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^{18}F-Sodium fluoride positron emission tomography: History, technical feasibility, mechanism of action, normal bio-distribution, and diagnostic performance in bone metastasis detection compared to other imaging modalities

Short running title: Role of ^{18}F-NaF in bone metastasis

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Abstract

The skeleton is overall the third most common metastatic site after the lungs and liver. Accurate diagnosis of osseous metastasis is critical for initial staging, treatment planning, restaging, treatment monitoring and survival prediction. Currently, ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) whole-body scan is the cornerstone of imaging to detect osseous metastasis. Though ^{18}F-sodium fluoride (^{18}F-NaF) was one of the oldest medical tracers, it was replaced by other tracers until recently, owing to its physical properties. Continued development of positron emission tomographic (PET) scanners have opened a new era for ^{18}F-NaF and given its higher sensitivity, there have been increasing applications in imaging. In this review, we will discuss the history, technical aspects, radiobiology, and bio-distribution of this tracer. Finally, we compared the accuracy of ^{18}F-NaF PET with other conventional imaging for detection of osseous metastasis.

Keywords:

^{18}F-sodium fluoride; PET-CT; bone scan; bone metastases; ^{99m}Tc-methylene diphosphonate

Introduction

The most common primaries for bony metastasis are breast and prostate cancers followed by pulmonary, renal, and thyroid malignancies. Appropriate diagnosis of bone metastasis is critical for initial staging, restaging, treatment monitoring and survival prediction. Currently, whole-body scintigraphy and single photon emission computed tomography (SPECT) with ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) is the imaging standard for detection of osseous metastasis. ^{18}F-sodium fluoride (^{18}F-NaF) is a positron emitting radiopharmaceutical used for skeletal imaging. It provides superior diagnostic information compared to ^{99m}Tc-MDP bone scan due to higher sensitivity and specificity in a wide variety of osseous metastasis (*1*). Combined information provided by positron emission tomography (PET) and computed tomography (CT) not only confers superiority in the characterization of malignant and benign processes, it also reduces the additional imaging work-up, thus shortening the diagnostic delays. The image quality, multi-planar information, and anatomical localization are further improved with better spatial resolution of modern equipment and scanners. Previous work including multiple case series, clinical trials, and meta-analysis have demonstrated advantages of ^{18}F-NaF PET-CT for lesion detection, evaluation and treatment planning of bony metastasis (*2-12*). In this article, we have discussed the history, technical aspects, mechanism of action, radiobiology and comparison of diagnostic performance of ^{18}F-NaF with ^{99m}Tc-MDP bone scan, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET scan, CT, and magnetic resonance imaging (MRI).

History

^{18}F-NaF is one of the oldest radiopharmaceuticals, which became standard for nuclear bone imaging in the 1960s using conventional gamma cameras, before the availability of PET scanners. In the 1970s it was largely replaced by ^{99m}Tc-labeled compounds because of better physical characteristics (e.g. longer half-life and lower photon energy) for imaging with gamma cameras (*13*). ^{18}F-NaF was initially approved by the United States Food and Drug Administration (FDA) in 1972 for bone scintigraphy but was subsequently withdrawn in 1975 for nonclinical reasons. In the 1990s, with the advent of whole-body PET scanner, it became possible to obtain high resolution and contrast imaging using ^{18}F-NaF. This led to the return of ^{18} F-NaF in 1993 for diagnostic imaging, followed by FDA approval in 2000. Progressive development, along with growing availability of PET-CT scanners, combined with years of the shortage of Molybdenum-99/Technetium-99 (^{99}Mo-^{99}Tc) generators led to further interest in ^{18}F-NaF. In 2011 it was approved by the Centers for Medicare and Medicaid Services (CMS) under the National Oncologic PET Registry (NOPR) registry for detection of osseous metastasis (*1*). The registry was closed to accrual on December 14, 2017, with over 65,000 ^{18}F-NaF PET scans performed on Medicare beneficiaries (*14,15*). As of this writing, CMS is not reimbursing the ^{18}F-NaF PET-CT scans in Medicare beneficiaries. Failure of CMS approval was due to the inability of various clinical studies to address the impact of ^{18}F-NaF PET scan on palliative/curative care, survival, or quality of care (*15*). This article will not only review the superior image quality demonstrated by ^{18}F-NaF PET, but also serve as a reference for documenting benefits of ^{18}F-NaF PET over bone scan.

Technical aspect

The ^{18}F 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. The ^{18}F has half-life of 109.7 minutes and decays into stable ^{18}O with ejection of a positron from the nucleus. This ejected positron annihilates with an electron producing two 511 keV photons. PET imaging is possible due to these two photons, which are emitted at about 180° from one another. Whereas the ^{99m}Tc is generator-produced with a half-life of 6 hours, ^{99m}Tc-MDP is manufactured by mixing ^{99m}Tc sodium pertechnetate with commercially available MDP kits.

Patient preparation is crucial before any imaging study. Unlike ^{18}F-FDG PET scan, when using ^{18}F-NaF, patients do not need to be in a fasting state and can take all their usual medications. Good hydration and frequent urination are strongly recommended to promote excretion of the tracer, which results in lower radiation dose and better image quality. With ^{18}F-NaF, images can be obtained as early as 30-45 minutes after injection. However, as compared to ^{99m}Tc-MDP, the effective radiation dose for ^{18}F-NaF is higher. For example, about 10 mCi dose of ^{18}F-NaF delivers 8.9 mSv to an adult patient, which is approximately 70% higher than the typical ^{99m}Tc-MDP dose. When the accompanying attenuation correction low dose CT is used, the effective radiation dose is usually less than 10 mSv. By convention, as with other radiopharmaceutical agents, ^{18}F-NaF PET-CT should be avoided in pregnant patients, unless the potential benefits outweigh the radiation risk to the mother and fetus. During lactation, the interruption of breastfeeding

is not advisable (*16,17*). Thus, there are potential risks and benefits associated with administration of ^{18}F-NaF which must be considered prior to patient selection for imaging. (Table 1)

Mechanism of action and radiobiology

^{18}F-NaF uptake mechanism in the bones is similar to the ^{99m}Tc-MDP but with better pharmacokinetics, faster clearance from blood, and higher uptake in the bones. ^{18}F-NaF has minimal protein binding which allows for a high first-pass extraction and fast soft tissue clearance (*18*). Approximately 50% of the injected tracer is taken up by the bones immediately after injection, with a high first pass extraction (*19*). The uptake of ^{18}F-NaF in a bone undergoing remodeling is 10 times that of normal bone (*20*). The remaining tracer is rapidly cleared from plasma and excreted by the kidneys with only 10% of tracer remaining in the blood after one hour, resulting in a very high bone to background contrast. The low protein binding and decreased background uptake allows ^{18}F-NaF PET scanning to be done one hour after administration of the radiotracer, earlier than ^{99m} Tc-MDP scanning which is typically 3-4 hours after injection. The urinary bladder receives the highest radiation dose followed by osteogenic cells and red marrow, respectively. ^{18}F-NaF binds to areas of new bone formation and is a marker of blood flow and osteoblastic activity, with blood flow being the rate-limiting step for uptake (*13,17*). The mechanism of uptake of ^{18}F-NaF in the bones is similar to that of ^{99m}Tc-MDP. The bone deposition is by the process of chemisorption, in which the OH^- ions in hydroxyapatite are exchanged with $^{18}F^-$ ions, converting hydroxyapatite to fluorapatite.

Though the uptake mechanisms of ^{18}F-NaF and ^{99m}Tc-MDP are similar, they exhibit differences in pharmacokinetics and radiobiology characteristics.

Normal bio-distribution

The bio-distribution of ^{18}F-NaF is dependent upon the differential regional blood flow and target organs (Fig. 1). The two primary target organs for ^{18}F-NaF uptake are the skeleton and urinary bladder (*21*). Though ^{18}F-NaF demonstrates uniform tracer distribution in bones, the non-homogenous patterns in adults are attributable to differences in regional blood flow and bone crystal surface area. Comparatively, in children and adolescents, intense and symmetric tracer uptake can be seen in the metaphysis. Urinary washout is the major route of excretion which leads to the visualization of kidneys, ureter, and urinary bladder. The intensity of tracer in the urinary tract depends on renal function, hydration state, and the time interval between tracer injection and imaging acquisition. Hyperemia in the soft tissue can cause soft tissue uptake. Active sclerotic lesions have diffuse increased uptake. An osteolytic lesion or lesion with minimal osteoblastic reaction can show a variable level of uptake, ranging from undetectable to a rim of activity to intense uptake. However, the mechanism of uptake is not limited to neoplastic processes, as any process, benign or malignant, which causes bone remodeling and increased turnover will show increased uptake. In the past, the degree of uptake was not considered sufficient to distinguish between benign and malignant lesions. Therefore, Standardized Uptake Values (SUV) were not routinely used in the interpretation of ^{18} F-NaF PET-CT scans (*17,18*). Although there seems to be controversy on the differentiation of benign versus malignant bone lesions

based on SUV, several reports indicate a SUV_{max} of 55-100 is concerning for a malignant process, whereas degenerative changes typically have an SUV_{max} of less than 50 (*22-24*). Also, the pattern of uptake may be characteristic or suggestive of a specific etiology while the CT component of PET-CT is very helpful in localizing and differentiating malignant from benign conditions.

The dose for ^{18}F-NaF for PET/CT is 40-100 μCi/kg in adults, with the maximum dose being 10 mCi. Given the smaller administered dose and shorter half-life of ^{18}F-NaF, the absorbed dose of ^{18}F-NaF is almost similar to ^{99m}Tc-MDP.(*17,18,21,25*) While images may be obtained as early as 30–45 minutes after injection of ^{18}F-NaF, it is preferable to wait for about 1-1.5 hours for better imaging quality. The recommended imaging protocol for ^{18}F-NaF PET is beyond the scope of this manuscript and readers are referred to the SNM protocol guideline (*17*).

Comparison:

^{18}F-NaF vs ^{99m}Tc-MDP

In comparison to the ^{99m}Tc-MDP whole-body scan, the ^{18}F-NaF has better image quality because of better spatial resolution (4-5mm), higher target-to-background ratio, and higher overall sensitivity in lesion detection (*17,26*). The increased spatial resolution of ^{18}F-NaF PET is especially helpful for detection of small metastases in the spine (Fig 2).

A major diagnostic application of ^{18}F-NaF PET scan that has been explored, is its use in the detection of osseous lesions of metastatic cancers such as breast, prostate, and lung cancers. With growing research on the relevance of ^{18}F-NaF PET in the field of

oncology, it has been proven to be an important tool in assessing the extent of metastatic burden when compared to traditional modalities such as planar ^{99m}Tc-MDP bone scintigraphy and ^{99m}Tc-MDP bone scintigraphy with SPECT for a variety of malignancies (*9-11,27-40*).

There is evidence that ^{18}F-NaF PET can be positive earlier than ^{99m}Tc-MDP whole-body bone scan in small lytic or blastic metastases (*33*). A meta-analysis of various studies also compared these modalities to report ^{18}F-NaF PET/CT as a superior diagnostic tool with a patient based pooled sensitivity of 96% and a pooled specificity of 98%, as well as a lesion based pooled sensitivity of 97% and pooled specificity of 98% (*5*).

A study on the evaluation of thyroid carcinoma patients for bony metastasis found ^{18}F-NaF PET/CT to be more sensitive in comparison to a planar bone scan (*12*). However, a different study showed only a limited osteosclerotic bone reaction from thyroid cancer metastases on ^{18}F-NaF PET (*41*).

Comparison between a standard ^{99m}Tc-based bone scan with and without SPECT to ^{18}F-NaF PET to evaluate for vertebral osseous metastasis in lung cancer patients showed a significant difference (*40*). Twelve patients had vertebral metastasis and the study showed that ^{18}F-NaF resulted in no false negatives, while the bone scan produced 6 false negatives and SPECT produced one. Further, the results of ^{18}F-NaF PET influenced the management in 11% of the study population.

Similarly, in the evaluation of hepatocellular carcinoma by a study from Taiwan, ^{18}F-NaF PET was found to have greater diagnostic and prognostic usefulness relative to ^{99m}Tc-MDP planar bone scintigraphy. It reported a greater accuracy on a lesion based basis

(95.7% vs 75.4%, p=0.0001) (*37*). Additionally, the study found a significant correlation between the presence of ^{18}F-NaF PET-CT-positive bone lesions and the overall survival, while such a correlation was not observed with bone scans.

Chakraborty et al found^{18}F-NaF PET/CT to have higher sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in detecting bone metastases in urinary bladder carcinoma than conventional ^{99m}Tc-MDP planar bone scan (*36*). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ^{99m}Tc-MDP planar bone scan were 82.35%, 64.51%, 56%, 86.95%, and 70.83%; of ^{99m}Tc-MDP SPECT/CT were 88.23%, 74.19%, 65.21%, 92%, and 79.16%; and of ^{18}F-NaF PET/ CT were 100%, 87.09%, 80.95%, 100%, and 91.66%, respectively. Furthermore, ^{18}F-fluoride PET/CT changed the management in 17 of 48 patients (35%).

A study on prostate cancer showed that the sensitivity, specificity, positive predictive value, and negative predictive value of planar bone scan were 70%, 57%, 64%, and 55%, respectively; 92%, 82%, 86%, and 90% for multi-FOV SPECT; 100%, 62%, 74%, and 100%, for ^{18}F-Fluoride PET, and 100% for all parameters for ^{18}F-Fluoride PET/CT (*35*). ^{18}F-Fluoride PET/CT was found to be statistically more sensitive and more specific than planar or SPECT bone scan ($P < 0.05$) and more specific than ^{18}F-Fluoride PET alone ($P < 0.001$). SPECT was statistically more sensitive and specific than planar bone scan ($P < 0.05$) but was less sensitive than ^{18}F-Fluoride PET ($P < 0.05$). Also, ^{18}F-NaF scan detected 81 more lesions, including 34 metastases which were overlooked on planar bone scan.

Another study compared ^{99m}Tc-MDP whole-body bone scan with ^{18}F-NaF PET/ CT and ^{18}F-fluoro-methylcholine (^{18}F-FCH) PET/CT (*42*). Poulsen et al showed sensitivity,

specificity, positive and negative predictive values and accuracy to be as follows: whole-body scan: 51, 82, 86, 43 and 61%; ^{18}F-NaF-PET/CT: 93, 54, 82, 78 and 81%; and ^{18}F-FCH-PET/CT: 85, 91, 95, 75 and 87%, respectively. The authors recommended combined ^{18}F-NaF PET/CT and ^{18}F-fluorocholine PET/CT as accurate in this clinical setting, and superior to standard bone scintigraphy. Similar results in other studies have resulted in a call for change in practice guidelines to 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 bony metastases of prostate cancer. (*43-45*).

Growing research on metastases detection has shown significantly better sensitivity, specificity, and diagnostic accuracy of ^{18}F-NaF PET or PET/CT over ^{99m}Tc-MDP bone scintigraphy (*30,33,35,46*). A meta-analysis based on 11 studies encompassing 425 patients to determine the diagnostic accuracy of ^{18}F-NaF PET for detection of metastatic disease showed a sensitivity and specificity of 96.2% and 98.5% respectively (*5*). 225 of the 425 patients analyzed on a lesion basis showed a sensitivity of 96.9% and specificity of 98.0%. Data analysis by ROC curve showed the diagnostic accuracy of PET or PET/CT to be significantly higher compared to planar and SPECT bone scintigraphy.

While the traditionally used ^{99m}Tc-MDP bone scintigraphy has a reasonable sensitivity, literature shows that the reduced specificity can be improved by using SPECT. The accuracy of metastasis detection is further increased with the usage of ^{18}F-NaF PET/CT (*47*). Data indicates improved accuracy of bone lesion detection with a high negative predictive value of ^{18}F-NaF PET/CT compared with ^{99m}Tc-MDP SPECT and planar

^{99m}Tc-MDP, which has significant clinical implications in ruling out the osseous metastatic disease with a high degree of confidence (*9,29,30,40*).

However, a recent study demonstrated that ^{18}F-NaF PET/CT was unable to detect bone metastases within 24 months of radical prostatectomy in patients with biochemical failure. This concluded that staging with ^{18}F-NaF PET/CT does not have a superior prognostic value in patients with normal bone scans in terms of improved patient-related outcomes after radical prostatectomy (*48*).

PET offers a higher resolution and as a result, ^{18}F-NaF PET scan is considered more sensitive than the traditionally used ^{99m}Tc-MDP bone scan to detect the minimal osteoblastic activity associated with lytic bone metastases (*27,38,49*). However, since the accumulation of fluoride is not tumor-specific, it has a reduced specificity for detection of metastatic lesions, sometimes making it difficult to differentiate from benign bone lesions such as degenerative disease, based on the intensity of tracer uptake or SUV. Furthermore, the comparison shows a significantly reduced specificity of ^{18}F-NaF PET (62%) compared with ^{99m}Tc-MDP SPECT due to the increased sensitivity of PET at detecting bone lesions, which are more likely to be benign, and therefore, result in false-positive results (*47*). Cancer patients who require a bone scan for metastasis evaluation are often elderly and have coexisting age-related benign bone lesions such as degenerative and/or arthritic bone disease. These benign bone processes share the same pattern of fluoride uptake as metastases, resulting in a higher false-positives seen if evaluated by PET alone. To overcome this, low-dose CT is incorporated with hybrid technology, resulting in an improved specificity of 100% with fluoride PET/CT (*27*) Fig 3.

In one prospective study with prostate cancer patients, ^{18}F-NaF PET/CT was able to detect an increased number of bone metastases than ^{99m}Tc-MDP bone scintigraphy, with the added advantage of detection at an earlier phase. The number of lesions identified on the first ^{18}F-NaF PET/CT and interval SUV change had a direct correlation with overall survival. As per this study, an increase in SUV by 50% or more correlated with increased mortality (*50*). Another meta-analysis on 14 studies and 507 patients, showed^{18}F-NaF PET/CT to be superior to ^{99m}Tc-MDP bone scintigraphy and SPECT in detecting osseous metastases during staging and restaging of high-risk prostate cancer (*51*).

^{18}F-NaF PETCT is also more accurate than ^{99m}Tc-MDP bone scintigraphy for monitoring of bone metastasis from prostate cancer after treatment with ^{223} Ra-chloride (*52*). ^{223}Ra-Chloride is an FDA approved alpha emitter used in patients with castration-resistant prostate cancer with bony metastases (*53*). Also, in a study on a small patient population, ^{18}F-NaF PET was superior to ^{99m}Tc-MDP whole-body bone scan for evaluation of treatment response in bone metastasis. (*54*).

In conclusion, the literature indicates that ^{18}F-NaF uptake occurs in osteolytic metastasis as well as osteoblastic metastasis (*49,55*).

^{18}F-NaF vs CT and MRI

Piccardo and colleagues studied 39 women with breast cancer with bone metastasis and reported that ^{18}F-NaF PET/CT significantly improved the sensitivity of detection by CT alone (91% and 77% respectively) (*27*). However, the specificity of ^{18}F-NaF PET/CT

was 91% while CT had a specificity of 93%. It has been shown that ^{18}F-NaF PET/CT is superior to the contrast-enhanced and unenhanced chest, abdomen, and pelvis CT as well as ^{99m}Tc-MDP bone scan for the detection of occult bone metastasis in patients suffering from prostate cancer (*56*).

In addition, ^{18}F-NaF PET is a useful tool to detect iatrogenic disorders such as bisphosphonate-induced osteonecrosis of the jaw. Current modalities for assessment, such as contrast-enhanced MRI and cone-beam CT have been proven to have a lower accuracy for this condition (*57*).

A study conducted by Poulsen and colleagues used MRI as a 'gold standard' reference for the detection of bone metastasis in prostate cancer patients. They reported that 114 lesions not detected by MRI were picked up by one or more of the modalities including whole-body bone scintigraphy, ^{18}F-NaF PET/CT and ^{18}F-FCH PET/CT. Of these, the most sensitive was ^{18}F-NaF-PET/CT with 68 lesions, while 10 lesions were detected by both ^{18}F-NaF-PET/CT and ^{18}F-FCH-PET/CT (*42*).

A meta-analysis of 14 studies and 507 patients reported a comparable diagnostic performance of ^{18}F-NaF-PET/CT to diffusion-weighted imaging (DWI-MRI) (*51*). However, more recent studies have shown significantly better sensitivity, specificity, overall accuracy than DWI-MRI (*58,59*).

^{18}F-NaF vs ^{18}F-FDG

A published study comparing the detection of bone metastasis by ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT in head and neck cancer patients at high risk for metastasis found to

have comparable lesion–based sensitivities of 69.4% and 57.1% respectively with a p-value of 0.126 (*60*). They were also found to similar AUC (area under the curve) values of 0.7561 vs. 0.7959 (p value 0.149). When combined, ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT demonstrated a significantly improved lesion-based sensitivity than a single modality ($p<0.001$). However, a similar advantage was not observed in patient-based analysis and therefore, their combined use is not advised (*61*).

Kruger and colleagues studied 126 non-small cell lung cancer patients and reported a comparison of ^{18}F-NaF PET with ^{18}F-FDG PET/CT for detection of bone metastasis (*10*). They found concordant metastases diagnosed in 13 of 18 patients. Interestingly, ^{18}F-FDG PET/CT detected a higher absolute number of bone metastases than ^{18}F-NaF PET (73 vs 55, $p<0.05$). However, ^{18}F-NaF PET diagnosed more patients with bone metastases, in that 4 patients showed positive findings on ^{18}F-NaF PET but negative findings on ^{18}F-FDG PET/CT.

Iagaru et al evaluated ^{18}F-NaF and ^{18}F-FDG for detection of skeletal metastasis in 52 patients (*11*). They reported superior detection of skeletal metastatic disease by ^{18}F-NaF PET/CT (24 vs 16) as well as better image quality in comparison to ^{18}F-FDG PET/CT. However, the study also showed that extraskeletal metastasis detection by ^{18}F-FDG PET/CT could alter management. Therefore, a combined approach to disease evaluation was suggested. Iagaru and colleagues conducted another study to test a combination of ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT as an imaging modality for cancer patients (*61*). They reported that the combined approach missed none of the lesions detected by ^{18}F-FDG PET/CT and only one skull lesion detected by ^{18}F-NaF PET/CT alone.

A recent retrospective study comparing ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT in detection of skull-base invasion and bony metastases in nasopharyngeal cancer detected more osseous metastases and more accurately assessed skull-base invasion on ^{18}F-NaF PET/CT than ^{18}F-FDG PET/CT. The ^{18}F-NaF PET/CT showed sensitivity, specificity, accuracy, PPV, and NPV for detecting skull-base invasion to be 100%, 94.7%, 97.8%, 96.3%, and 100%, respectively, whereas for ^{18}F-FDG PET/CT these measures were 65.4%, 100%, 80%, 100%, and 67.9%, respectively. The sensitivity and specificity for detecting bone metastatic lesions were 98.3%, and 65.7%, respectively for ^{18}F-NaF PET/CT; and 42.9%, and 97.1%, respectively, for ^{18}F-FDG PET/CT (*62*). Table 2.

Studies comparing ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT in multiple myeloma patients found only a 39% correlation of disease assessment with 343 and 135 lesions picked up by ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT, respectively (*63*). Interestingly, three patients identified with multiple focal lesions by ^{18}F-FDG PET/CT showed no identifiable lesions on ^{18}F-NaF PET/CT. In addition, evaluation of the pelvic area with ^{18}F-NaF and ^{18}F-FDG PET/CT scans demonstrated 24 and 77 lesions, respectively.

In one prospective study on patients with prostate and breast cancers, (^{18}F-NaF/^{18}F-FDG PET/CT was superior to whole-body MRI and ^{99m}Tc-MDP scintigraphy for detection of bone metastasis. The performance of ^{18}F-NaF/^{18}F-FDG PET/CT was similar to a combination of whole-body MRI and bone scintigraphy (*64*) (Fig 4).

Conclusion

Detection of bony metastases in patients with malignancy is a matter of high clinical importance as it can significantly impact treatment and outcome. ^{18}F-NaF PET has shown excellent diagnostic performance in the detection of bone metastases. Through advancements in PET scanners in recent decades, ^{18}F-NaF PET is now feasible and its radiation dose is comparable to a conventional ^{99m}Tc-MDP bone scan. By having a better spatial resolution, better image quality, higher target to the background and higher sensitivity, ^{18}F-NaF PET is superior to a conventional ^{99m}Tc-MDP bone scan. It has also shown superiority to other imaging modalities, including CT, MRI and ^{18}F-FDG PET-CT. The challenge posed by the low specificity of this modality has been partially solved by using simultaneous anatomic imaging as a part of PET/CT or PET/MR. Further, the development of new scanners and reconstruction methods will make it possible to perform ^{18}F-NaF PET with a much lower dose. Currently, ^{18}F-NaF PET/CT scans are not being reimbursed by the CMS and additional prospective studies are needed to demonstrate the clinical impact of ^{18}F-NaF PET/CT in various malignancies.

References:

1. Mick CG, James T, Hill JD, Williams P, Perry M. Molecular imaging in oncology: (18)F-sodium fluoride PET imaging of osseous metastatic disease. *AJR Am J Roentgenol.* 2014;203:263-271.

2. Harley SJ, Hoffmann R, Bartholomeusz D, et al. 18-Fluoride labeled sodium fluoride positron emission tomography with computer tomography: the impact of pretreatment staging in intermediate- and high-risk prostate cancer. *Prostate Int.* 2018;6:50-54.

3. Panagiotidis E, Lam K, Mistry A, Seshadri N, Vinjamuri S. Skeletal Metastases and Benign Mimics on NaF PET/CT: A Pictorial Review. *AJR Am J Roentgenol.* 2018;211:W64-W74.

4. Shen CT, Qiu ZL, Han TT, Luo QY. Performance of 18F-fluoride PET or PET/CT for the detection of bone metastases: a meta-analysis. *Clin Nucl Med.* 2015;40:103-110.

5. Tateishi U, Morita S, Taguri M, et al. A meta-analysis of (18)F-Fluoride positron emission tomography for assessment of metastatic bone tumor. *Ann Nucl Med.* 2010;24:523-531.

6. Hillner BE, Siegel BA, Hanna L, Duan F, Quinn B, Shields AF. 18F-fluoride PET used for treatment monitoring of systemic cancer therapy: results from the National Oncologic PET Registry. *J Nucl Med.* 2015;56:222-228.

7. Hillner BE, Siegel BA, Hanna L, et al. Impact of (18)F-Fluoride PET on Intended Management of Patients with Cancers Other Than Prostate Cancer: Results from the National Oncologic PET Registry. *J Nucl Med.* 2014;55:1054-1061.

8. Hillner BE, Siegel BA, Hanna L, Duan F, Shields AF, Coleman RE. Impact of 18F-fluoride PET in patients with known prostate cancer: initial results from the National Oncologic PET Registry. *J Nucl Med.* 2014;55:574-581.

9. Bortot DC, Amorim BJ, Oki GC, et al. (1)(8)F-Fluoride PET/CT is highly effective for excluding bone metastases even in patients with equivocal bone scintigraphy. *Eur J Nucl Med Mol Imaging.* 2012;39:1730-1736.

10. Kruger S, Buck AK, Mottaghy FM, et al. Detection of bone metastases in patients with lung cancer: 99mTc-MDP planar bone scintigraphy, 18F-fluoride PET or 18F-FDG PET/CT. *Eur J Nucl Med Mol Imaging.* 2009;36:1807-1812.

11. Iagaru A, Mittra E, Dick DW, Gambhir SS. Prospective evaluation of (99m)Tc MDP scintigraphy, (18)F NaF PET/CT, and (18)F FDG PET/CT for detection of skeletal metastases. *Mol Imaging Biol.* 2012;14:252-259.

12. Ota N, Kato K, Iwano S, et al. Comparison of (1)(8)F-fluoride PET/CT, (1)(8)F-FDG PET/CT and bone scintigraphy (planar and SPECT) in detection of bone metastases of differentiated thyroid cancer: a pilot study. *Br J Radiol.* 2014;87:20130444.

13. Czernin J, Satyamurthy N, Schiepers C. Molecular mechanisms of bone 18F-NaF deposition. *J Nucl Med.* 2010;51:1826-1829.

14. https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=233. Assessed September 17, 2019.

15. Hillner BE, Hanna L, Makineni R, et al. Intended Versus Inferred Treatment After (18)F-Fluoride PET Performed for Evaluation of Osseous Metastatic Disease in the National Oncologic PET Registry. *J Nucl Med.* 2018;59:421-426.

16. Jadvar H, Colletti PM, Delgado-Bolton R, et al. Appropriate Use Criteria for (18)F-FDG PET/CT in Restaging and Treatment Response Assessment of Malignant Disease. *J Nucl Med.* 2017;58:2026-2037.

17. Segall G, Delbeke D, Stabin MG, et al. SNM practice guideline for sodium 18F-fluoride PET/CT bone scans 1.0. *J Nucl Med.* 2010;51:1813-1820.

18. Langsteger W, Rezaee A, Pirich C, Beheshti M. (18)F-NaF-PET/CT and (99m)Tc-MDP Bone Scintigraphy in the Detection of Bone Metastases in Prostate Cancer. *Semin Nucl Med.* 2016;46:491-501.

19. Beheshti M, Mottaghy FM, Paycha F, et al. (18)F-NaF PET/CT: EANM procedure guidelines for bone imaging. *Eur J Nucl Med Mol Imaging.* 2015;42:1767-1777.

20. Bastawrous S, Bhargava P, Behnia F, Djang DS, Haseley DR. Newer PET application with an old tracer: role of 18F-NaF skeletal PET/CT in oncologic practice. *Radiographics.* 2014;34:1295-1316.

21. Grant FD, Fahey FH, Packard AB, Davis RT, Alavi A, Treves ST. Skeletal PET with 18F-fluoride: applying new technology to an old tracer. *J Nucl Med.* 2008;49:68-78.

22. Vali R, Beheshti M, Waldenberger P, et al. Assessment of malignant and benign bone lesions by static F-18 Fluoride PET-CT: Additional value of SUV! *Journal of Nuclear Medicine.* 2008;49:150P-150P %@ 0161-5505.

23. Muzahir S, Jeraj R, Liu G, et al. Differentiation of metastatic vs degenerative joint disease using semi-quantitative analysis with (18)F-NaF PET/CT in castrate resistant prostate cancer patients. *Am J Nucl Med Mol Imaging.* 2015;5:162-168.

24. Oldan JD, Hawkins AS, Chin BB. (18)F Sodium Fluoride PET/CT in Patients with Prostate Cancer: Quantification of Normal Tissues, Benign Degenerative Lesions, and Malignant Lesions. *World J Nucl Med.* 2016;15:102-108.

25. Beheshti M, Mottaghy FM, Paycha F, et al. Correction to: 18F-NaF PET/CT: EANM procedure guidelines for bone imaging. *Eur J Nucl Med Mol Imaging.* 2018;45:322.

26. Park-Holohan SJ, Blake GM, Fogelman I. Quantitative studies of bone using (18)F-fluoride and (99m)Tc-methylene diphosphonate: evaluation of renal and whole-blood kinetics. *Nucl Med Commun.* 2001;22:1037-1044.

27. Even-Sapir E, Metser U, Flusser G, et al. Assessment of malignant skeletal disease: initial experience with 18F-fluoride PET/CT and comparison between 18F-fluoride PET and 18F-fluoride PET/CT. *J Nucl Med.* 2004;45:272-278.

28. Iagaru A, Mittra E, Mosci C, et al. Combined 18F-fluoride and 18F-FDG PET/CT scanning for evaluation of malignancy: results of an international multicenter trial. *J Nucl Med.* 2013;54:176-183.

29. Damle NA, Bal C, Bandopadhyaya GP, et al. The role of 18F-fluoride PET-CT in the detection of bone metastases in patients with breast, lung and prostate carcinoma: a comparison with FDG PET/CT and 99mTc-MDP bone scan. *Jpn J Radiol.* 2013;31:262-269.

30. Withofs N, Grayet B, Tancredi T, et al. (1)(8)F-fluoride PET/CT for assessing bone involvement in prostate and breast cancers. *Nucl Med Commun.* 2011;32:168-176.

31. Segall GM. PET/CT with sodium 18F-fluoride for management of patients with prostate cancer. *J Nucl Med.* 2014;55:531-533.

32. Cook GJ, Fogelman I. Detection of bone metastases in cancer patients by 18F-fluoride and 18F-fluorodeoxyglucose positron emission tomography. *Q J Nucl Med.* 2001;45:47-52.

33. Schirrmeister H, Guhlmann A, Elsner K, et al. Sensitivity in detecting osseous lesions depends on anatomic localization: planar bone scintigraphy versus 18F PET. *J Nucl Med.* 1999;40:1623-1629.

34. Hetzel M, Arslandemir C, Konig HH, et al. F-18 NaF PET for detection of bone metastases in lung cancer: accuracy, cost-effectiveness, and impact on patient management. *J Bone Miner Res.* 2003;18:2206-2214.

35. Even-Sapir E, Metser U, Mishani E, Lievshitz G, Lerman H, Leibovitch I. The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. *J Nucl Med.* 2006;47:287-297.

36. Chakraborty D, Bhattacharya A, Mete UK, Mittal BR. Comparison of 18F fluoride PET/CT and 99mTc-MDP bone scan in the detection of skeletal metastases in urinary bladder carcinoma. *Clin Nucl Med.* 2013;38:616-621.

37. Yen RF, Chen CY, Cheng MF, et al. The diagnostic and prognostic effectiveness of F-18 sodium fluoride PET-CT in detecting bone metastases for hepatocellular carcinoma patients. *Nucl Med Commun.* 2010;31:637-645.

38. Schirrmeister H, Guhlmann A, Kotzerke J, et al. Early detection and accurate description of extent of metastatic bone disease in breast cancer with fluoride ion and positron emission tomography. *J Clin Oncol.* 1999;17:2381-2389.

39. Iagaru A, Young P, Mittra E, Dick DW, Herfkens R, Gambhir SS. Pilot prospective evaluation of 99mTc-MDP scintigraphy, 18F NaF PET/CT, 18F FDG PET/CT and whole-body MRI for detection of skeletal metastases. *Clin Nucl Med.* 2013;38:e290-296.

40. Schirrmeister H, Glatting G, Hetzel J, et al. Prospective evaluation of the clinical value of planar bone scans, SPECT, and (18)F-labeled NaF PET in newly diagnosed lung cancer. *J Nucl Med.* 2001;42:1800-1804.

41. Schirrmeister H, Buck A, Guhlmann A, Reske SN. Anatomical distribution and sclerotic activity of bone metastases from thyroid cancer assessed with F-18 sodium fluoride positron emission tomography. *Thyroid.* 2001;11:677-683.

42. Poulsen MH, Petersen H, Hoilund-Carlsen PF, et al. Spine metastases in prostate cancer: comparison of technetium-99m-MDP whole-body bone scintigraphy, [(18) F]choline positron emission tomography(PET)/computed tomography (CT) and [(18) F]NaF PET/CT. *BJU Int.* 2014;114:818-823.

43. Wondergem M, van der Zant FM, van der Ploeg T, Knol RJ. A literature review of 18F-fluoride PET/CT and 18F-choline or 11C-choline PET/CT for detection of bone metastases in patients with prostate cancer. *Nucl Med Commun.* 2013;34:935-945.

44. Kjolhede H, Ahlgren G, Almquist H, et al. Combined 18F-fluorocholine and 18F-fluoride positron emission tomography/computed tomography imaging for staging of high-risk prostate cancer. *BJU Int.* 2012;110:1501-1506.

45. Langsteger W, Balogova S, Huchet V, et al. Fluorocholine (18F) and sodium fluoride (18F) PET/CT in the detection of prostate cancer: prospective comparison of diagnostic performance determined by masked reading. *Q J Nucl Med Mol Imaging.* 2011;55:448-457.

46. Kawaguchi M, Tateishi U, Shizukuishi K, Suzuki A, Inoue T. 18F-fluoride uptake in bone metastasis: morphologic and metabolic analysis on integrated PET/CT. *Ann Nucl Med.* 2010;24:241-247.

47. Kulshrestha RK, Vinjamuri S, England A, Nightingale J, Hogg P. The Role of 18F-Sodium Fluoride PET/CT Bone Scans in the Diagnosis of Metastatic Bone Disease from Breast and Prostate Cancer. *J Nucl Med Technol.* 2016;44:217-222.

48. Zacho H, Jochumsen MR, Langkilde NC, et al. No added value of (18)F-sodium fluoride PET/CT for the detection of bone metastases in patients with newly diagnosed prostate cancer with normal bone scintigraphy. *J Nucl Med.* 2019.

49. Petren-Mallmin M, Andreasson I, Ljunggren O, et al. Skeletal metastases from breast cancer: uptake of 18F-fluoride measured with positron emission tomography in correlation with CT. *Skeletal Radiol.* 1998;27:72-76.

50. Apolo AB, Lindenberg L, Shih JH, et al. Prospective Study Evaluating Na18F PET/CT in Predicting Clinical Outcomes and Survival in Advanced Prostate Cancer. *J Nucl Med.* 2016;57:886-892.

51. Sheikhbahaei S, Jones KM, Werner RA, et al. (18)F-NaF-PET/CT for the detection of bone metastasis in prostate cancer: a meta-analysis of diagnostic accuracy studies. *Ann Nucl Med.* 2019;33:351-361.

52. Cook G, Jr., Parker C, Chua S, Johnson B, Aksnes AK, Lewington VJ. 18F-fluoride PET: changes in uptake as a method to assess response in bone metastases from castrate-resistant prostate cancer patients treated with 223Ra-chloride (Alpharadin). *EJNMMI Res.* 2011;1:4.

53. Gupta N, Devgan A, Bansal I, et al. Usefulness of radium-223 in patients with bone metastases. *Proc (Bayl Univ Med Cent).* 2017;30:424-426.

54. Zukotynski KA, Kim CK, Gerbaudo VH, et al. (18)F-FDG-PET/CT and (18)F-NaF-PET/CT in men with castrate-resistant prostate cancer. *Am J Nucl Med Mol Imaging.* 2015;5:72-82.

55. Araz M, Aras G, Kucuk ON. The role of 18F-NaF PET/CT in metastatic bone disease. *J Bone Oncol.* 2015;4:92-97.

56. Jadvar H, Desai B, Ji L, et al. Prospective evaluation of 18F-NaF and 18F-FDG PET/CT in detection of occult metastatic disease in biochemical recurrence of prostate cancer. *Clin Nucl Med.* 2012;37:637-643.

57. Kurata S, Tateishi U, Shizukuishi K, et al. Assessment of atherosclerosis in oncologic patients using (1)(8)F-fluoride PET/CT. *Ann Nucl Med.* 2013;27:481-486.

58. Zacho HD, Nielsen JB, Afshar-Oromieh A, et al. Prospective comparison of (68)Ga-PSMA PET/CT, (18)F-sodium fluoride PET/CT and diffusion weighted-MRI at for the detection of bone metastases in biochemically recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* 2018;45:1884-1897.

59. Dyrberg E, Hendel HW, Huynh THV, et al. (68)Ga-PSMA-PET/CT in comparison with (18)F-fluoride-PET/CT and whole-body MRI for the detection of bone metastases in patients with prostate cancer: a prospective diagnostic accuracy study. *Eur Radiol.* 2019;29:1221-1230.

60. Chan SC, Wang HM, Ng SH, et al. Utility of 18F-fluoride PET/CT and 18F-FDG PET/CT in the detection of bony metastases in heightened-risk head and neck cancer patients. *J Nucl Med.* 2012;53:1730-1735.

61. Iagaru A, Mittra E, Yaghoubi SS, et al. Novel strategy for a cocktail 18F-fluoride and 18F-FDG PET/CT scan for evaluation of malignancy: results of the pilot-phase study. *J Nucl Med.* 2009;50:501-505.

62. Zhang Y, Chen Y, Huang Z, Zhang L, Wan Q, Lei L. Comparison of (18)F-NaF PET/CT and (18)F-FDG PET/CT for Detection of Skull-Base Invasion and Osseous Metastases in Nasopharyngeal Carcinoma. *Contrast Media Mol Imaging.* 2018;2018:8271313.

63. Sachpekidis C, Goldschmidt H, Hose D, et al. PET/CT studies of multiple myeloma using (18) F-FDG and (18) F-NaF: comparison of distribution patterns and tracers' pharmacokinetics. *Eur J Nucl Med Mol Imaging.* 2014;41:1343-1353.

64. Minamimoto R, Loening A, Jamali M, et al. Prospective Comparison of 99mTc-MDP Scintigraphy, Combined 18F-NaF and 18F-FDG PET/CT, and Whole-Body MRI in Patients with Breast and Prostate Cancer. *J Nucl Med.* 2015;56:1862-1868.

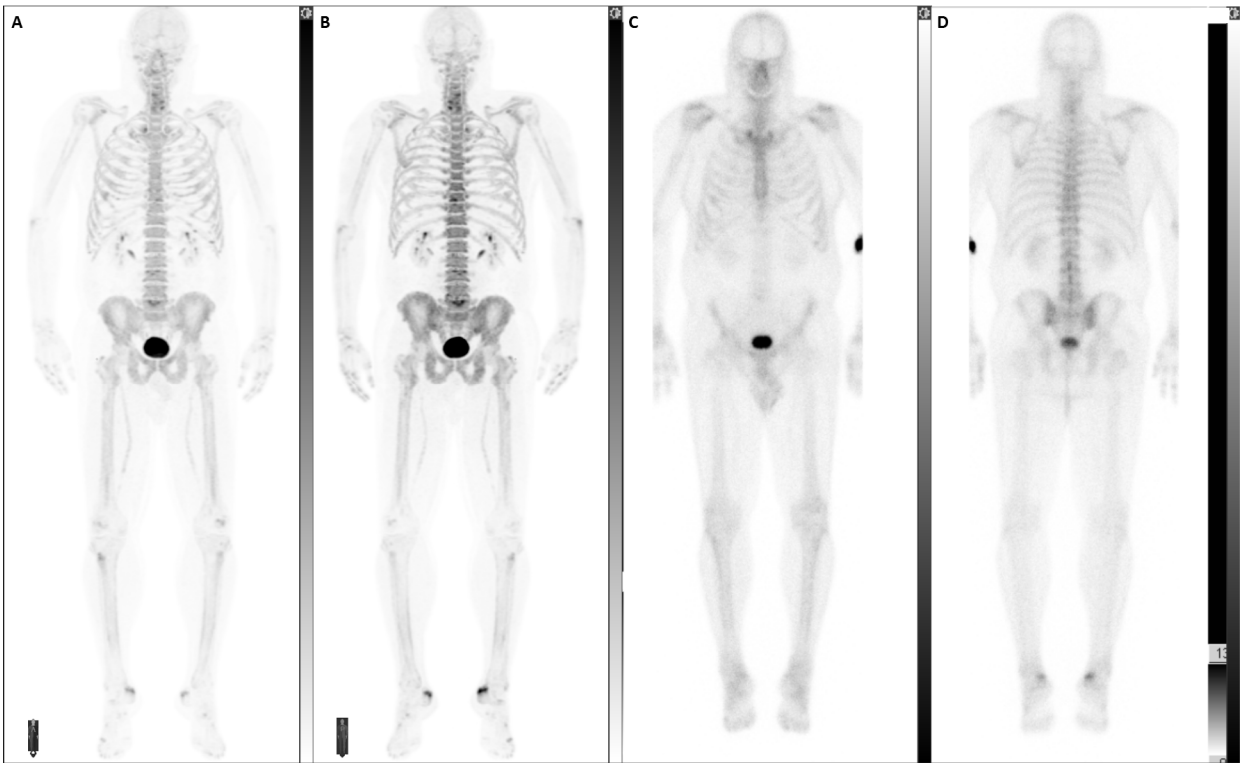

FIGURE 1. A 66-y-old man with history of prostate adenocarcinoma status post androgen deprivation therapy and definitive radiotherapy presents for evaluation of bony metastasis. (A, B) Anterior and posterior maximum intensity projection (MIP) views of the ^{18}F-NaF PET scan show normal physiological bio-distribution. Mild scattered degenerative changes seen in the spine. (C, D) Anterior and posterior views of the whole body ^{99m}Tc-MDP bone scan of same patient performed three weeks earlier show normal physiological bio-distribution. Both scans show no metastatic lesions.

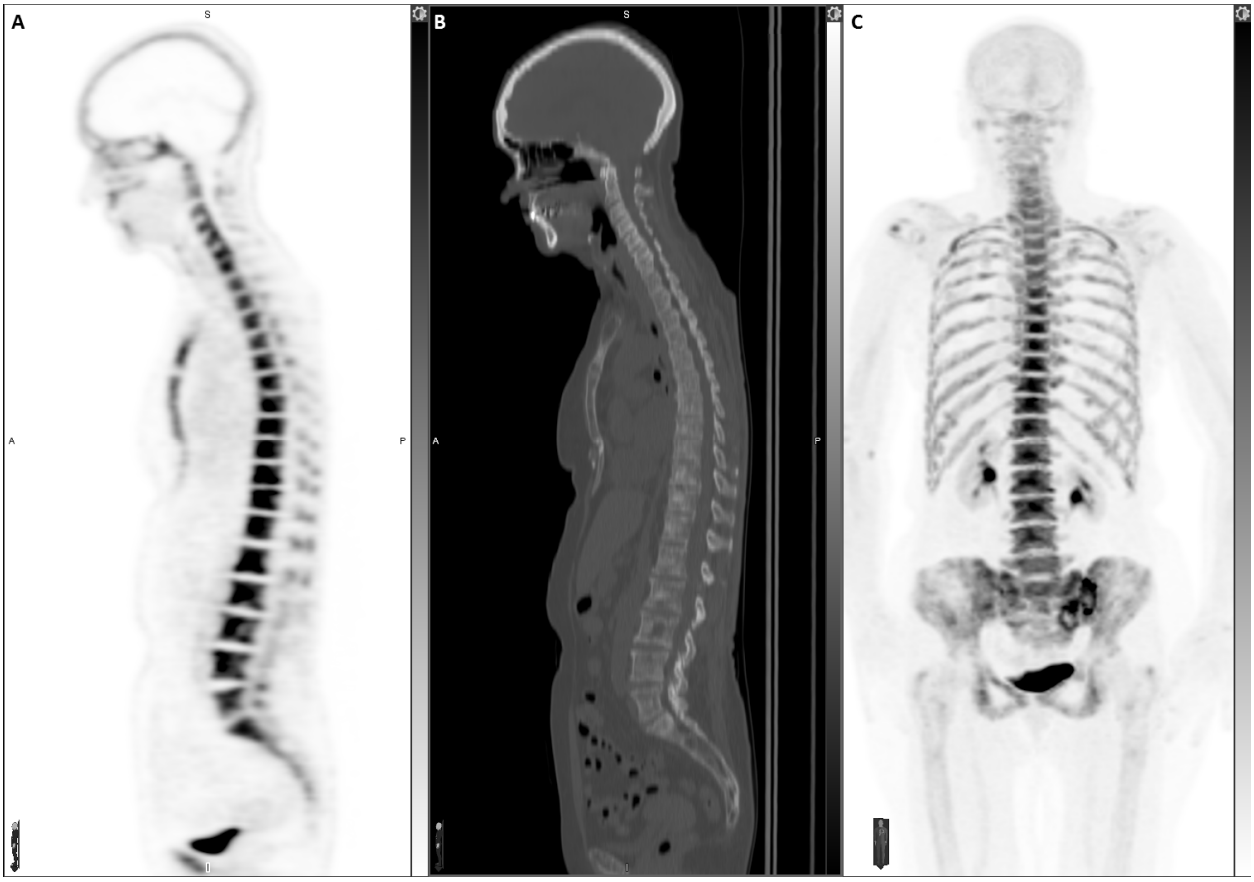

FIGURE 2. A 81-y-old women with history of metastatic breast cancer. Sagittal views of the (A) ^{18}F-NaF PET and (B) CT scan and (C) Anterior maximum intensity projection (MIP) view show diffuse sclerotic metastasis to the entire spine, sternum with abnormal increased tracer uptake. MIP image also demonstrate abnormal uptake in the ribs and pelvis.

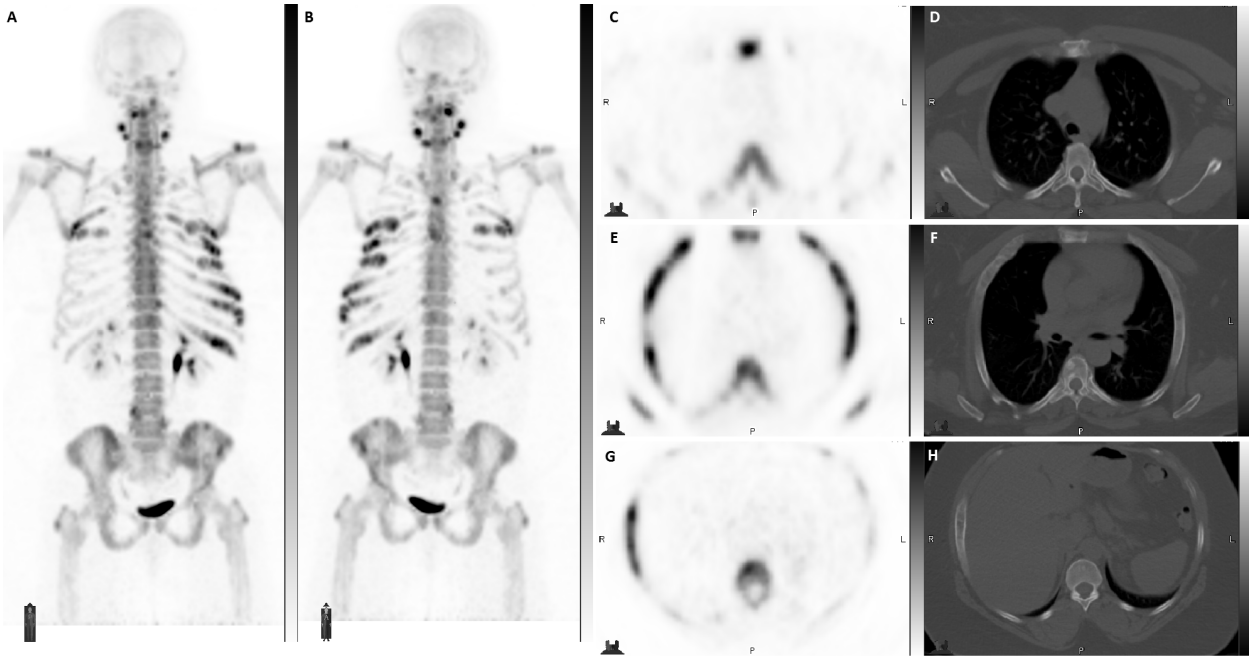

FIGURE 3. A 48-y-old women with history of plasma cell dyscrasia. (A, B) Anterior and posterior maximum intensity projection (MIP) views of the ^{18}F-NaF PET scan show multifocal area of abnormal increased tracer uptake in the spine, bilateral ribs and mandible. (C-H) Selected axial PET and CT bone window images shows expansible lesion involving bilateral ribs with ground glass density and associated abnormal tracer uptake. These lesion were stable on multiple follow-up scans and were attributable to the polyostotic fibrous dysplasia.

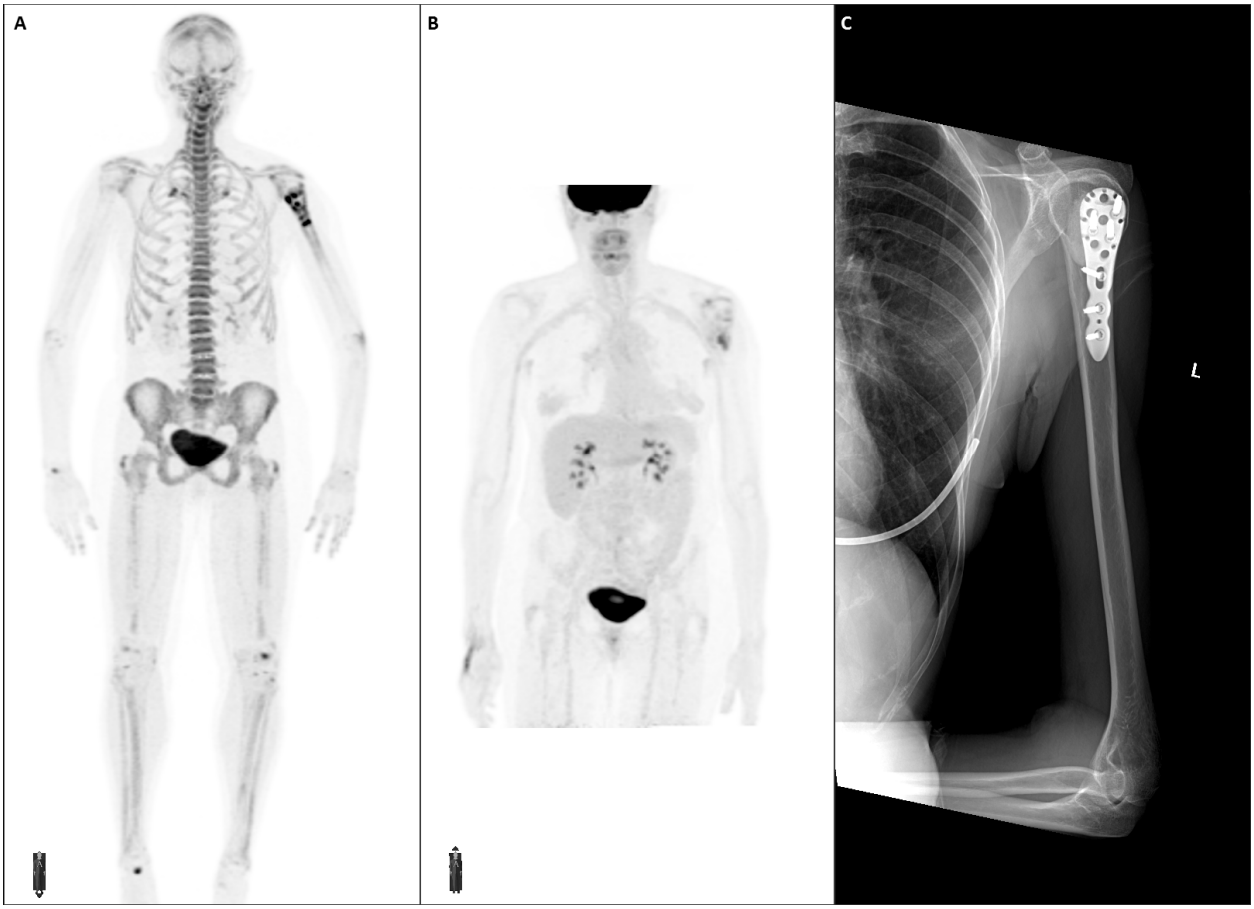

FIGURE 4. A 58-y-old women with history of metastatic colorectal cancer. Lytic metastasis to the left proximal humerus status post radiation therapy and fixation hardware. Anterior maximum intensity projection (MIP) view of the ^{18}F-NaF (A) and ^{18}F-FDG (B) PET scans shows heterogeneous increased tracer uptake in the left proximal humerus secondary to bone remodeling. No other area of abnormal tracer activity seen elsewhere. (C) X-ray of the left humerus show cement and fixation hardware.

Table 1: Comparison Table between ^{18}F-NaF and ^{99m}Tc-MDP (*1,17*)

Characteristics	**^{18}F-NaF**	**^{99m}Tc-MDP**
Production	Cyclotron	Generator
Half-life	109.7 minutes	6 hours
Photon energy	511 keV	140 keV
Spatial Resolution	Higher (4-5 mm)	Lower
Critical organ	Urinary Bladder	Bones
Typical Dose	5-10 mCi	20-30 mCi
Injection to imaging time	30-60 minutes	3-4 hours
Effective dose	8.9 mSv (10 mCi)	5.3 mSv (25 mCi)

Table 2: Comparison various studies comparing ^{18}F-NaF with other radiotracers

Study		Sn	Sp	PPV	NPV	Ac
Meta-analysis of ^{18}F-NaF by Tateishi U et al(*5*) in both benign and malignant lesions	Patient based pooled	96%	98%			
	Lesion based pooled	97%	98%			
Bone metastases detection in hepatocellular carcinoma(*37*)	^{99m}Tc-MDP	73.3%	79.2%	86.8%	61.3%	75.4%
	^{18}F-NaF PET/CT	93.3%	100%	100%	88.9%	97.5%
Bone metastases detection in urinary blabber cancer(*36*)	^{99m}Tc-MDP	82.35%	64.51%	56%	86.95%	70.83%
	^{99m}Tc-MDP SPECT/CT	88.23%	74.19%	65.21%	92%	79.16%
	^{18}F-NaF PET/CT	100%	87.09%	80.95%	100%	91.66%
High-risk prostate cancer(*35*)	^{99m}Tc-MDP	70%	57%	64%	55%	
	^{99m}Tc-MDP SPECT/CT	92%	82%	86%	90%	
	^{18}F-NaF PET	100%	62%	74%	100%	
	^{18}F-NaF PET/CT	100%	100%	100%	100%	
Spine metastases in prostate cancer using(*42*)	^{99m}Tc-MDP	51%	82%	86%	43%	61%
	^{18}F-NaF PET/CT	93%	54%	82%	78%	81%
	^{18}F-FCH PET/CT	85%	91%	95%	75%	87%
Bone metastases detection in head and neck cancer(*60*)	^{18}F-NaF PET/CT	69.4%				
	^{18}F-FDG PET/CT	57.1%				
Detecting skull base invasion in	^{18}F-NaF PET/CT	100%	94.7%	96.3%	100%	97.8%

nasopharyngeal cancer(*62*)	^{18}F-FDG PET/CT	65.4%	100%	100%	67.9%	80%
Detecting bone metastases in nasopharyngeal cancer(*62*)	^{18}F-NaF PET/CT	98.3%	65.7%			
	^{18}F-FDG PET/CT	42.9%	97.1%			

Sensitivity (Sn), Specificity (Sp), Positive predictive values (PPV), Negative predictive values (NPV), Accuracy (Ac)