Spectrum of false positive ^{18}F-sodium fluoride (NaF) bone PET/CT findings in Oncology imaging; A narrative pictorial review of cases from a single institution

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Keywords: ^{18}F-NaF PET/CT - Cancer - Bone metastases - Benign bone lesions - ^{18}F-NaF case series

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Received:
10 January 2020
Accepted revised:
9 April 2020

Abstract
Fluorine-18-sodium fluoride (^{18}F-NaF) is a positron emission tomography (PET) bone imaging agent mainly used for oncology staging but may also be used in the evaluation of benign bone and joint pathology conditions. Fluorine-18-NaF is an excellent bone-seeking agent with high bone uptake owing to favorable biodistribution with rapid single-pass extraction, limited plasma protein binding and prompt renal clearance. Fluorine-18-NaF PET/computed tomography (CT) is highly sensitive in identifying both sclerotic and lytic bone metastatic lesions. Occasionally ^{18}F-NaF uptake in benign bone lesions can mimic malignantpathology. In these cases, the pattern of ^{18}F-NaF uptake may elicit a specific diagnosis and correlation with clinical information and morphological information from correlative CT is essential for a correct diagnosis. In the present article, we present a series of clinical cases demonstrating examples of ^{18}F-NaF uptake in benign lesions which can simulate malignant pathology in patients undergoing cancer staging.

Hell J Nucl Med 2020; 23(1): 67-75 *Published online: 30 April 2020*

Introduction

Fluorine-18-sodium fluoride (^{18}F-NaF) is a first-rate bone-seeking agent with high bone uptake owing to favorable biodistribution owed to its rapid single-pass extraction, limited plasma protein binding and prompt clearance from soft tissues [1]. It has a high sensitivity for detecting skeletal metastases surpassing conventional bone scintigraphy [2]. There have been reports of encouraging results obtained when used for characterizing benign bone pathology [3]. Fluorine-18-NaF positron emission tomography/computed tomography (PET/CT) provides definitive diagnosis in a majority of the cases with a high inter-observer agreement thus improving diagnostic confidence. This improved diagnostic performance is ascribed to better bone versus soft tissue dissemination leading to improved signal to noise ratio and higher spatial resolution [4]. Anatomical co-localization with CT also improves the specificity in the assessment of focal bone and soft tissue pathology.

In routine practice ^{18}F-NaF scan is used for skeletal oncological staging to confirm or refute the presence of skeletal metastasis. Its interpretation is based on the pattern of bone uptake, identified as sites of increased tracer uptake which can be focal or diffuse. In some cases, bone pathology can exhibit as decreased or absent uptake. Fluorine-18-NaF PET/CT is highly sensitive in identifying sites of osteosclerosis, however ^{18}F-NaF PET is less specific because osteoblastic activity profile cannot conclusively differentiate malignant from benign lesions [5]. This review article aims to present a spectrum of cases of ^{18}F-NaF uptake in benign bone pathology identified in patients referred for oncological staging in Kuwait Cancer control Centre. The aim is to familiarize readers with the potential pitfalls of this emerging modality.

Methods

Institutional ^{18}F-NaF PET/CT acquisition protocol

Image acquisition was performed according to the institutional protocol of the Kuwait Cancer Control Centre after intravenous (IV) injection of 185-370MBq or 2.2MBq/kg ^{18}F-NaF followed by an uptake period of between 60-90 minutes [6]. Positron emission to-

mography data was obtained in a three-dimensional mode at 2-3 minutes per bed position modified to the patient BMI (i.e 2 minutes for BMI <35kg/m^2; 2.5 minutes (35.0 to 39.9 kg/m^2) and 3 minutes for BMI >40kg/m^2). The images were acquired from vertex to toes and were reconstructed with a standard iterative algorithm (OSEM-ordered-subset expectation maximization, 3 iterative steps and 32 subsets) and filter cutoff 6.4mm as recommended by the vendor. A non-contrast CT was performed using an auto tube current of 50-120mA regulated by an automated algorithm (based on planar view) aimed at achieving a noise index of 20, 120kVp, and a pitch 1.3. Computed tomography axial images were reconstructed in a 512×512 matrix, with a slice thickness of 3.75 mm. [6]. Hospital research and ethical committee approved this narrative review and informed consent was waivered. There is no conflict of interest to declare.

History, production, pharmacokinetics and mechanism of uptake

Fluorine-18-NaF is one of the oldest radiopharmaceuticals which was introduced in the 1960s for nuclear bone imaging and was initially approved by the U.S. Food and Drug Administration in 1972 for bone scintigraphy but later in 1970s it was largely replaced by ^{99m}Tc-labeled compounds because of their better physical characteristics for imaging with γ-cameras [1]. The reemergence of ^{18}F-NaF bone imaging was ignited by the introduction of PET and PET/CT in 1990's and it became possible to obtain high-resolution and high-contrast imaging using ^{18}F-NaF. Progressive development, the growing availability of PET/CT scanners, and instances of ^{99}Mo–^{99}Tc generators shortage has led to further interest in ^{18}F-NaF in 2000s.

Fluorine-18 is produced by bombarding ^{18}O-enriched water with high-energy protons in a cyclotron. The carrier-free ^{18}F produced is eluted with 0.9% sodium chloride solution, resulting in formation of ^{18}F-NaF. Once produced, the ^{18}F-NaF is commercially available as an isotonic, sterile, colorless, pyrogen-free solution [7].

Fluorine-18-NaF bone biodistribution is related to blood flow and nearly all ^{18}F-NaF administered is taken up by bone after a single pass of blood, leading to a first-pass extraction of almost 100% [8]. The uptake of ^{18}F-NaF in bones is twice that of technetium-99m methylene diphosphonate (^{99m}Tc-MDP). The uptake mechanism of ^{18}F-NaF is similar to ^{99m}Tc-MDP, i.e. following chemisorption, of fluoride ions onto the hydroxyapatite surface, they exchange with the hydroxyl (OH^-) ions in the crystal, forming fluoroapatite. The favorable biodistribution i.e. insignificant plasma binding, prompt clearance is reflected by high target-to-back-ground ratios [1]. Around 30% of the injected dose is loca-lized in the Red blood cells, however, this does not interfere with bone uptake, as ^{18}F-NaF freely diffuses across the cell membrane.

Benign mimics or false positive uptake of ^{18}F-NaF

Studies have demonstrated that ^{18}F-NaF-PET/CT has a better diagnostic performance than conventional skeletal scintigraphy, and it is able to identify bone deposits earlier in the disease process than ^{99m}Tc-MDP planar imaging [2]. Langsteger et al. (2011) [9] reported in a prospective study of 42 patients with prostate cancer, that ^{18}F-NaF PET/CT had good diagnostic ability as evidenced by sensitivity, specificity, and accuracy of 91%, 83%, and 88% for the diagnosis of malignant bone deposits, however when compared to ^{18}F-fluorocholine (FCH) in the group of patients referred for suspicion of recurrence, ^{18}F-NaF was less specific (96% vs. 91%, P=0.033 with Obuchowski's correction). The results imply that whilst ^{18}F-NaF PET/CT is quite sensitive, it does have relatively low specificity and therefore it is important to identify false positives findings including uptake in benign lesions. Jambor et al. (2016) [10] described ^{18}F-NaF PET/CT being relatively more sensitive and precise with low rates of ambiguous findings than ^{99m}Tc-MDP bone scan, ^{99m}Tc-MDP single photon emission tomography (SPET), and ^{99m}Tc-MDP SPET/CT when used for oncological staging.

Similar to skeletal imaging with ^{99m}Tc-MDP, ^{18}F-NaF also accumulates in benign lesions due to increased bone turn over, which can mimic malignantpathology including metastases in oncology patients [11]. In the literature, several benign conditions have been described with increased ^{18}F-NaF accumulation for example inflammation and infection (osteomyelitis) [12], past trauma [13], fractures [14], fibrous dysplasia [15], Paget's disease [16], enchondroma, osteonecrosis [17], osteoid osteoma, myositis ossificans [18], enthesopathies [19] and normal variants like hyperostosis frontalis [20] and ischiopubic synchondrosis [21].

Fluorine-18-NaF accumulation depends on the balance and activity of osteoblastic and osteolytic remodeling. It mainly accumulates in the surface layer of the bone (where "remodeling" processes are more intense). Multiple factors can affect the intensity of increased localization which includes the degree of blood flow and the extent of bone turnover which in turn can be affected by a number of factors including bone stress, physiological remodeling and direct insult. Accumulation of ^{18}F-NaF within metastases is 3-10 times greater compared to healthy bone tissue [1]. As expected, uptake is higher in freshly laid bone (osteoid) because of more abundant binding sites. Benign bone lesions also accumulate ^{18}F-NaF in a similar way as it is taken up by metastatic bone disease and given the high sensitivity of ^{18}F-NaF PET/ CT, the intensity of uptake can also be significantly high in benign foci. Hence the intensity of ^{18}F-NaF uptake in its own right cannot be solely used to distinguish benign versus malignant pathology. However, the overall configuration of ^{18}F-NaF uptake, may be more suggestive (or in some cases for example rib fractures even characteristic) of a specific diagnosis. In this context review of the morphological information from the CT and any other recent imaging is considered essential for diagnosis (Table 1).

Correct interpretation of ^{18}F-NaF PET/CT has a learning curve which involves familiarization with the pattern of normal heterogeneous tracer uptake. Fluorine-18-NaF PET/CT use in daily clinical practice is increasing due to better availability of PET scanners. With the growing use, benign causes of ^{18}F-NaF uptake will also be encountered frequently during skeletal staging and recognition of benign ^{18}F-NaF uptake is

critical to avoid false positive interpretations, potentially leading to over diagnosis and upstaging. In this review, we provide examples of mimics of ^{18}F-NaF localization due to benign conditions. Fluorine-18-NaF uptake in benign causes include enchondroma (Figure 1), fibrous dysplasia (Figure 2), normal variants (Figures 3-5), hemangiomas (Figures 6, 7), Paget's disease (Figures 8, 9), uptake in Schmorl's node (Figure 10), osteonecrosis (Figure 11) and Baastrup's disease (Figure 12). These examples will provide readers with a good spectrum of visual findings and help avoid misinterpretation in routine clinical practice. Once again, we would reemphasize the use of all associated and available relevant radiological images for final diagnosis. It is pertinent to mention that if there is diagnostic uncertainty, reporters should not shy away from advising ancillary imaging, for example magnetic resonance imaging (MRI), for further characterization. Finally, it is essential to acknowledge that not all sites of possible benign uptake can be characterized conclusively on imaging alone and follow-up imaging can be an appropriate strategy in some of these cases.

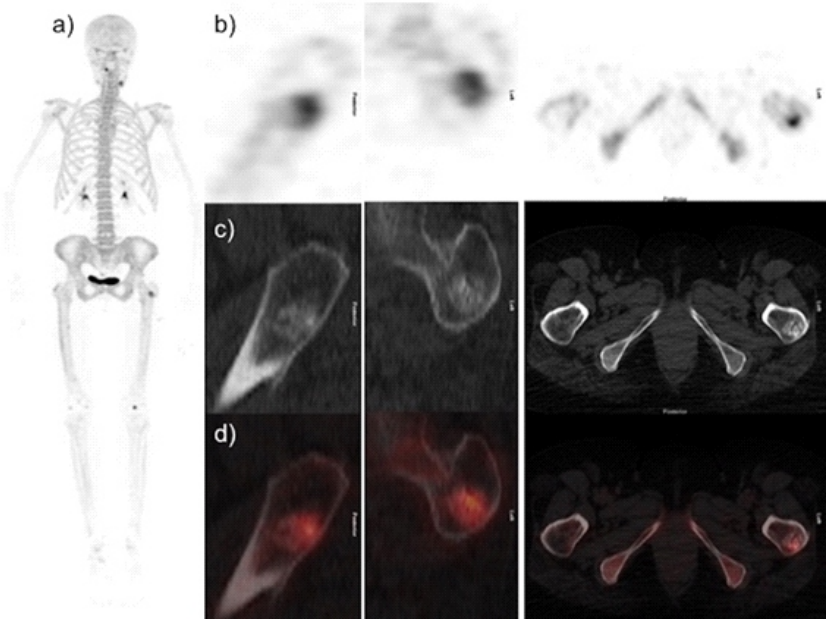

Figure 1. Enchondroma. A 44 year old female with newly diagnosed breast cancer. Fluorine-18-NaF PET/CT performed after the injection of 4.7mCi ^{18}F-NaF for staging. a) MIP ^{18}F-NaF, b) cross-section ^{18}F-NaF PET images show increased tracer activity in the left trochanteric region. c) Non-contrast enhanced CT images show dense chondroid calcifications (in a rings and arcs pattern), d) with increased uptake on fused ^{18}F-NaF PET/CT images. The lesion lacks aggressive features and is suggestive of an enchondroma and has remained stable on follow-up imaging.

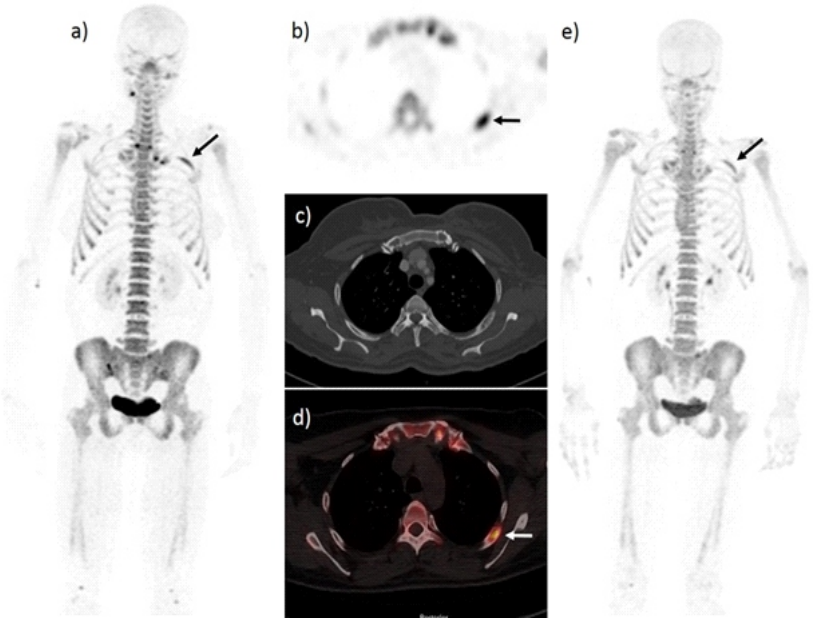

Figure 2. Monostotic fibrous dysplasia. A 41 year old female with breast cancer. Fluorine-18-NaF-PET/CT performed after the injection of 3.7mCi ^{18}F-NaF for staging. a) MIP ^{18}F-NaF, b) transaxial ^{18}F-NaF PET images show a linear area of increased tracer uptake in the posterior arch of the left 4th rib. b) Non-contrast enhanced CT shows an expansile bone lesion with cortical destruction and ground glass density matrix. d) Corresponding fused PET/CT images show increased tracer uptake. Findings represent monostotic fibrous dysplasia. e) A follow-up scan after 1 year showed stable osteoblastic activity and no bone secondaries.

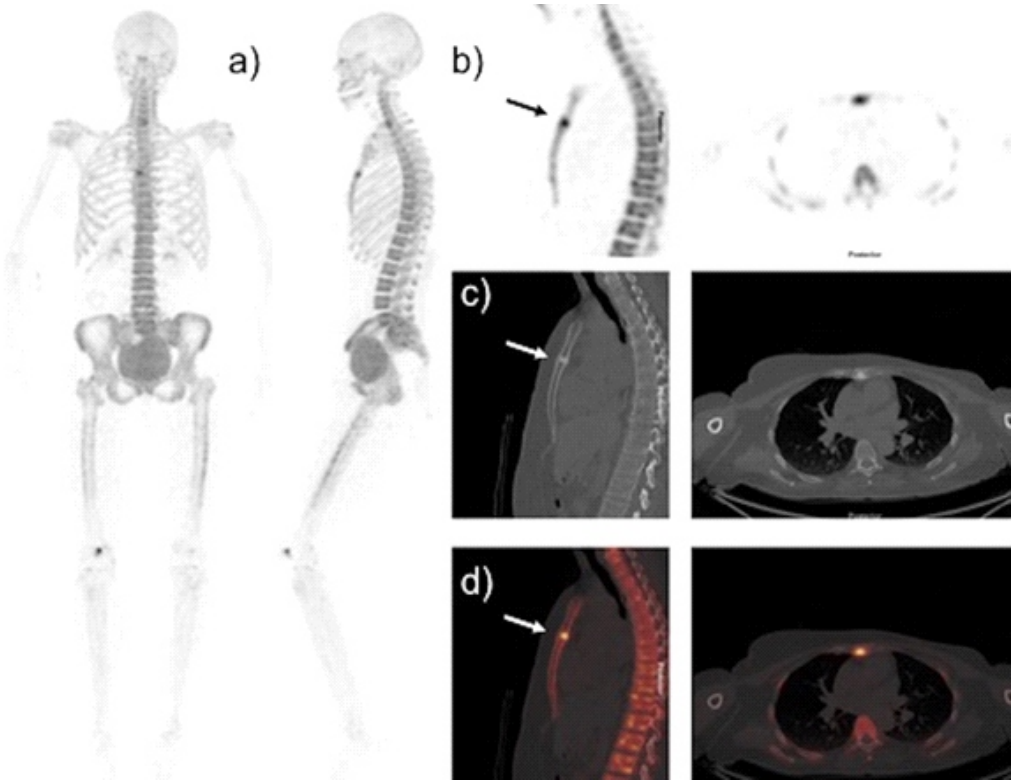

Figure 3. Normal variant uptake at sternal angle. A 46 year old female with breast cancer. Fluorine-18-NaF PET/CT performed after the injection of 5.6mCi of ^{18}F-NaF. a) Fluorine-18-NaF PET/CT MIP anterior and lateral images, b-d) sagittal and transaxial NaF PET, CT, and fused PET/CT images show focal increased tracer uptake in the sternal angle (arrow) representing a normal physiological variant uptake. There are degenerative changes in the right patellofemoral joint. There is no evidence of bone secondaries.

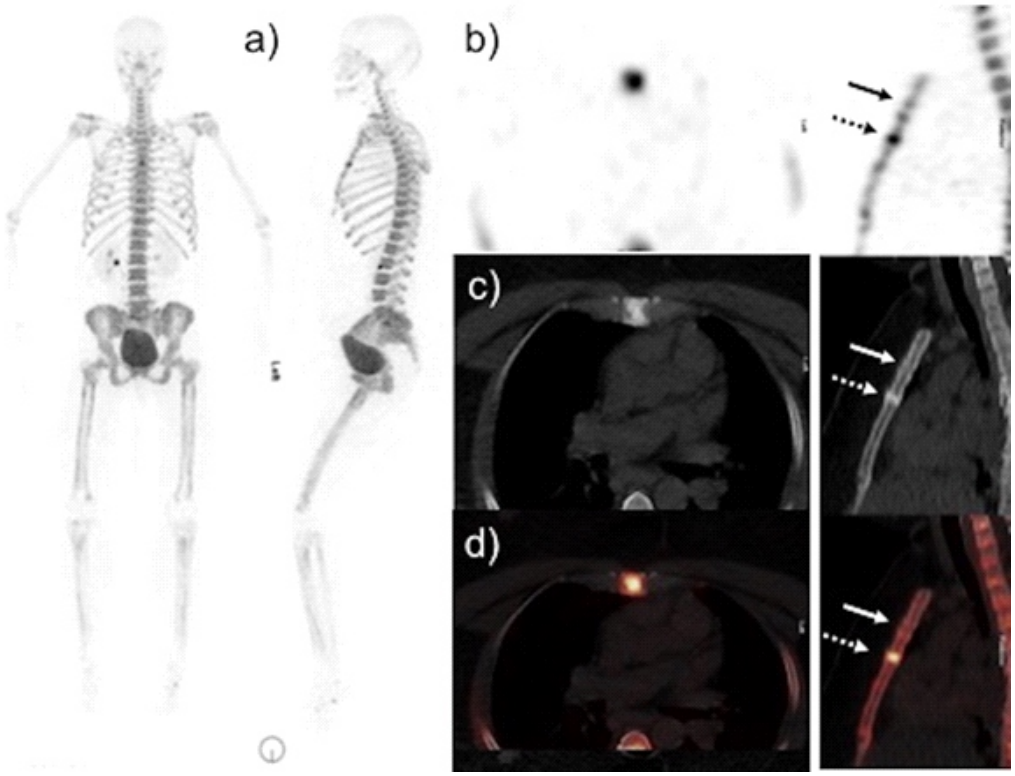

Figure 4. Normal variant uptake at sternal synchondrosis. A 56 year old female patient with breast cancer. Fluorine-18-NaF PET/CT performed after the injection of 4.6mCi of ^{18}F-NaF. a) ^{18}F-NaF MIP anterior and lateral images, b) transaxial and sagittal ^{18}F-NaF images show increased tracer uptake in the body of the sternum. c) Non-contrast enhanced CT images show sclerosis (dotted arrow) in the body of the sternum with a normal manubriosternal joint (solid arrow). d) Fused PET/CT images show increased tracer uptake in a persistent sternal synchondrosis, which is a normal variant. There was no evidence of bone secondaries.

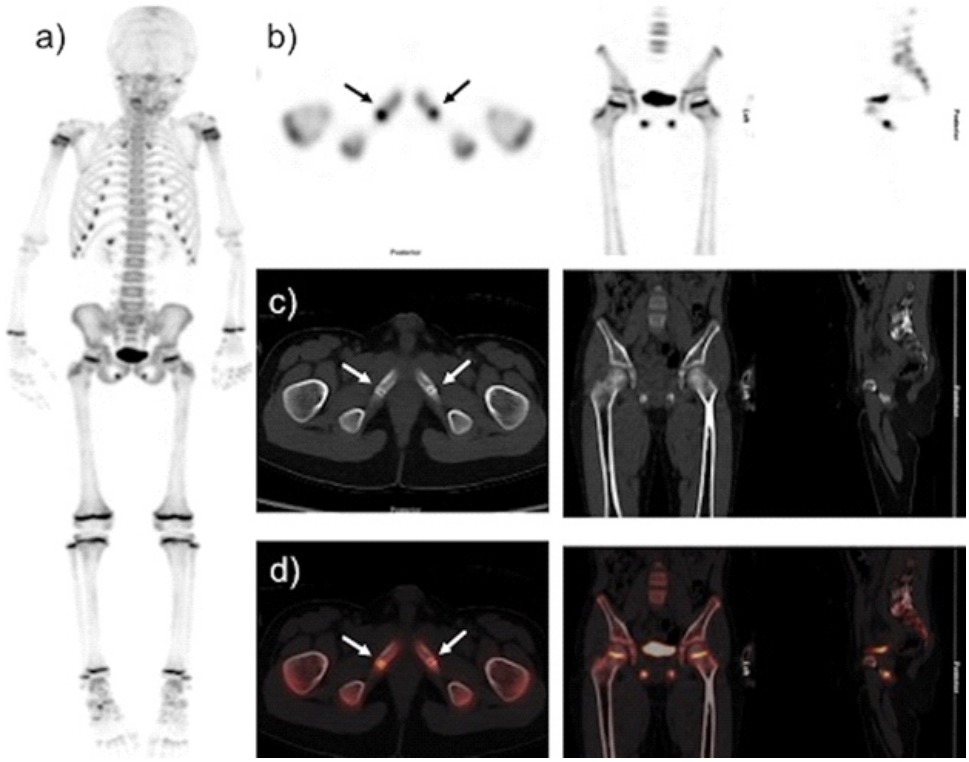

Figure 5. Normal variant uptake at ischiopubic synchondrosis. A 8 year old boy with a medical history of Ewing's sarcoma treated two years ago, presenting with back pain. Fluorine-18-NaF PET/CT performed after the injection of 2.6mCi of ^{18}F-NaF for the detection of recurrence. a) ^{18}F-NaF MIP anterior projection, b-d) transaxial, coronal, and sagittal ^{18}F-NaF PET, CT, and fused PET/CT images show a focal area of increased tracer uptake in the inferior pubic ramus on both sides, corresponding with the ischiopubic synchondrosis. This finding is a normal variant. In addition, increased uptake of tracer is seen in the epiphysial growth plates of the upper and lower limbs. There was no evidence of recurrence.

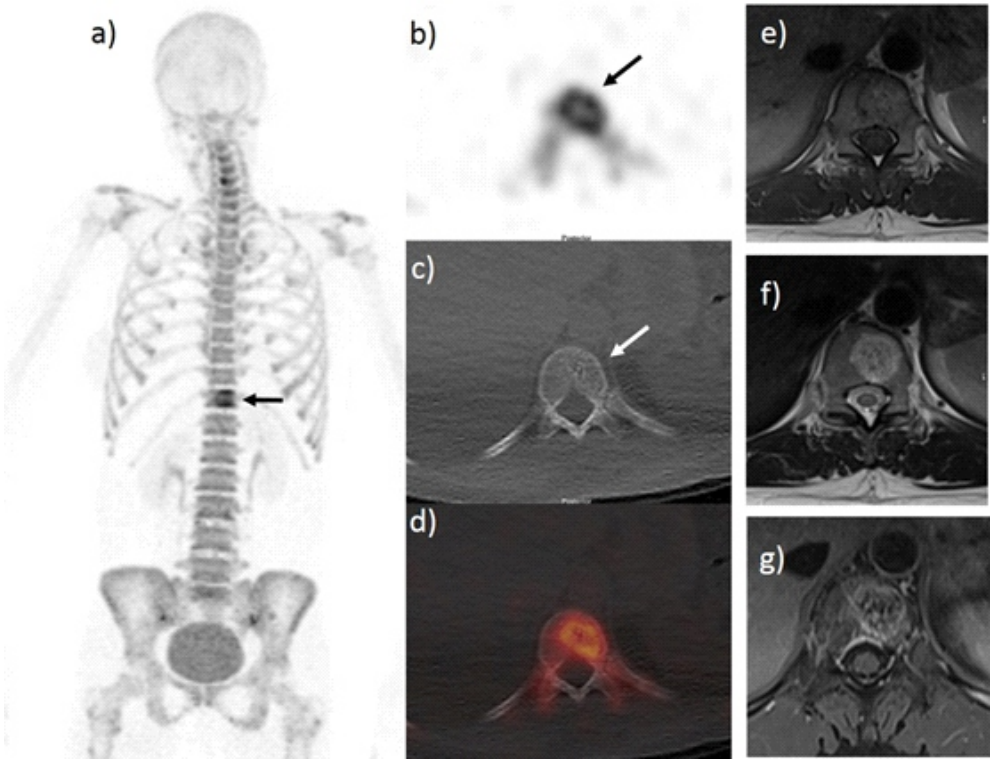

Figure 6. Vertebral hemangioma. A 42 year old male with left breast cancer. a) ^{18}F-NaF MIP image shows increased tracer uptake in the left side of the 11th dorsal vertebra. b) Cross-sectional ^{18}F-NaF images show a photon deficient area with increased tracer activity in the rim. c) Non-contrast enhanced CT shows a well-defined predominantly lytic lesion with coarse trabeculae ("corduroy cloth" or "jail bar" pattern) with d) increased tracer uptake on fused images. e) T1 and f) T2 weighted MRI images show a corresponding area of well-defined abnormal mixed high T1/T2 signal intensity g) with contrast enhancement after gadolinium administration. These findings are in keeping with a vertebral hemangioma. The study is negative for bone secondaries.

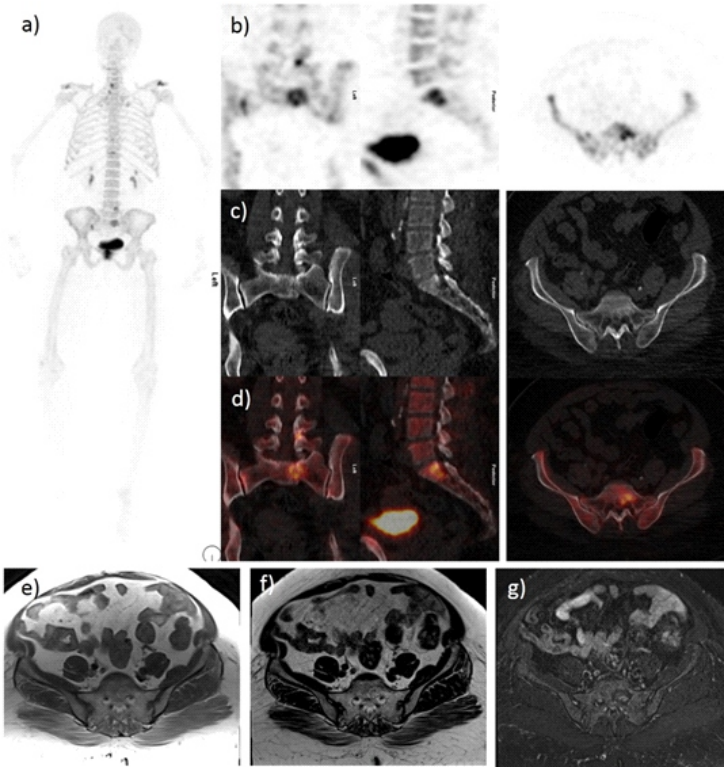

Figure 7. Vertebral hemangioma. A 57 year old male with left breast cancer a) ^{18}F-NaF MIP image shows a focal area of increased tracer uptake in the left sacral wing. b) Cross-sectional ^{18}F-NaF images show increased tracer uptake in the left side of S1. c) Non-contrast enhanced CT shows a well-defined sclerotic lesion corresponding to d) the area of increased tracer uptake on fused images. e) T1 and f) T2 weighted MRI images show a corresponding abnormal high T1/T2 signal intensity and g) show fat content on fat suppression image. These findings are suggestive of hemangioma. Increased tracer uptake is also seen in osteo-arthritic/degenerative changes in the acromioclavicular joints, the left facet joint of L4/L5 vertebrae, the right sacroiliac joint, and the pubic symphysis. There was no evidence of bone secondaries.

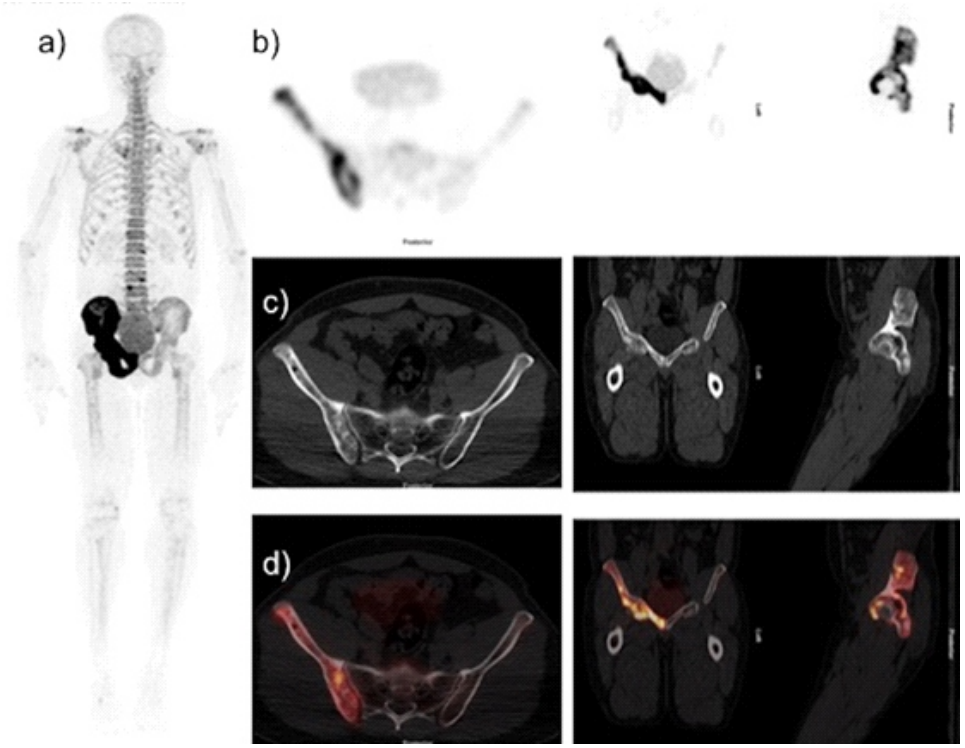

Figure 8. Monostotic Paget's disease. A 55 year old male with newly diagnosed Gleason score 7 (4+3) prostate cancer, complaining of right hip pain. Laboratory investigations show elevated serum alkaline phosphatase (ALP) (221U/l) and high prostate specific antigen (PSA) (14ng/mL). Fluorine-18-NaF PET/CT performed after the injection of 4.2mCi ^{18}F-NaF for initial staging. a) ^{18}F-NaF MIP and b) cross-sectional ^{18}F-NaF images show diffuse and intense tracer uptake in the right hemipelvis. c) Non-contrast enhanced CT images show cortical thickening and sclerosis, d) corresponding with the area of intense uptake on fused ^{18}F-NaF-PET/CT images. Increased tracer uptake is also noted in the endplates of L1, L3-L4 vertebrae, secondary to degenerative changes. The scan findings are consistent with early monostotic Paget's disease of the right hemipelvis no features of bone secondaries.

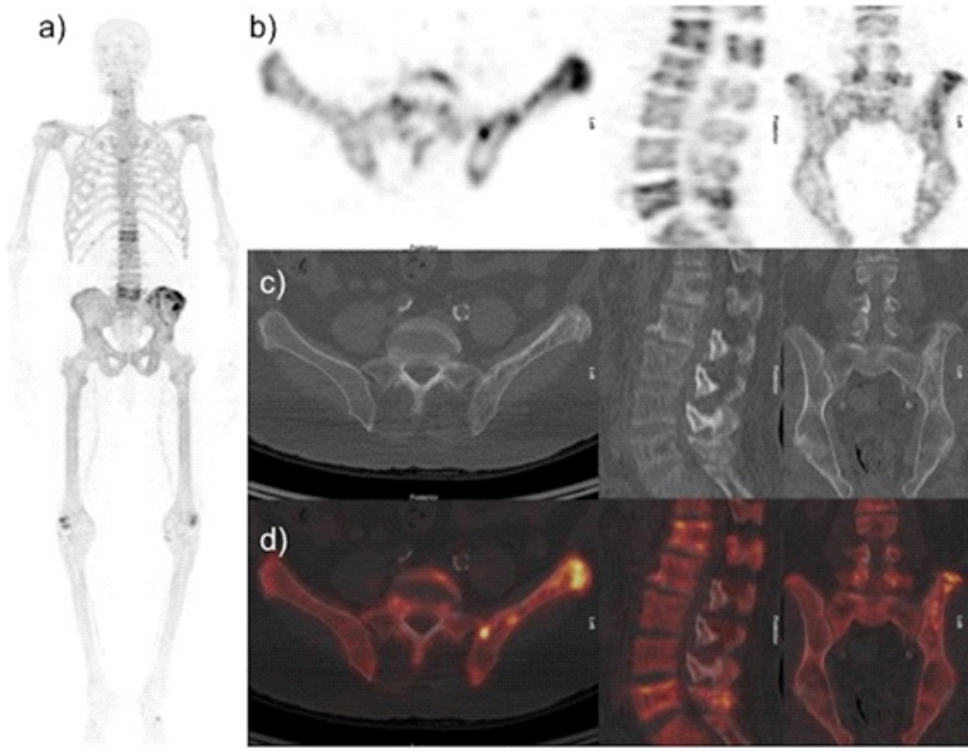

Figure 9. Polyostotic Paget's disease. A 64 year old male with a history of prostate cancer and prostatectomy 5 years ago now presents with a slowly rising PSA. Fluorine-18-NaF PET/CT is performed for restaging a) ^{18}F-NaF MIP and b) sagittal ^{18}F-NaF images show intense tracer uptake in the body of L1 and L5 vertebrae, and the left iliac bone. c) Non-contrast enhanced CT images show cortical and, trabecular thickening with sclerosis at L1, L5 vertebrae and left iliac bone with corresponding intense uptake on fused ^{18}F-NaF PET/CT images (d). The vertebral disease has a small osteolytic component which suggest mixed early and established polyostotic Paget's disease. There is no evidence of bone secondaries was seen.

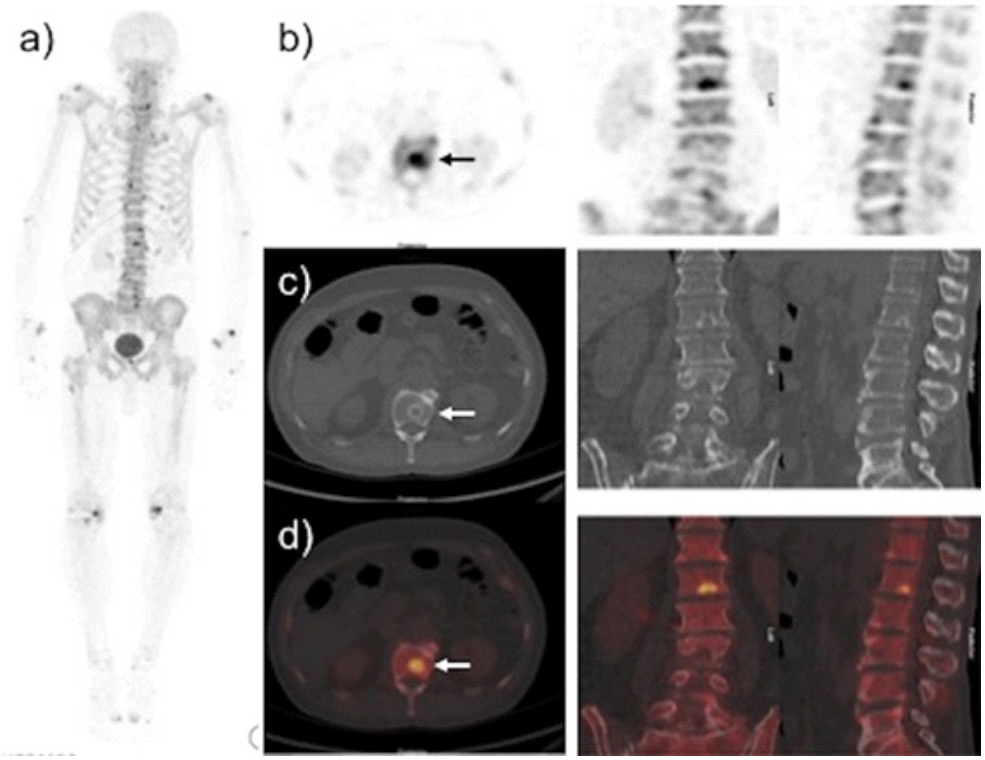

Figure 10. Fluorine-18-NaF uptake at Schmorl's node. A 80 year old female with breast cancer with low back pain. ^{18}F-NaF-PET/CT performed after the injection of 4.1mCi of ^{18}F-NaF for staging. a-b) ^{18}F-NaF MIP anterior images show increased tracer uptake in the dorsolumbar spine and both knee joints. c) Non-contrast enhanced CT images shows a small nodular well marginated low density lesion along the (arrow) the inferior endplate of the L1 vertebra (Schmorl's node) and multiple osteophytes in the dorsolumbar spine d) with corresponding tracer uptake on fused images. The scan findings are consistent with degenerative changes of the dorsolumbar spine.

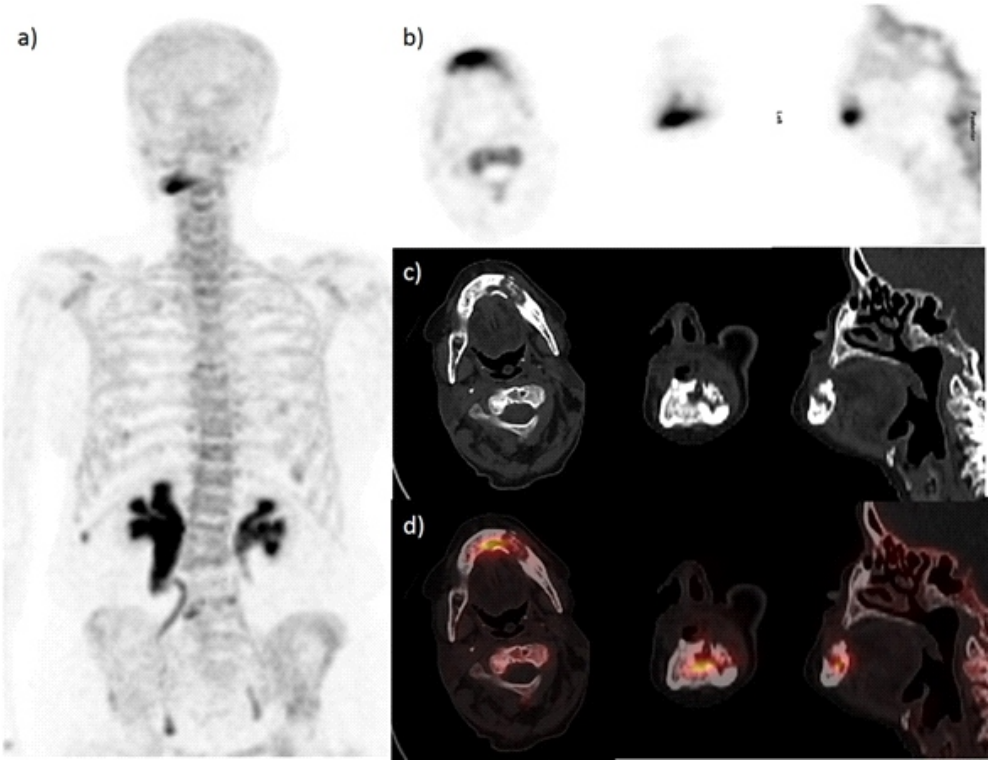

Figure 11. Jaw osteonecrosis. A 76 year old female with a history of metastatic breast cancer currently receiving endocrine and bisphosphonate therapy. She previously received an antalgic irradiation of the lumbar spine. a-b) 4.1mCi ^{18}F-NaF MIP anterior images show increased tracer uptake in the right side of the mandible. c) Non-contrast enhanced CT images show predominantly osteolytic changes with cortical disruption and limited periosteal reaction in the right mandibular ramus d) corresponding with increased tracer uptake on fused images. Reduced tracer uptake is seen in the lumbosacral region, likely due to the post-radiation effect. The findings in the mandible are consistent with jaw osteonecrosis, which was confirmed on biopsy. A note is made for incidental right hydroureteronephrosis. There are no other sites of osteoblastic lesions seen.

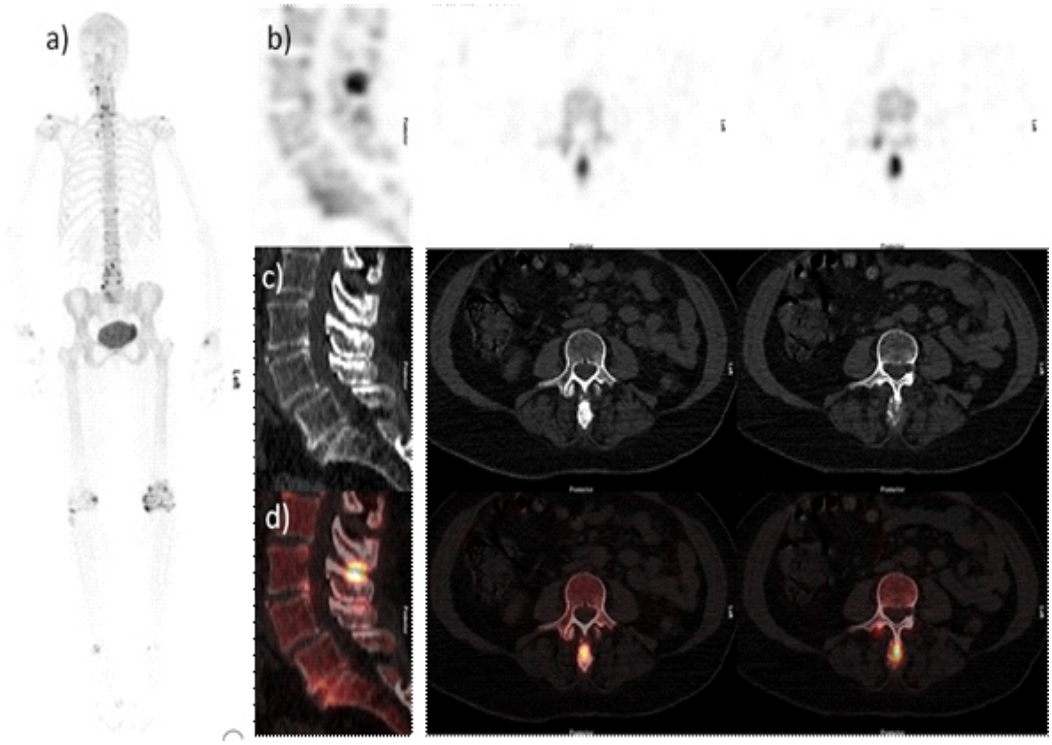

Figure 12. Baastrup's disease. A 65 year old female with breast cancer complaining of low back pain. Fluorine-18-NaF PET/CT performed after the injection of 4.0mCi of ^{18}F-NaF for staging. a) ^{18}F-NaF MIP anterior images show increased tracer uptake in the lower lumbar spine and both knee joints. b-c) Non-contrast enhanced CT shows hypertrophy/sclerosis of the spinous process of L2-L5 vertebrae d) with corresponding focal increased tracer uptake at L2/L3 vertebrae on fused images. There is grade 1 anterolisthesis of the L4/L5 vertebrae. Scan findings are consistent with Baastrup's disease and spondylolisthesis.

In conclusion, ^{18}F-NaF PET/CT is a promising modality for characterization of osseous malignant disease. Nonetheless uptake in benign sites is not uncommon and incorrect classification of these sites may lead to false positive and incorrect management. Our article aims to highlight the spectrum of benign mimics of ^{18}F-NaF findings seen in patients with cancer staging, the knowledge of which is crucial, as misinterpretation can lead to unnecessary investigations and alter management. Computed tomography component is beneficial for accurate localization and characterization of these benign mimics. Confident recognition of benign mimics ^{18}F-NaF uptake in routine clinical practice is therefore essential.

Teaching Points

1. Fluorine-18-NaF PET-CT is an emerging and promising bone imaging agent mainly used in imaging cancer patients but may also be useful in the evaluation of benign bone and joint conditions.
2. Fluorine-18-NaF is an excellent bone-seeking agent owing to high bone uptake, rapid single-pass extraction, negligible plasma protein binding and rapid blood and renal clearance.
3. Studies have demonstrated superior diagnostic performance of ^{18}F-NaF-PET/CT as compared to conventional bone scintigraphy.
4. Not uncommonly, ^{18}F-NaF uptake in benign bone lesions can mimic malignantpathology. In these cases, the pattern of ^{18}F-NaF uptake, clinical information and morphological information from correlative CT is essential for a correct diagnosis.
5. Confidence in recognition of benign mimics ^{18}F-NaF uptake in routine clinical practice is crucial, as misinterpretation can lead to unnecessary investigations and alter management.

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