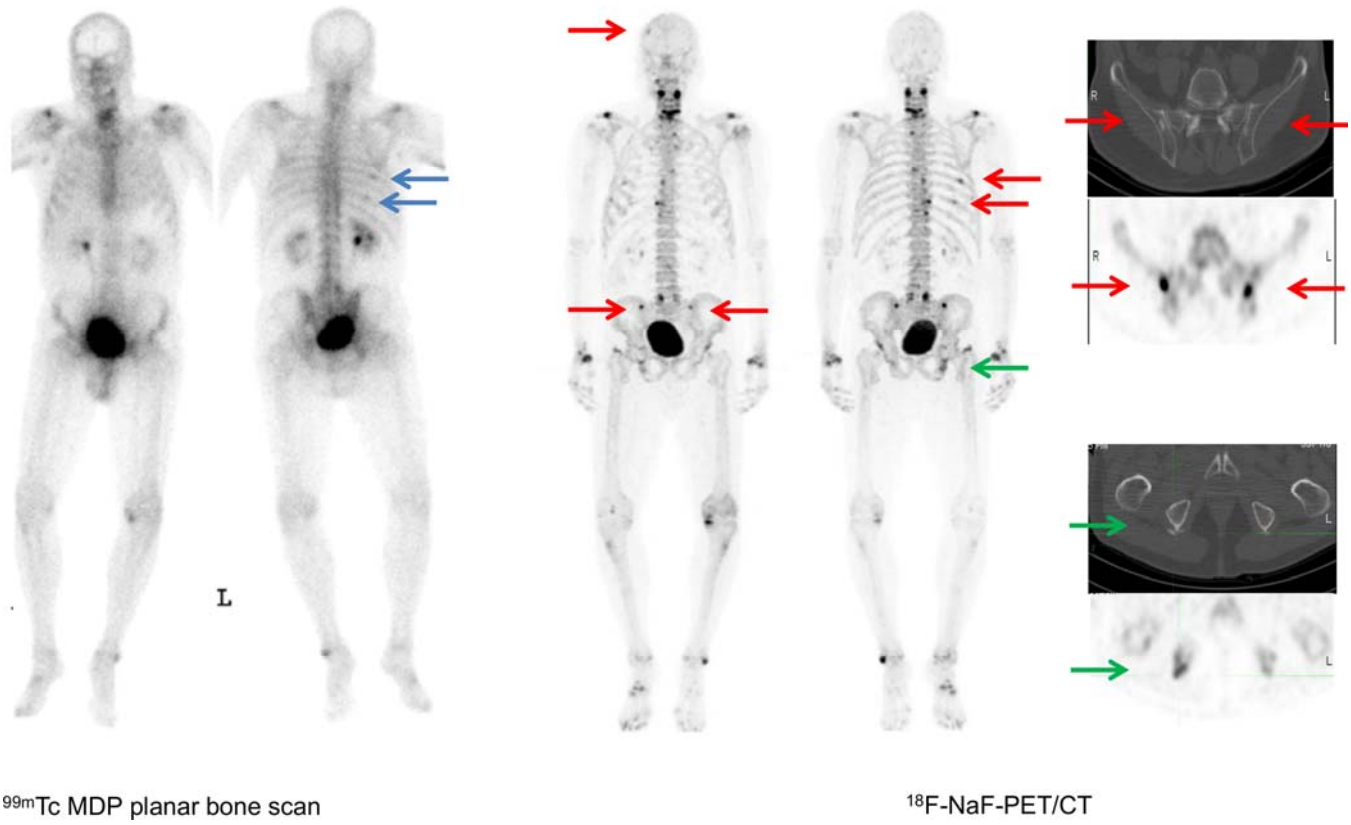


FIGURE 3. TcBS and NaF-PET/CT in a 74-year-old male with high-risk prostate cancer. TcBS shows right rib lesions categorized as indeterminate (blue arrows). NaF-PET/CT confirms lesions as malignant and shows additional malignant lesions in the skull, ribs, and pelvis (red arrows). Other uptake (green arrow) is consistent with degenerative change.

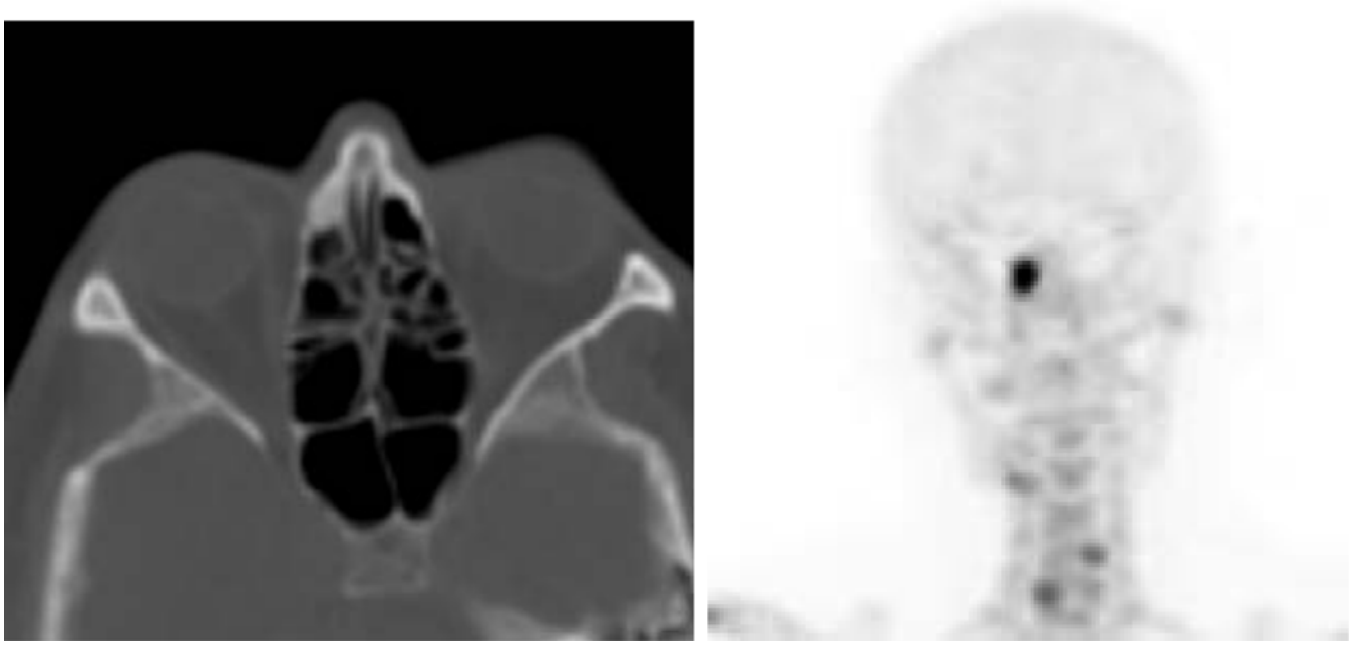


FIGURE 4. Incidental finding of fibrous dysplasia on NaF-PET/CT. Right nasal bone appears characteristically opaque and expansile.

TABLE 1. Patient Demographics and Clinical Characteristics

Characteristics	Patients *n* = 60	
	Known bone metastases at enrollment	
	Negative *n* = 30	Positive *n* = 30
Age		
Median	65	64.5
Range	43-79	44-79
Baseline PSA		
Median	10.97	9.93
Range	0.01-190	0.1-593
Gleason score		
4	1 (3%)	0
6	4 (13%)	3 (10%)
7	7 (23%)	10 (33%)
8	8 (27%)	5 (17%)
9	9 (30%)	11 (37%)
10	0	1 (3%)
On treatment at NIH		
Yes	6 (20%)	11 (37%)
No	24 (80%)	19 (63%)
Managed at NIH multidisciplinary clinic		
Yes	10 (33%)	2 (7%)
No	20 (66%)	28 (93%)
Primary therapy		
Radical prostatectomy	14 (47%)	13 (43%)
External beam radiation	8 (26%)	7 (23%)
Brachytherapy	2 (7%)	0
Castration status		
Sensitive	21 (70%)	13 (43%)
Resistant	9 (30%)	17 (57%)
Therapy while on study		
GnRH agonist/antagonist (leuprorelin/degarelix)	28	26
Antiandrogen (bicalutamide, nilutamide)	14	13
Ketoconazole	1	4
Enzalutamide	0	1
Abiraterone	0	1
Docetaxel, bevacizumab, lenalidomide, prednisone (ARTP)	0	10
Taxane	0	2
Bisphosphonate (zoledronic acid/dasatinib)	3	6
Sipuleucel-T	0	3
Vaccine study (TARP, Prostvac)	3	4
TRC105	1	1
Radiation	4	4

Abbreviations: PSA, prostate specific antigen; NIH, National Institutes of Health; GnRH Gonadotropin-releasing hormone; TARP, T cell receptor γ alternate reading frame protein

TABLE 2. Distribution of Malignant Bone Metastases on NaF-PET/CT

Location	Number of scans with ≥ 1 lesions at anatomical site
Skull	19 (13%)
Spine	34 (24%)
Pelvic bones	40 (28%)
Thorax	34 (24%)
Long bones	15 (11%)
Superscan	8

TABLE 3. Summary of NaF-PET/CT Number of Lesions with Respect to Clinical Impression at Each Time Point

NaF-PET/CT ***n*** **= 60**	**Number of lesions Median (range)**			***P*** **value**
	Metastatic by TcBS (Arm 1)	**Nonmetastatic** by TcBS (Arm 2)		
NaF-PET/CT Baseline	**5 (0–52)**	**0 (0–4)**		**< 0.0001**
	Clinical impression from baseline			
	Improved	**Stable**	**Progressed**	
6 months	**3 (0–29)**	**2 (0–24)**	**14 (2–65)**	**0.0078**
12 months	**6 (1–29)**	**1 (0–26)**	**25 (0–59)**	**0.0029**

TABLE 4. Detection of Lesions by NaF-PET/CT and TcBS in a Patient-Based Analysis (*n* = 68 Scans)

	TcBS		
NaF-PET/CT	**POSITIVE**	**INDETERMINATE**	**NEGATIVE**
POSITIVE	**37**	**14**	**6**
INDETERMINATE	**0**	**3**	**0**
NEGATIVE	**1**	**2**	**5**