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Sodium ^{18}F-Fluoride PET/CT of Bone, Joint and Other Disorders

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Abstract

The use of ^{18}F-sodium fluoride (^{18}F-NaF) with positron emission tomography-computed tomography (PET/CT) is increasing. This resurgence of an old tracer has been fueled by several factors including superior diagnostic performance over standard ^{99m}Tc-based bone scintigraphy, growth in the availability of PET/CT imaging systems, increase in the number of regional commercial distribution centers for PET radiotracers, the recent concerns about potential chronic shortages with ^{99m}Tc based radiotracers, and the recent decision by the Centers for Medicare and Medicaid Services to reimburse for ^{18}F-NaF PET/CT for evaluation of patients with known or suspected bone metastases through the National Oncologic PET Registry. The major goal of this article is to review the current evidence on the diagnostic utility of ^{18}F-NaF in the imaging assessment of bone and joint in a variety of clinical conditions.

Keywords

^{18}F-NaF; fluoride; PET; CT; bone; joint

Standard bone scintigraphy with ^{99m}Tc-based radiotracers (e.g. ^{99m}Tc methylene diphosphonate or MDP) remains one of the most common imaging procedures worldwide for a variety of disorders. These conditions include imaging evaluation for infection (e.g. osteomyelitis), non-infectious inflammation (e.g. arthritis), trauma, metabolic bone disease, benign and malignant neoplasms, and specific states in children. Both planar technique and in selected cases, single photon emission tomography (SPECT) are performed. The scan may also include dynamic image data acquisition (3-phase) and involve only a specific region of the body or the whole skeleton. The procedure guidelines and the common imaging findings with various conditions using standard bone scintigraphy have been reviewed extensively in many excellent reviews and medical imaging textbooks (1). Bone scintigraphy is most effective when correlated to other relevant imaging modalities such as

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radiography, computed tomography (CT), and magnetic resonance imaging (MRI) that often assists with improving specificity.

Despite the historical legacy and widespread current clinical practice that employs ^{99m}Tc-based bone scintigraphy, the use of positron emission tomography (PET) with ^{18}F-sodium fluoride (^{18}F-NaF) is increasing. ^{18}F-NaF was introduced in 1962 and approved for clinical use by the U.S. Food and Drug Administration in 1972 (2, 3). However, despite the early recognition of the superior diagnostic performance of ^{18}F-NaF, the tracer was not widely used in view of limited supply and relatively high cost, the technical limitations of gamma cameras with high-energy photon imaging and, at the time, the paucity of PET scanners. Since 2001, when combined PET/computed tomography (PET/CT) scanners became commercially available, the use of this imaging system with the most common PET radiotracer, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has rapidly increased, particularly in the evaluation of patients with cancer. The growing availability of PET/CT scanners, establishment of commercial regional distribution centers for PET radiotracers, and the recent problems with shortages of ^{99m}Tc-labeled tracers, prompted a resurgence of use of ^{18}F-NaF in bone scintigraphy (4–6). A major reinforcement in use was also the decision by the Centers for Medicare and Medicaid Services on February 7, 2011, to reimburse for ^{18}F-NaF PET/CT through the coverage with evidence development program managed by the National Oncologic PET Registry (NOPR) to assess the effect of ^{18}F-NaF PET/CT on referring physicians' intended management of patients with known or suspected bone metastases (7).

In this article, we review the mechanism of uptake, biodistribution, and dosimetry of ^{18}F-NaF followed by a concise summary of the published evidence on its utility in a variety of bone and joint conditions.

Biodistribution and Radiation Dosimetry

Czernin and colleagues summarized the mechanism of 1^{18}F-NaF uptake in the bone (8). ^{18}F-NaF is rapidly cleared from plasma in a biexponential manner with most of the tracer retained by bone after a single pass. The tracer uptake by the bone is due to chemisorption with exchange of $^{18}F^-$ ion for OH^- ion on the surface of the hydroxyapatite matrix of bone forming fluoroapatite and migration of $^{18}F^-$ ion into the crystalline matrix of bone. There is minimal binding to serum protein and rapid renal clearance that contributes to the high quality of images with high bone-to-background ratio in a shorter time than for standard ^{99m}Tc-based tracers (9, 10). ^{18}F-NaF may be used with dynamic PET data acquisition to obtain quantitative measurements of the tracer pharmacokinetics that then can be useful in specific research and clinical applications (11–16).

Procedure guideline for use of ^{18}F-NaF PET/CT has been published (17). The radiotracer is injected intravenously with an adult activity dose of 185–370 MBq (5–10 mCi). Imaging may begin after 30–45 min of uptake phase in patients with normal renal function. The effective dose for ^{18}F-NaF is 0.024 mSv/MBq (0.089 mrem/mCi). The effective dose is 8.9 mSv (0.89 rem) for a typical activity dose of 370 MBq (10 mCi). This effective dose is approximately 70% higher than the effective dose of 0.0057 mSv/MBq (0.021 rem/mCi)

for ^{99m}Tc-MDP, which translates to an effective dose of 5.3 mSv (0.53 rem) for a typical activity of 925 MBq (25 mCi) (17). However, given the high bone-to-background ratio (i.e. high signal-to-noise ratio) of ^{18}F-NaF, the effective dose may be lowered without major untoward effect on image quality by reducing the injected activity (e.g. by about half) such that the effective dose would then be comparable to that for ^{99m}Tc-MDP (18). Bladder receives the largest radiation dose of 0.22 mGy/MBq (0.81 rad/mCi) with voiding interval of 3.5 h (17).

Pediatrics

The guidelines for clinical indications, image acquisition, image processing, and image interpretation of bone scans in children with either ^{99m}Tc-labeled radiotracers and ^{18}F-NaF PET have been published (19). Pediatric activity is typically weight-based at 2.22 MBq/kg (0.06 mCi/kg), with a range of 18.5–185 MBq (0.5–5 mCi). The effective dose is 0.086 mSv/MBq (0.32 rem/mCi) for a 5-year old child. The urinary bladder receives the largest radiation dose of 0.61 mGy/MBq (2.3 rad/mCi) at a voiding interval 3.5 h (17).

In view of the higher sensitivity and excellent quality images of ^{18}F-NaF PET in a shorter amount of time in comparison to standard bone scintigraphy, this imaging modality may be an excellent alternative to ^{99m}Tc MDP bone scans for assessment of bone pain and diseases in children (20). A major use of bone scintigraphy in children is for assessment of skeletal trauma in child abuse (21). Drubach et al performed a retrospective study of the diagnostic utility of ^{18}F-NaF PET in 22 patients younger than 2 years. Skeletal survey was obtained in all patients at baseline and in 14 patients during follow-up (22). The reference standard was based on independent interpretation of baseline and follow-up skeletal survey studies. ^{18}F-NaF PET demonstrated sensitivities of 85% for all fractures, 92% for thoracic fractures, 93% for posterior rib fractures, and 67% for classic metaphyseal lesions (CMLs). In contrast, the baseline skeletal survey showed corresponding sensitivities of 72%, 68%, 73%, and 80%, respectively. Therefore, ^{18}F-NaF PET/CT was overall advantageous over skeletal survey for detection of almost all suspicious fractures except for CMLs that may require an initial radiographic skeletal survey.

Localization and appropriate treatment of back pain in young children and adolescents are also important clinical endeavors (23). In an investigation of 94 young patients between the ages of 4 and 26 years, ^{18}F-NaF PET was able to localize the possible cause of back pain in 55% of patients (24). In descending order of occurrence, these conditions included pars interarticularis/pedicle stress, spinous process injury, vertebral body ring apophyseal injury, stress at a transitional vertebra-sacral articulation, and sacroiliac joint inflammation/stress.

Benign Bone, Joint and Other Diseases

^{18}F-NaF PET may be useful in the metabolic evaluation of benign bone, joint, and other clinical conditions. Furthermore, the CT portion of the ^{18}F-NaF PET/CT provides not only precise information on anatomic localization but also may reveal previously unknown clinically significant extraosseous findings in about 11% of patients (25).

During evaluation of patients for osseous metastatic disease, it is often observed that there is high ^{18}F-NaF uptake in joint degenerative and arthritic changes (Fig. 1). This commonly observed feature has been used to investigate the potential utility of ^{18}F-NaF PET/CT in this clinical setting. For example, ^{18}F-NaF PET may be useful in the detection of bone remodeling in early stage osteoarthritis of the temporomandibular and hip joints, ankylosing spondylitis, patellofemoral compartment pain, spontaneous osteonecrosis of the knee, femoral head osteonecrosis, characterization of bone mineralization around joint arthroplasties, early detection of aspetic loosening of total knee arthroplasty, differentiation of septic from aseptic loosening of total hip arthroplasty, and determination of treatment efficacy of bone active agents in patients with diminished bone mineral density (26–36). The osteointegration of cancellous bone allografts in bone defect fillers around the acetabular component of the loosened total hip replacement may also be monitored quantitatively with ^{18}F-NaF PET (38, 39). Similar findings have been reported for assessment of perfusion and viability of osseous (e.g. revascularized fibula graft) and osseocutaneus flaps for mandibular reconstruction and for allogenic bone grafts of the limbs (40–42). In patients with recurrent back pain after spinal fusion surgery (e.g. due to failed posterior lumbar interbody fusion), ^{18}F-NaF PET/CT may have a role in identifying abnormalities that require surgical reintervention (43, 44).

In a proof-of-principle investigation, ^{18}F-NaF PET has been shown to be superior to other imaging modalities in characterization of pulmonary alveolar microlithiasis, a rare disease in which multiple microscopic calcium phosphate microliths are deposited in the alveoli (45). Other pilot studies of patients with either otosclerosis or hyperostosis cranialis interna have shown that the metabolic activities of the affected bones, as measured by ^{18}F-NaF PET, may be useful for assessment of these clinical conditions (46, 47). Moreover, ^{18}F-NaF PET/CT appears to be the most accurate imaging modality and advantageous over contrast-enhanced MRI and cone beam CT in the assessment of the bisphosphonate-induced osteonecrosis of the jaw (48).

Since ^{18}F-NaF is taken up at sites of calcification, another interesting potential application may be in the assessment of atherosclerosis (49). In fact, use of PET with ^{18}F-FDG and 18F-NaF may provide important insight into the evolutionary phases of the atherosclerotic plaque from a vulnerable inflammatory state to development of plaque microcalcification, which then helps to understand the complex biology of plaque rupture (50). Dweck and colleagues prospectively evaluated 119 volunteers with and without aortic valve disease and scanned them for determination of coronary calcium score as well as ^{18}F-NaF and ^{18}F-FDG uptake levels (51). Patients with increased coronary ^{18}F-NaF uptake level had higher rates of prior cardiovascular events, angina, and Framingham risk scores, suggesting that coronary ^{18}F-NaF uptake may represent a new imaging biomarker for plaque assessment. In another study that employed both ^{18}F-NaF and ^{18}F-FDG PET, the coincident uptake of both radiotracers was noted in only 6.5% of arterial atherosclerotic lesion suggesting that these radiotracers may provide distinct information on the spectrum of the pathophysiologic processes involved in atherosclerosis (52).

Malignant Diseases

There is growing convincing evidence that ^{18}F-NaF PET/CT is diagnostically superior to standard ^{99m}Tc-based bone scintigraphy for more accurate detection and determination of the extent osseous metastatic disease in a variety of cancers (53–60). A recent meta-analysis of 10 studies comparing standard bone scintigraphy with ^{18}F-NaF PET/CT reported a patient-based pooled sensitivity of 96% and pooled specificity of 98%, respectively, and a lesion-based pooled sensitivity of 97% and pooled specificity of 98%, which were substantially better compared to ^{99m}Tc-based bone scintigraphy (61). Despite the superior diagnostic performance of ^{18}F-NaF PET in comparison to standard bone scan, it should be noted that the well-recognized entities of “superscan” and treatment-related “flare” are similar between these imaging modalities (62, 63).

Combined ^{18}F-NaF fluoride and ^{18}F-FDG PET/CT has also been proposed for assessment of both osseous and soft tissue lesions in the setting of a single imaging session for streamlining of care and potential reduction in the overall imaging cost (64–67). However, additional experience will be needed before such single-injection maneuver is adopted in view of issues such as dual tracer interference in semi-quantitative uptake measurements and potential challenge in comparing baseline dual-tracer studies to post-treatment single or dual-tracer scans.

In this section, we briefly review the major reports on the utility of ^{18}F-NaF PET or PET/CT in various cancers.

Head and Neck Cancer

In an investigation of 80 patients with head and neck cancer who were at increased risk for metastases, ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT were performed within 2 weeks of each other (68). Both scans showed similar lesion-based sensitivity (69.4% vs. 57.1%, p=0.126). Combined information detected more lesions than either scan alone, however, there was no statistically significant difference with patient-based analysis.

Thyroid Cancer

Ota et al evaluated 11 patients with differentiated thyroid carcinoma with suspected bone metastases after total thyroidectomy who underwent ^{131}I radioiodine therapy (69). Standard bone scintigraphy and ^{18}F-NaF PET/CT were performed and the findings were compared to those on radioiodine scan and CT (or MRI if available) as standard of reference. ^{18}F-NaF PET/CT was significantly more sensitive in detecting bone metastases from thyroid cancer in comparison to planar bone scan. However, another investigation showed only limited osteosclertic bone reaction from thyroid cancer metastases on ^{18}F-NaF PET (70)

Lung Cancer

Standard ^{99m}Tc-based bone scan with and without SPECT were compared to ^{18}F-NaF PET in 53 patients with small cell lung cancer or locally advanced non-small cell lung cancer for detection of vertebral bone metastases (71). Of the twelve patients with vertebral metastases, bone scan produced 6 false negatives, SPECT produced 1 false-negative and ^{18}F-NaF PET

resulted in no false-negatives. Moreover, ^{18}F-NaF PET impacted clinical management in 11% of patients.

Breast Cancer

^{18}F-NaF PET/CT has been shown to be superior to CT alone for detection of bone metastases from breast cancer (72). The investigation by Piccardo and colleagues compared ^{18}F-NaF PET/CT and CT alone in 39 breast cancer patients with bone metastases (73). A repeat CT at 12 month served as standard of reference. The sensitivity and specificity for ^{18}F-NaF PET/CT were 91% and 91%, respectively. The sensitivity and specificity for CT alone were 77% and 93%, respectively.

Interestingly, it appears that there is an age-related change in the amount of ^{18}F-NaF uptake in the bone of pre- and post-menopausal women (e.g. positive association between humeral shaft uptake and advancing age and negative association between lumbar spine uptake and advancing age)(74). As such, the background normal bone activity and tumor-to-background activity ratio may be different in pre- and post-menopausal women with bone metastases from breast cancer.

Hepatocellular Carcinoma

An investigation from Taiwan compared ^{18}F-NaF PET/CT and standard 99mTC-based bone scintigraphy in 34 patients with hepatocellular carcinoma (74). On a lesion-based basis, ^{18}F-NaF PET/CT had higher accuracy of detecting lesions in comparison to bone scan (96% versus 75%, p=0.0001). Moreover, ^{18}F-NaF PET/CT had also prognostic value in terms of overall survival while bone scan did not.

Multiple Myeloma

An early study of 7 patients with either whole-body MRI or whole-body radiographic survey as standard of reference identified 89% of the lesions on ^{18}F-NaF PET/CT (76). Sachpekidis et al performed a similar study with 18F-FDG PET/CT serving as reference standard (77). The correlation of lesion detection was only 39% between ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT, suggesting that ^{18}F-FDG PET/CT may be more useful in the skeletal assessment of patients with multiple myeloma.

Bladder Cancer

A report of 48 patients with urinary bladder carcinoma compared standard planar and SPECT bone scintigraphy with ^{18}F-NaF PET/CT (78). The sensitivity and specificity for detection of bone metastases were 82.4% and 64.5% for standard planar bone scan, 88.2% and 74.2% for SPECT/CT and 100% and 87.1% for ^{18}F-NaF PET/CT, respectively. ^{18}F-NaF PET/CT also changed the clinical management in 35% of patients. The study concluded that 18F-NaF PET/CT may serve as a cost-effective screening procedure for detection of skeletal metastases in high-risk patients with urinary bladder carcinoma.

Prostate Cancer

Bone is the most common site for metastases from prostate cancer. Most of these bone metastases appears osteoblastic (sclerotic) on radiography. Roudier et al demonstrated

through bone histomorphometry that the osteolytic-osteopenic component of the osteoblastic lesions, which are woven bone formed directly from the tumor stroma and not from the adjacent bone surface, might be responsible for the frequent fractures observed phenotypically as skeletal related events with their associated significant morbidity and cost (79).

Even-Sapir and colleagues compared ^{99m}Tc-MDP planar bone scintigraphy, SPECT, ^{18}F-NaF PET, and ^{18}F-NaF PET/CT in 25 men with newly diagnosed prostate cancer (Gleason scores of 8 or higher or serum prostate specific antigen (PSA) levels of 20 ng/mL or higher or nonspecific sclerotic lesions on CT) and 19 patients who were referred for evaluation of suspected recurrence or progression of disease (80). A clinical follow-up of 6–15 months was used as reference standard. In a patient based analysis, the sensitivity and specificity were 70% and 57%, respectively, for planar bone scintigraphy, 92% and 82% for SPECT, 100% and 62% for ^{18}F-NaF PET, and 100% and 100% for ^{18}F-NaF PET/CT. The high sensitivity and specificity of ^{18}F-NaF PET/CT may also allow for detection of occult bone metastases that are missed on standard bone scintigraphy, at lower PSA ranges than conventionally recognized. In a recent investigation for our PET/CT Center at the University of Southern California, we reported a true-positive detection rate of 16.2% for occult osseous metastases in 37 men with biochemical recurrence of prostate cancer who had negative conventional scans (Fig. 2) (81).

A recent investigation compared ^{99m}Tc-MDP bone scintigraphy, 18F-fluorocholine PET/CT and ^{18}F-NaF PET/CT with MRI as reference standard in detecting spine metastases from prostate cancer (82). The sensitivity and specificity were 51% and 82% for bone scintigraphy, 85% and 91% for 18F-fluorocholine, and 93% and 54% for ^{18}F-NaF PET/CT. The authors concluded that combined ^{18}F-NaF PET/CT and ^{18}F-fluorocholine PET/CT is accurate in this clinical setting and superior to standard bone scintigraphy. Similar results have been reported by others suggesting that practice guidelines should include ^{18}F-NaF PET/CT and (^{11}C or ^{18}F)-choline PET/CT in preference over ^{99m}Tc-based bone scan for detection and monitoring of bone metastases in patients with prostate cancer (83–85).

Beheshti and colleagues compared ^{18}F-fluorocholine PET/CT and ^{18}F-NaF PET/CT in 38 men with prostate cancer, 17 preoperatively at the time of initial diagnosis and 21 patients postoperatively for suspected recurrence (86). There was moderate agreement between the two radiotracers on both lesion-based (kappa=0.57) and patient-based (kappa=0.76) analyses. The authors also noted a significant negative correlation between tracer intensity as measured by standardized uptake value and the CT density of the lesions as measured in Hounsfield units for both tracers. The sensitivity and specificity were 81% and 93% for ^{18}F-NaF PET/CT and 77% and 91% for 18F-fluorocholine, respectively. The authors concluded that while 18F-fluorocholine might be superior for detection of early marrow metastases, but ^{18}F-NaF PET/CT might provide additional useful information when ^{18}F-fluorocholine is negative at sites of suspicious sclerotic lesions.

The early results of the prospective data that were collected under Medicare's Coverage with Evidence Development policy using the NOPR process in men with known prostate cancer showed high overall impact in the management of these patients (87). The patients were

examined at the time of initial staging (Group I, n=1024), suspected first bone metastasis (Group II, n=1997), and suspected progression of osseous metastases (Group III, n=510). The post ^{18}F-NaF PET management plans changed in 77% of Group I, 52% of Group II, and 71% of Group III, respectively. The overall change in intended management ranged from 44% to 52%. Even after adjusting for prior plans for additional imaging evaluation (imaging-adjusted impact), the overall impact ranged from 12% to 16%. Bone metastases were recorded in 14%, 29%, and 76%, of patients in Groups, I, II, and III, respectively.

With respect to treatment response evaluation in metastatic prostate cancer, one small cases series demonstrated that ^{18}F-NaF PET/CT may be useful for semi-quantitative assessment of response to alpha particle treatment with the recently FDA approved ^{223}Ra-dichloride in castrate resistant prostate cancer (88). Additional studies will be needed to define the role of ^{18}F-NaF PET/CT in assessment therapy response in patients with metastatic prostate cancer (Fig. 3).

Conclusion

In comparison to ^{99m}Tc-based bone scintigraphy, ^{18}F-NaF PET/CT provides higher diagnostic performance with higher quality images within a shorter period from injection time and with relatively similar radiation dosimetry, albeit at currently higher scan cost. However, this higher cost may be at least partly be mitigated by increased patient throughput, avoidance of performing additional separate CT scans, and increased availability, access, and use of PET/CT, particularly in an environment at risk for potential chronic ^{99m}Tc shortages.

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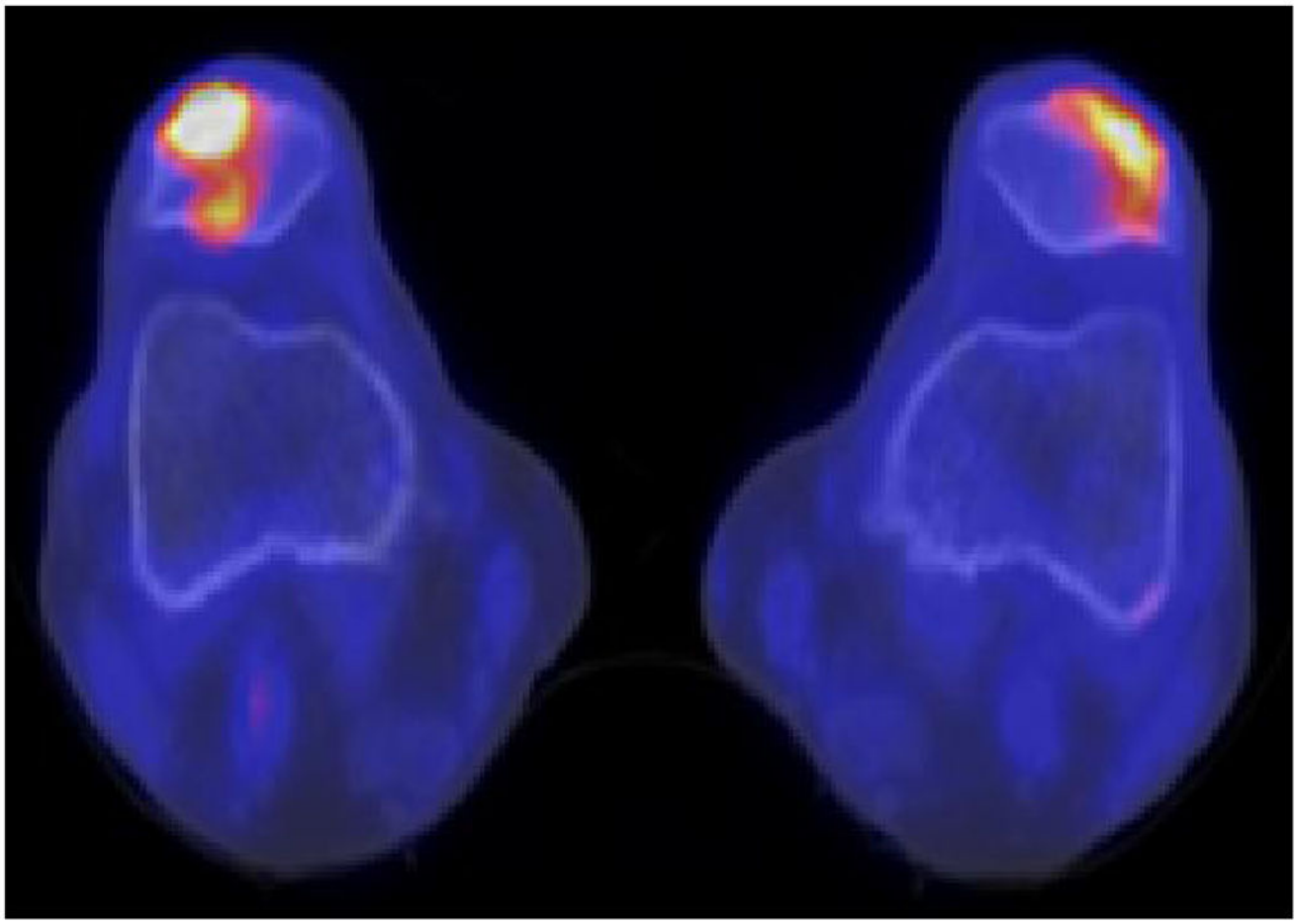
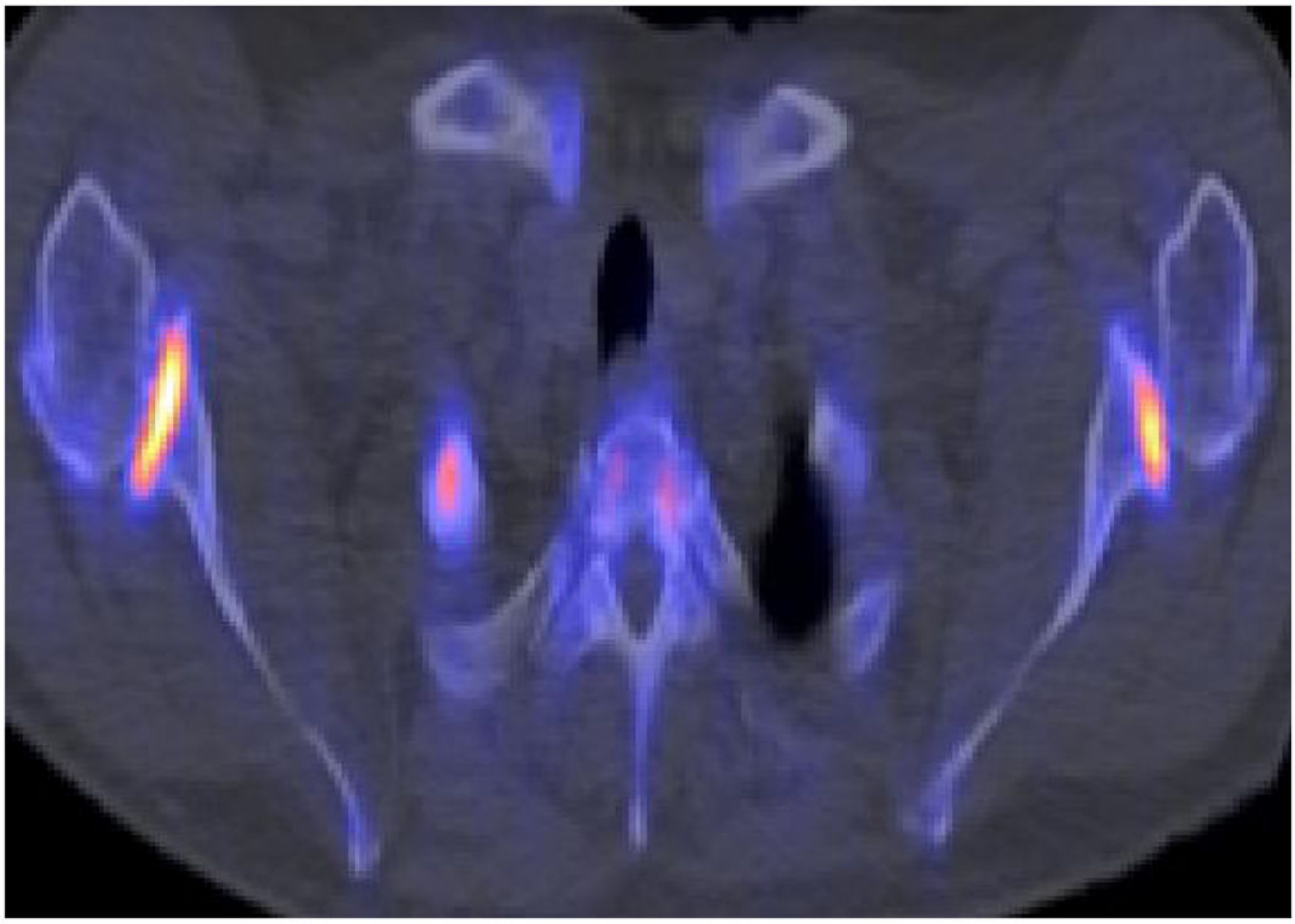




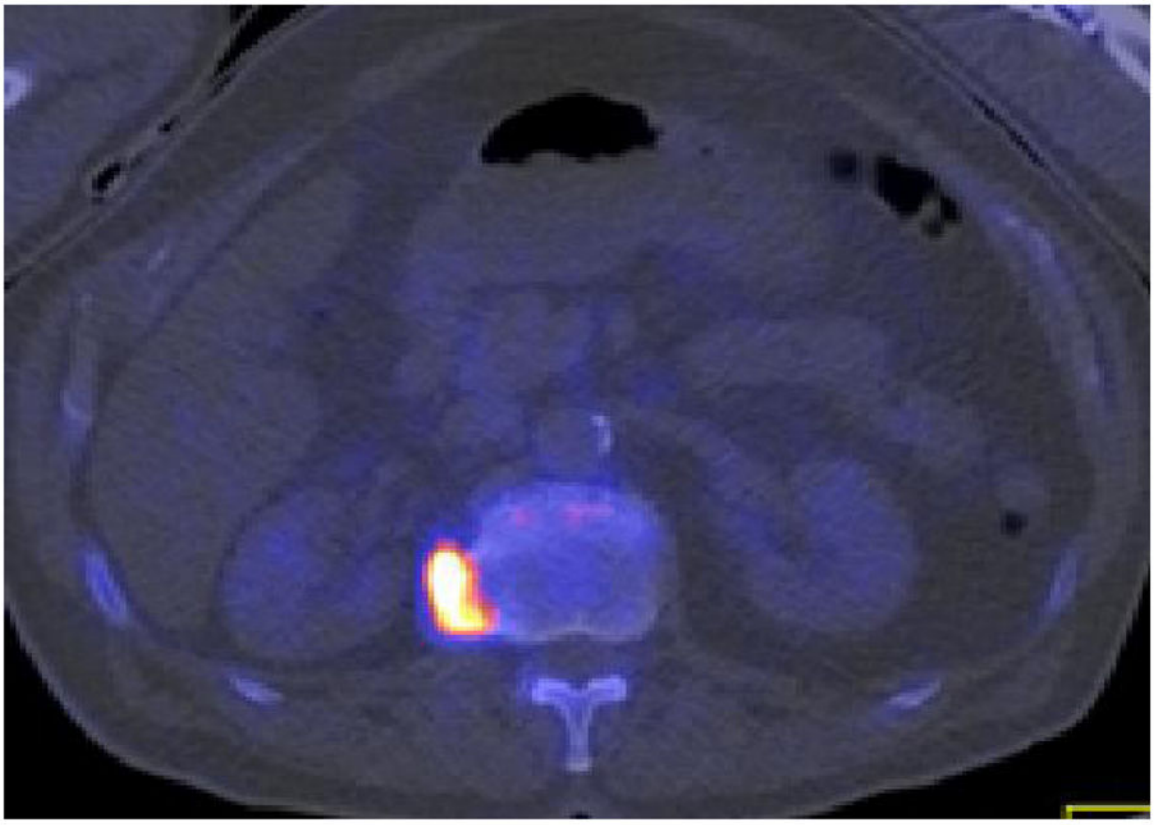
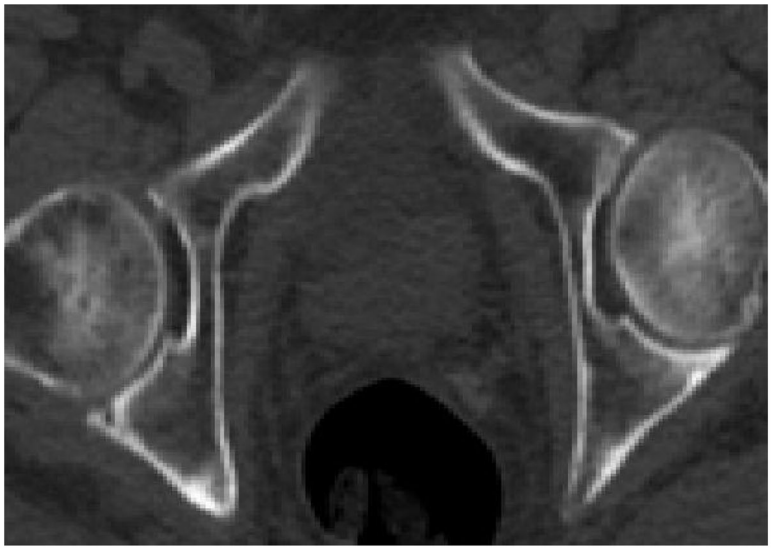
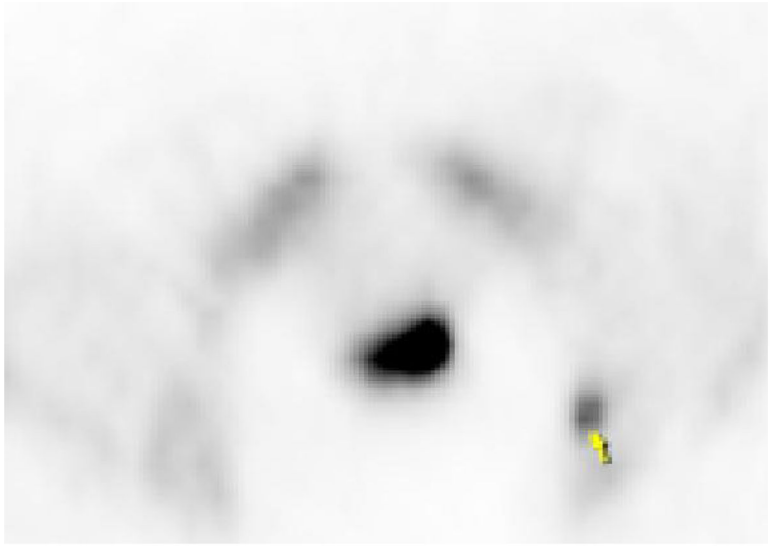


Fig. 1.
Benign causes of increased 18F-NaF uptake; (A) enthesopathy, (B) degenerative joint disease, and (C) osteophytosis.





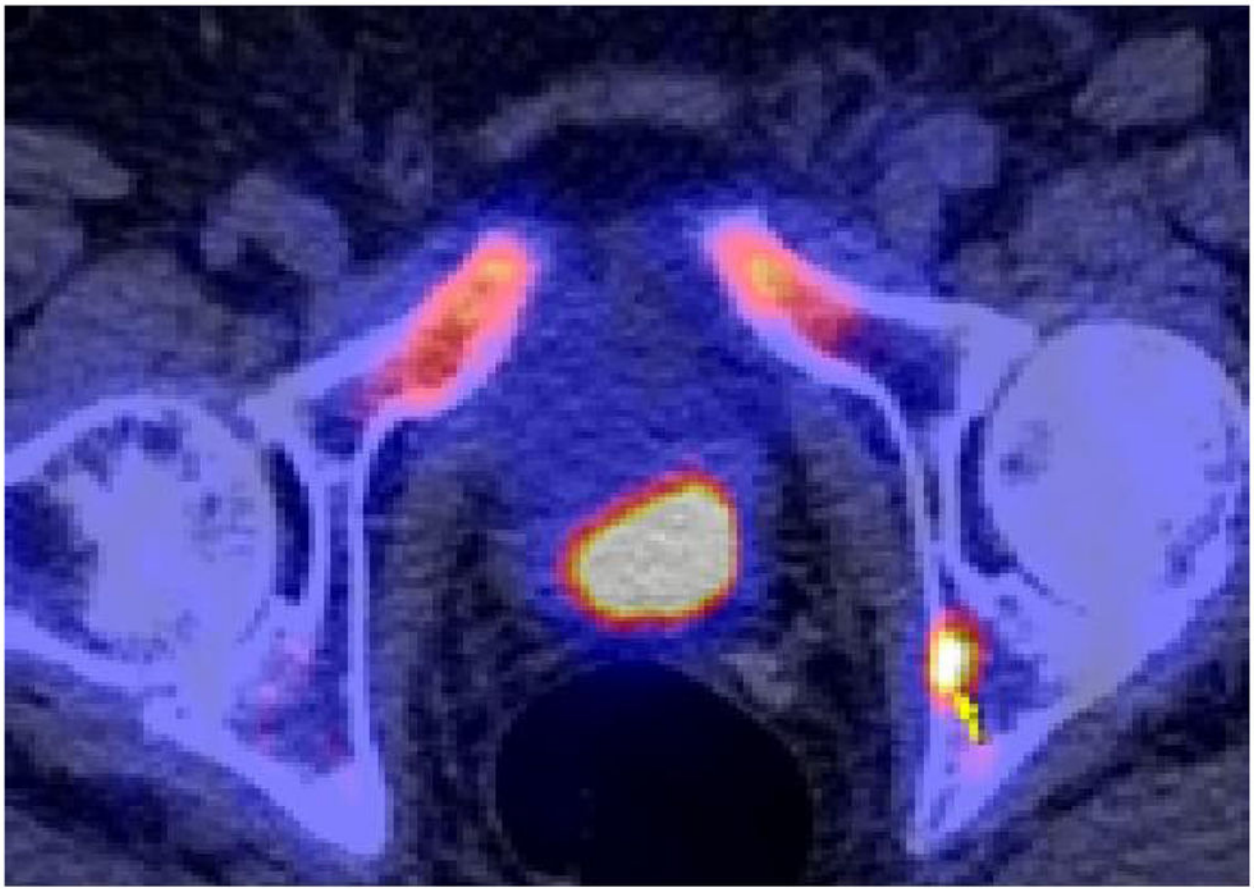


Fig. 2.

Biochemical recurrence of prostate cancer with negative conventional 99mTc-MDP bone scintigraphy. 18F-NaF PET/CT demonstrated focal hyperactivity (arrow) in the left acetabulum corresponding to subtle sclerosis on CT; (A) CT, (B) 18F-NaF PET, (C) fused PET/CT.

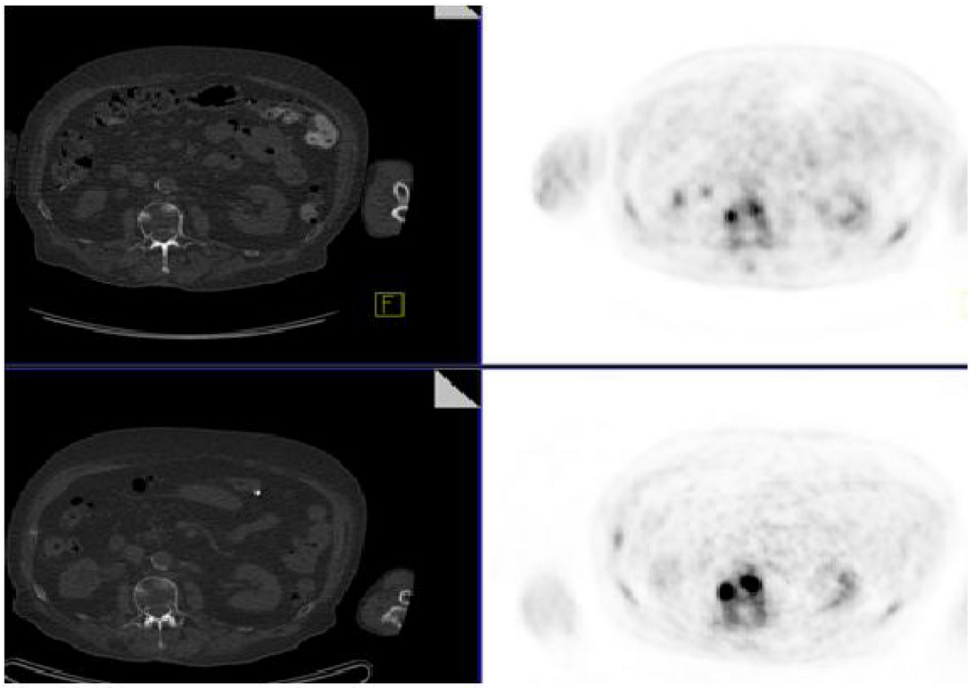


Fig. 3.

Metastatic prostate cancer, (A, Bottom) before (PSA 13.3 ng/mL) and (B, Top) after (PSA 9.6 ng/mL) androgen deprivation therapy. Treatment induced increase in sclerosis and decrease in 18F-NaF uptake of the vertebral lesions. Left Panel: CT at bone window level, Right Panel: 18F-NaF PET.