Newer PET Application with an Old Tracer: Role of $^{18}$F-NaF Skeletal PET/CT in Oncologic Practice

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Abnormalities: FDG = $^{18}$F-fluorodeoxyglucose, MDP = methylene diphosphonate, MIP = maximum intensity projection

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Introduction

Metastases to bone are a common source of malignancy in the skeleton, and they occur much more frequently than primary bone tumors. Of all primary neoplasms, breast and prostate tumors are most likely to metastasize to bone, followed by thyroid, renal, and lung tumors (1). Bone metastases can be osteolytic, osteoblastic, or mixed. The incidence of bone involvement is typically low at the initial cancer diagnosis; however, the incidence is higher in patients with late-stage and recurrent disease. For instance, the frequency of bone metastases in patients with breast cancer is 1%–2% at initial diagnosis, compared with one-third of all patients with recurrent disease who...
have bone metastases (2). Complications of bone metastases include pain, pathologic fractures, hypercalcemia, cord compression, and bone marrow suppression (1). Appropriate management and treatment of bone metastases affect patient morbidity and health care costs. Therefore, accurate imaging tools are needed for proper staging, assessment of treatment response, and long-term oncologic management.

For many decades, the imaging of osseous metastases has largely been accomplished by using scintigraphy with technetium 99m (99mTc) methylene diphosphonate (MDP). However, even before the initial use of 99mTc-MDP, a bone-specific positron-emitting agent had already been in use. This agent, sodium fluoride labeled with fluorine 18 (sodium fluoride F 18 \[^{18}\text{F}-\text{NaF}\]), was introduced into clinical practice in 1962 as a radiotracer for skeletal imaging (3). Early experience proved that \(^{18}\text{F}-\text{NaF}\) was an excellent bone-seeking agent, given the rapid and high uptake of \(^{18}\text{F}-\text{NaF}\) in bone, and this agent was eventually approved by the U.S. Food and Drug Administration in 1972 (4). However, the imaging performance of \(^{18}\text{F}-\text{NaF}\) with conventional Anger-type gamma cameras was limited by its high-energy 511-keV photons, thus necessitating imaging with rectilinear scanners. Given the optimal performance of gamma cameras with the 140-keV photons of 99mTc-MDP, imaging with \(^{18}\text{F}-\text{NaF}\) was eventually replaced by imaging with 99mTc-MDP in the 1970s (4,5).

The current widespread availability of hybrid positron emission tomographic (PET) and computed tomographic (CT) dual-modality systems (PET/CT) has sparked a renewed interest in the use of \(^{18}\text{F}-\text{NaF}\) for skeletal imaging. PET/CT imaging allows high-resolution functional imaging of the skeleton with greater sensitivity than that of planar scintigraphy. \(^{18}\text{F}-\text{NaF}\) PET examinations are interpreted with fused CT images to allow morphologic characterization and improved differentiation between benign and malignant lesions. In this article, we present the role of \(^{18}\text{F}-\text{NaF}\) PET/CT and highlight the clinical utility and limitations of \(^{18}\text{F}-\text{NaF}\) PET/CT in the evaluation of metastatic skeletal disease. A brief review of the pertinent literature is included, as well as illustrative oncologic and nononcologic case examples.

The purpose of this article is to review the current role of \(^{18}\text{F}-\text{NaF}\) PET/CT, with an emphasis on the clinical utility, limitations, and imaging appearances of oncologic and nononcologic skeletal processes. First, the radiopharmaceutical and its pharmacokinetics and biologic properties are described, followed by a comparison with 99mTc-MDP. Then \(^{18}\text{F}-\text{NaF}\) PET/CT is covered:

**Pharmacokinetics and Biologic Properties**

Before the advent of PET, \(^{18}\text{F}-\text{NaF}\) had been recognized as a bone-seeking agent. Blau et al (3) first introduced bone imaging with \(^{18}\text{F}-\text{NaF}\) in 1962. These investigators described animal data demonstrating that the concentrations of \(^{18}\text{F}\) ions are 10 times higher in areas of regenerating bone, compared with areas of normal bone (3). After intravenous administration of \(^{18}\text{F}-\text{NaF}\), the \(^{18}\text{F}\) ions briskly equilibrate with plasma in a biexponential fashion and are then rapidly cleared as a result of bone deposition and excretion by the kidneys. Most of the \(^{18}\text{F}-\text{NaF}\) carried by the blood flow is harbored within bone after a single pass of the blood (8,9).

The mechanism of skeletal uptake of \(^{18}\text{F}-\text{NaF}\) is based on ion exchange, which is similar to that of 99mTc-MDP. Bone hardness is due to a crystalline matrix of calcium and phosphate known as hydroxyapatite, which is composed of many different positive and negative ions (9,10). Bone tissue is continuously renewing itself through remodeling, and this remodeling occurs at the bone surface (11). \(^{18}\text{F}\) ions exchange with hydroxyl ions (OH\(^-\)) on the surface of the hydroxyapatite to form fluoroapatite. This exchange occurs at a rapid rate; however, the actual incorporation of \(^{18}\text{F}\) ions into the crystalline matrix of bone may take days or weeks (4,8,9).

Uptake of \(^{18}\text{F}-\text{NaF}\) is a function of osseous blood flow and reflects bone remodeling, and the uptake indicates osteoblastic activity by identifying reactive changes in the underlying affected bone (8). Abnormal areas of increased \(^{18}\text{F}-\text{NaF}\)
uptake depicted on PET/CT images are due to processes that increase exposure of the surface of bone and provide a higher availability of binding sites, such as osteolytic and osteoblastic processes. The rate-limiting step in the passing of $^{18}$F ions from blood to bone is thought to be blood flow. Differences in regional blood flow will demonstrate a nonuniform pattern of uptake (4,8). Mechanisms leading to increased uptake are not limited to neoplastic processes and include any process of bone remodeling. Normal physiologic uptake in adults is generally uniform (Fig 1) (12).

The unique characteristics of $^{18}$F-NaF make it a desirable radiotracer for bone imaging. $^{18}$F-NaF has minimal binding to serum proteins, which allows a rapid single-pass extraction and fast clearance from the soft tissues. Compared with $^{99m}$Tc-MDP, the bone uptake of $^{18}$F-NaF is twice as great (11,13). This greater bone uptake and the faster soft-tissue clearance lead to shorter $^{18}$F-NaF imaging times, as well as increased bone-to-background ratios for $^{18}$F ions, a finding that improves the diagnostic accuracy. Additionally, about 30% of $^{18}$F ions are taken up by circulating red blood cells, and these ions remain available for incorporation into bone. The kinetics of $^{18}$F-NaF is not affected by plasma protein binding, in contrast to $^{99m}$Tc-MDP, which shows considerable protein binding. About 30% of the $^{99m}$Tc-MDP is protein bound immediately after injection, and this value rises to 70% at 24 hours after injection (11,14,15). This protein-bound $^{99m}$Tc-MDP is cleared slowly, necessitating a 3–4-hour wait before imaging. On the other hand, $^{18}$F-NaF PET/CT imaging can be performed less than 1 hour after injection, given the low protein binding, which allows shorter times for the imaging examination. Areas of abnormal $^{18}$F-NaF uptake result from processes that increase the exposed bone crystal surface and/or the blood flow (7,8,11).

The total examination time for $^{18}$F-NaF PET/CT is overall shorter, compared with that for $^{99m}$Tc-MDP bone imaging; the shorter examination time decreases the potential for patient motion artifacts.
and improves work-flow productivity. Additionally, the faster turnaround times of dictated $^{18}$F-NaF PET/CT reports allow more rapid diagnosis and initiation of treatment and provide greater convenience to referring physicians and patients (7).

**Comparison of $^{18}$F-NaF and $^{99m}$Tc-MDP as Bone Agents**

Two agents are available for bone imaging: $^{99m}$Tc-MDP and $^{18}$F-NaF. $^{99m}$Tc-MDP is time tested, is easily accessible from generators, and is used with gamma cameras, which are more widely available, compared with PET/CT systems (16). Conventional planar bone scintigraphy with $^{99m}$Tc-MDP can be used to detect bone metastases several months earlier than radiography does, and bone scintigraphy is one of the most frequently performed nuclear medicine examinations in the United States and Europe (17). Conventional bone scintigraphic images are sensitive; however, they suffer from low specificity and require anatomic correlation to increase the specificity. The addition of combined single photon emission computed tomography (SPECT) and CT dual-modality imaging (SPECT/CT) to conventional bone scintigraphy markedly improves diagnostic accuracy and allows anatomic localization and morphologic characterization of lesions (18). Correlation with other imaging modalities, such as radiography and/or magnetic resonance (MR) imaging, is often required to improve the specific-
ity (14). CT and MR imaging will demonstrate more metastases than planar $^{99m}$Tc-MDP bone scintigraphy does; however, whole-body CT and MR imaging are impractical, and radionuclide bone scintigraphy remains the most appropriate modality for whole-body surveys (2).

The $^{18}$F-NaF used in $^{18}$F-NaF PET/CT examinations is easily produced in cyclotrons and is not subject to the same risks of nationwide shortages that were recently seen with $^{99m}$Tc. The number of imaging examinations with $^{18}$F-NaF is rising, given the improvements in hybrid PET/CT scanners, which increase the diagnostic accuracy and specificity of bone imaging. The accumulation of $^{18}$F-NaF at PET/CT imaging is not tumor specific and has low specificity similar to that of $^{99m}$Tc-MDP bone scintigraphy. Differentiating metastases from benign causes such as degeneration, which often occurs in older cancer patients, can be difficult to do solely on the basis of radiotracer uptake. Benign bone processes often display the same degree of uptake, which leads to a higher chance of false positives if the findings are interpreted with PET alone. Interpretation of the findings from $^{18}$F-NaF PET/CT examinations with the use of hybrid PET/CT technology is the standard of care and has been shown to greatly improve specificity. Additionally, the improved bone-to-background ratio and the higher spatial resolution of $^{18}$F-NaF PET/CT lead to better delineation and anatomic location of bone lesions (Fig 2).

In a study conducted to compare the specificity of $^{18}$F-NaF PET/CT and $^{18}$F-NaF PET in 44 oncologic patients, investigators found a higher specificity for $^{18}$F-NaF PET/CT (97%), compared with $^{18}$F-NaF PET alone (72%), in the evaluation of malignant bone lesions (19). In a later prospective study, the same group of investigators evaluated 44 patients with high-risk prostate cancer who underwent $^{18}$F-NaF PET, $^{18}$F-NaF PET/CT, $^{99m}$Tc-MDP planar scintigraphy, and $^{99m}$Tc-MDP SPECT (20). For $^{99m}$Tc-MDP, the sensitivity and specificity were 70% and 57% for $^{99m}$Tc-MDP planar bone scintigraphy, compared with 92% and 82%, respectively, for $^{99m}$Tc-MDP SPECT. For $^{18}$F-NaF, the sensitivity and specificity were 100% and 62% for $^{18}$F-NaF PET alone and were 100% and 100% for $^{18}$F-NaF PET/CT. The use of $^{18}$F-NaF PET alone shows greater sensitivity than $^{99m}$Tc-MDP bone scintigraphy in the detection of bone metastases; however, $^{18}$F-NaF PET alone has a lower specificity than $^{99m}$Tc-MDP SPECT. The addition of fusion PET/CT to $^{18}$F-NaF PET significantly improved specificity to 100% ($P < .001$) (20). The differences between $^{18}$F-NaF and $^{99m}$Tc-MDP as bone imaging agents are summarized in Table 1.

In a recent study, investigators compared $^{18}$F-NaF PET/CT with $^{99m}$Tc-MDP SPECT/CT and $^{99m}$Tc-MDP planar bone scintigraphy in the detection of skeletal metastases from urinary bladder carcinoma (21). $^{18}$F-NaF PET/CT was found to be more sensitive and specific than $^{99m}$Tc-MDP SPECT/CT and planar $^{99m}$Tc-MDP examinations. $^{18}$F-NaF PET/CT allowed a correct diagnosis in all 17 patients with metastases, whereas $^{99m}$Tc-MDP SPECT/CT allowed the detection of true-positive findings in only 15 patients. Although both radiotracers tend to yield false-positive results for benign processes such as Paget disease and degeneration, these investigators found more false-positive results with $^{99m}$Tc-MDP SPECT/CT. The increased specificity of $^{18}$F-NaF PET/CT findings was thought to be secondary to the high-resolution CT images of the PET/CT examination (21). The addition of SPECT/CT fusion images to $^{99m}$Tc-MDP bone scintigraphic images has been shown to improve diagnostic accuracy and increase sensitivity and specificity more than the addition of SPECT alone in the evaluation of bone lesions (22). Considering the cost of $^{18}$F-NaF PET/CT

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**Table 1: Comparison of $^{18}$F-NaF and $^{99m}$Tc-MDP as Bone Imaging Agents**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$^{18}$F-NaF</th>
<th>$^{99m}$Tc-MDP</th>
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<tbody>
<tr>
<td>Protein binding</td>
<td>Minimal plasma binding</td>
<td>Varies from 25% at administration to 70% at 24 h</td>
</tr>
<tr>
<td>Spatial resolution</td>
<td>Higher resolution of PET systems</td>
<td>Lower resolution of gamma cameras</td>
</tr>
<tr>
<td>Half-life</td>
<td>110 min</td>
<td>6 h</td>
</tr>
<tr>
<td>First-pass extraction</td>
<td>Nearly 100%</td>
<td>60%–70%</td>
</tr>
<tr>
<td>Clearance from blood</td>
<td>Fast, results in improved bone-to-background ratio</td>
<td>Slower</td>
</tr>
<tr>
<td>Time from injection to imaging (h)</td>
<td>0.5–1.5</td>
<td>3–4</td>
</tr>
<tr>
<td>Capability for dynamic imaging</td>
<td>Limited</td>
<td>Dynamic (three-phase) bone scintigraphy</td>
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Figure 3. Unsuspected bone metastases in a 77-year-old-man with prostate carcinoma and a rising prostate-specific antigen level. (a, b) Anterior (a) and posterior (b) $^{99m}$Tc-MDP bone scintigraphic images show a small area of suspicious uptake (arrow) in the right iliac wing. (c) Anterior $^{18}$F-NaF PET MIP image helps confirm the right iliac wing lesion (black arrow) and shows additional previously undetected bone lesions in the T7 vertebral body (circle) and the left sacroiliac joint (white arrow).

examinations, $^{99m}$Tc-MDP SPECT/CT may be a useful initial examination for the detection of bone metastases (21).

Early studies with $^{18}$F-NaF were conducted before the widespread availability of hybrid PET/CT scanners; however, the findings still showed promising results for $^{18}$F-NaF PET alone in the evaluation of bone metastases. In a study of 44 patients with lung, prostate, and thyroid primary carcinomas, Schirrmeister et al (23) confirmed that $^{18}$F-NaF PET allowed the detection of all metastases and the identification of twice as many benign and malignant osseous lesions as did $^{99m}$Tc-MDP scintigraphy. These investigators reported that imaging with $^{18}$F-NaF enabled the detection of small, early metastatic spinal lesions before lytic or blastic processes were depicted on $^{99m}$Tc-MDP bone scintigraphic images (Fig 3). This earlier detection may be due to the individual mechanisms by which $^{18}$F-NaF and $^{99m}$Tc-MDP are incorporated into bone, as well as differences in imaging parameters (23,24). The inherent high spatial resolution of current PET/CT systems provides superior image quality for the detection of bone metastases. The spatial resolution of PET/CT is approximately 4–5 mm measured by full width at half maximum (FWHM), compared with 10–15 mm for planar or tomographic gamma cameras used for $^{99m}$Tc-MDP bone scintigraphy (13). This difference in spatial resolution is particularly important in the evaluation of the spine, in which PET/CT allows the detection of small spinal lesions. For example, PET/CT, with its superior resolution, can distinguish between benign facet arthropathy and a metastatic lesion to the pedicle more often than gamma camera bone scintigraphy can (Figs 4, 5).

In another earlier study, Schirrmeister et al (2) examined 34 patients with breast cancer and compared the accuracy of the detection of bone metastases with $^{18}$F-NaF PET and planar $^{99m}$Tc-MDP bone scintigraphy. Confirmation of metastatic lesions was performed with CT and MR imaging as reference methods. $^{18}$F-NaF PET allowed the detection of 64 metastatic lesions in 17 of the 34 patients, and $^{99m}$Tc-MDP scintigraphy allowed accurate detection of only 29 lesions in 11 patients. The inclusion of $^{99m}$Tc-MDP SPECT bone imaging did not allow the identification of additional metastases. Overall,
Figure 4. Facet arthropathy in a 63-year-old woman with infiltrating lobular breast carcinoma. (a) Axial $^{18}$F-NaF PET image shows radiotracer uptake (arrows) along the lumbar facet joints. (b) Axial CT image helps confirm lumbar facet arthropathy (arrows). Anatomic correlation with CT findings allows morphologic characterization and improves the specificity. This accumulation of radiotracer can confidently be called facet arthropathy, rather than metastases, because of the characteristic uptake pattern.

Figure 5. Metastasis in a 70-year-old man with prostate carcinoma. (a) Axial $^{18}$F-NaF PET image shows abnormal accumulation of $^{18}$F-NaF (arrow) in the posterior elements of T3 in a larger area than would be expected for facet arthropathy. (b) Axial CT image helps confirm a sclerotic metastasis (arrow) in the right lamina and pedicle of the T3 vertebral body.

Imaging with $^{18}$F-NaF PET changed management in four patients when previously undetected bone metastases were discovered. These investigators concluded that the extent of metastatic bone disease was greatly underestimated with conventional bone scintigraphy, compared with $^{18}$F-NaF PET, in 11 of 17 patients (2).

Dynamic imaging capabilities are more limited with PET. Specifically, the radionuclide angiographic and blood pool phase images of a traditional $^{99m}$Tc-MDP three-phase bone scintigraphic examination are not routinely possible with $^{18}$F-NaF PET/CT because standard images can be acquired 90 minutes after injection. However, $^{18}$F-NaF PET/CT has emerging potential to become a substitute for two-phase bone scintigraphy in the identification of bone inflammation (25). Depending on the type of PET scanner used, $^{18}$F-NaF PET/CT could be performed similarly to a three-phase bone scintigraphic examination by obtaining a short dynamic acquisition within the first 10 minutes after the injection. This acquisition could conceivably represent the angiographic and blood pool phases of three-phase bone scintigraphy (25,26). The utility of such an approach has not been thoroughly investigated, and prospective studies are needed before its incorporation into routine clinical practice.

Clinical Indications
Initially approved for imaging areas of altered osteogenic activity, $^{18}$F-NaF PET/CT is primarily used as a method for the detection of skeletal metastases in cancer patients, including anatomic localization and assessment of the extent of disease (12). Quantitative imaging methods also exist for evaluating regional skeletal kinetics. Currently, there are no appropriateness criteria established for $^{18}$F-NaF PET/CT imaging; however, in 2010, the Society of Nuclear Medicine and Molecular Imaging approved a practice guideline for the performance and interpretation...
of $^{18}$F-NaF PET/CT bone imaging (12). The guideline states that in addition to metastatic disease evaluation, other clinical indications for $^{18}$F-NaF PET/CT may be appropriate in selected individuals (Table 2) (12).

For example, back pain in adolescents has been evaluated with $^{18}$F-NaF PET/CT imaging (27). Of the 15 patients enrolled in this study, nine patients had increased $^{18}$F-NaF uptake, and one patient demonstrated a herniated lumbar disk, with no associated $^{18}$F-NaF uptake. Pathologic entities that included spondylolysis, osteoid osteoma, fractures, osteitis pubis, and sacroiliitis were correctly identified by abnormal radiotracer uptake with corresponding morphologic abnormalities at CT (27). The results of this study demonstrated the utility of $^{18}$F-NaF PET/CT in the accurate diagnosis of pathologic causes of back pain in adolescents, which can often be a challenging task.

The use of $^{18}$F-NaF PET/CT for the evaluation of child abuse has also been demonstrated. Although a radiographic skeletal survey remains the initial modality of choice for the evaluation of suspected child abuse, identifying the full extent of injuries can be difficult. In the findings from a recent study (28), investigators concluded that $^{18}$F-NaF PET/CT was highly sensitive in the detection of fractures related to child abuse, particularly rib fractures, which are the most common injury in abused young children. $^{18}$F-NaF PET/CT allowed the detection of more posterior rib fractures than baseline skeletal surveys did (28,29).

Skeletal $^{18}$F-NaF PET has utility in the prediction of bone viability and bone healing after surgery or trauma (30,31). In one study, investigators evaluated patients who underwent hip-resurfacing arthroplasty, a surgical alternative to total hip replacement. This procedure carries risks of avascular necrosis and femoral neck fracture. The viability of the remaining femoral head after surgery can be evaluated with $^{18}$F-NaF PET, despite the overlying metal component, which typically limits the use of radiography, CT, and MR imaging. Fourteen patients were evaluated at various times in a 1-year postoperative period after hip resurfacing. $^{18}$F-NaF PET was deemed a sensitive and useful method to evaluate bone metabolism, clearly demonstrating femoral head anatomy and areas of heterotopic ossification (32). In another study of five patients with osteonecrosis of the femoral head, $^{18}$F-NaF PET was used to measure regional blood flow and proved useful in predicting the outcome for eventual joint replacement (7,33).

The diagnosis of fracture nonunion or delayed union can be challenging, and evaluation with radiography is often unreliable. Missing a diagnosis of fracture nonunion can lead to complications, including chronic pain and a decreased quality of life. Hsu et al (34) investigated the role of quantitative $^{18}$F-NaF PET in the early identification of impaired fracture healing in rat femurs. Two study groups were assessed, one with standard femoral fractures and the other with a spacer at the fracture site to interfere with direct bone apposition, thus simulating nonunion. $^{18}$F-NaF PET images were compared with radiographs at weekly intervals. $^{18}$F-NaF began localizing in the standard fracture site within 1 week after injury, and uptake continued to increase with time. Conversely, only minimal uptake was observed in the impaired healing group. On the basis of these observations, investigators suggested that $^{18}$F-NaF PET has the potential to be used to predict fracture nonunion earlier than other imaging techniques (34).

Functional imaging with $^{18}$F-NaF PET allows the quantitative assessment of bone metabolism at certain locations in the skeleton (5). Investigative groups have evaluated the kinetics of $^{18}$F-NaF in the assessment of bone turnover in patients with Paget disease and those with renal osteodystrophy (35,36). Compared with healthy bone, pagetic bone demonstrated higher values of plasma clearance and the plasma clearance of $^{18}$F-NaF to the total bone tissue, reflecting increased regional bone formation and blood flow (35). Characterization of the kinetic behavior of $^{18}$F-NaF will allow improvements in monitoring the response to

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<th>Table 2: Clinical Indications for $^{18}$F-NaF PET/CT</th>
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<td>Detection of skeletal metastasis</td>
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<td>Initial staging</td>
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<td>Disease extent</td>
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<td>Response to therapy</td>
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<td>Unexplained back pain in pediatric and adolescent populations</td>
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<td>Suspected stress injuries</td>
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<td>Unexplained adult bone pain and/or back pain</td>
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<td>Trauma</td>
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<td>Suspected occult fracture</td>
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<td>Child abuse</td>
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<td>Early detection of rib fractures</td>
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<td>Bone graft viability</td>
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<td>Fracture nonunion</td>
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<td>Osteonecrosis of the femoral head and mandible</td>
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<td>Metabolic bone diseases</td>
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<td>Renal osteodystrophy</td>
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<td>Paget disease</td>
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therapy for Paget disease (35,37). Bone metabolic activity has also been evaluated in patients with renal osteodystrophy by using $^{18}$F-NaF PET (36). In a study evaluating renal osteodystrophy, significantly higher rates of $^{18}$F ion transport into bone occurred in patients with hyperparathyroidism, compared with nonaffected patients ($P < .01$). This increased rate correlated well with serum markers of bone turnover, such as the serum alkaline phosphatase level (36). $^{18}$F-NaF has also been used successfully to quantify bone metabolism at various anatomic sites in patients with hyperostosis cranialis interna (38). Quantitative uptake of $^{18}$F-NaF can be measured to assess the response to therapy in patients with osteoporosis (39). Because bone turnover is an important factor in the assessment of fracture risk, $^{18}$F-NaF PET can be used to evaluate the relationship between regional bone turnover and changes in bone mineral density (40). Quantitative measurements of individual therapeutic responses could prove invaluable in the evaluation of new therapies.

There is an emerging role for combined $^{18}$F-NaF PET/CT and FDG PET/CT in the characterization of the biology of atherosclerotic plaques. Derlin et al (41) correlated vascular inflammation (macrophage activity) and active mineral deposition (calcification) with the atherosclerotic plaque burden. Active arterial calcification involves osteoblast- and osteoclast-like cells, and these investigators determined that 77% of the arterial lesions with increased $^{18}$F-NaF accumulation contained calcification. $^{18}$F-NaF could be used to distinguish between plaque with and without calcification and also provided functional information with regard to the pathophysiologic processes in atherosclerotic lesions with calcification. Future studies are needed to determine how radiotracer uptake with $^{18}$F-NaF and FDG may affect the individual risk of atherosclerotic lesions, particularly vulnerable plaques that are prone to rupture.

$^{18}$F-NaF PET/CT Protocol

The Society of Nuclear Medicine and Molecular Imaging has published recent practical guidelines for $^{18}$F-NaF PET/CT bone imaging, including a recommended protocol and doses (12). Current PET/CT scanners use low-dose CT for attenuation correction and anatomic localization, which markedly improves specificity. Whole-body helical CT is performed immediately before or after the emission imaging. Emission imaging may begin as early as 30–45 minutes after administration of $^{18}$F-NaF; however, it is preferable to wait longer for superior-quality whole-body images. The recommended activity for adults is 185–370 MBq (5–10 mCi) injected intravenously; and pediatric activity is based on weight, typically 2.22 MBq/kg (0.06 mCi/kg), with the total activity not to exceed 185 MBq (5 mCi). Whole-body oncologic surveys can be performed with a dose of 370 MBq (10 mCi) of $^{18}$F-NaF administered intravenously, with care to ensure that the injection site does not correspond to the area of interest. Emission images are acquired 90 minutes after injection, and collection in the three-dimensional mode is recommended. Patients are placed supine in the PET/CT scanner and are imaged for five to seven bed positions from the top of the skull through the upper thighs, with an acquisition time of 2–5 minutes per position on average; however, this time will vary depending on the patient’s body mass index, the amount of injected radioactivity, and camera differences. For whole-body images, this acquisition is followed by an additional five to seven bed positions from the pelvis through the toes, with an acquisition time of 3 minutes per position, if extremity imaging is desired (12). For nononcologic survey imaging, the area of interest may be localized to the lumbosacral spine for example, and in that case, one or two bed positions will be sufficient (7). Images are acquired with a $128 \times 128$ or $256 \times 256$ matrix; and for reconstruction, a three-dimensional maximum likelihood expectation maximization (MLEM) algorithm is typically used. The optimal number of iterations and subsets, as well as other reconstruction parameters, will depend on the camera type and patient factors. MIP images can be generated to facilitate detection of suspicious regions (12,16).

$^{18}$F-NaF is well distributed throughout the skeleton, and, therefore, adequate images can be obtained without the use of attenuation correction; however, interpretation with non–attenuation-corrected images is not recommended. Interpretation with attenuation-corrected images provides invaluable anatomic information, improves the accuracy of differentiating between benign and malignant lesions, and increases the detection of smaller lesions. Interpretation of studies without attenuation correction is not recommended because of the increased potential for artifacts (7,12). For example, without attenuation correction, the thoracic spine will appear to have increased radiotracer uptake with $^{18}$F-NaF, which may affect the individual risk of atherosclerotic lesions, particularly vulnerable plaques that are prone to rupture.
Figure 6. Osteoblastic bone metastases in a 59-year-old woman with metastatic poorly differentiated breast carcinoma. (a) Anterior $^{18}$F-NaF PET MIP image shows multiple areas of abnormal accumulation of $^{18}$F-NaF within the cervical, thoracic, and lumbar spine, bilateral ribs, the right scapula, and the pelvis that are compatible with metastases. (b) Correlative axial CT image through the lower portion of the chest shows osteoblastic metastases in the thoracic spine (white arrow) and in the adjacent left rib (black arrow). (c) Axial CT image shows an osteoblastic metastasis (arrow) in the right ilium.

Radiotracer uptake in the bladder will not obscure pelvic lesions and degrade image quality. Metal objects should be removed to prevent attenuation artifacts. Hydration is also encouraged to enhance renal excretion of the radiotracer, which improves the target-to-background ratios, and to decrease the radiation dose (12).

**Radiation Dosimetry**

Radiation dosimetry of $^{18}$F-NaF PET/CT involves consideration of several factors, particularly relative to the radiation dose of $^{99m}$Tc-MDP. Such factors include the dose administered, the different energies of the $^{18}$F 511-keV positrons and the $^{99m}$Tc 140-keV photons, which deliver different patterns of radiation, and the individual radiotracer’s half-life. The 511-keV photon has a soft-tissue half-value layer of 7.3 cm, compared with 4.6 cm for a 140-keV photon of $^{99m}$Tc. This difference means that the 511-keV photons deliver energy to more-distant organs, and the 140-keV photons deliver energy to structures closer to the source organ. With regard to half-life, the shorter half-life of $^{18}$F-NaF (110 minutes), compared with the half-life of $^{99m}$Tc-MDP (6 hours), provides a shorter exposure time, in essence leading to lower radiation exposure (7). With consideration of the aforementioned individual characteristics, the overall effective whole-body dose for $^{18}$F-NaF is higher, compared with that for $^{99m}$Tc-MDP, for most patients at the prescribed dose. For a typical injected dose of 370 MBq (10 mCi) of $^{18}$F-NaF, the reported effective dose is 8.9 mSv (0.89 rem). In comparison, the reported effective dose is 5.3 mSv (0.53 rem) for 925 MBq (25 mCi) of administered $^{99m}$Tc-MDP (12). The specified effective dose of $^{18}$F-NaF is only for the PET portion of the examination. The addition of the CT component of a PET/CT study provides an additional dose, which is highly variable, given the diversity of protocols and CT scanners. Ranges have been reported from less than 1 mSv for CT attenuation correction alone to about 8 mSv for a diagnostic CT examination (16). For an adult whole-body CT examination, the estimated value for the effective CT dose used for localization and attenuation correction is 3.2 mSv (12). In routine clinical practice, all $^{18}$F-NaF PET studies will be performed with hybrid PET/CT imaging, and the radiation dose to the patient represents the combination of the dose from the PET radiopharmaceutical and the dose...
Figure 7. Bone metastases in a 59-year-old woman with a history of metastatic invasive ductal carcinoma of the breast. (a) Restaging anterior FDG PET MIP image shows several bone metastases, including those in the thoracic spine (oval) and lumbar spine (circle), as well as the left ischium (black arrow) and the proximal portion of the left femur (white arrow). (b) Anterior $^{18}$F-NaF PET MIP image shows overall greater metastatic disease burden throughout the spine, with improved anatomic localization of additional skeletal metastases. For example, there is improved anatomic delineation of metastases in the right scapula (arrowhead) and the right first rib (arrow). Previously undetected metastases are now depicted in the right superior ilium (circle). The patient’s treatment plan included palliative radiation therapy to the thoracic spine.

Figure 8. Lytic bone metastasis in an 80-year-old woman with breast cancer. (a) Axial $^{18}$F-NaF PET image shows a left iliac lesion with central photopenia surrounded by a peripheral rim of radiotracer uptake (arrow). (b) Axial CT image through the pelvis helps confirm a lytic metastatic lesion (arrow) in the left ilium.

from the CT portion of the study. The total effective dose of an $^{18}$F-NaF PET/CT examination is about 12.1 mSv, compared with approximately 7.4 mSv for a $^{99m}$Tc-MDP SPECT study (16).

The bladder receives the highest radiation dose with $^{18}$F-NaF, with an effective dose of 0.024 mSv/MBq (0.089 rem/mCi), and patients are encouraged to be well hydrated at the start of their examination to allow rapid radiotracer excretion. The bone surfaces receive the highest dose with $^{99m}$Tc-MDP, with an effective dose of 0.0057 mSv/MBq (0.021 rem/mCi) (12).
Detection of malignant lesions with $^{18}$F-NaF has proved highly sensitive, given the optimal pharmacokinetics of the radiotracer in combination with the performance of PET/CT technology. One of the earliest applications of $^{18}$F-NaF was the imaging of primary bone metastases. A coronal STIR MR image shows a hyperintense mass (arrow) in the L2 vertebral body, a finding that helps confirm a metastasis. This example shows that hypometabolic metastases on FDG PET images may be better depicted on $^{18}$F-NaF PET images.

**Figure 9.** Discordant bone findings between FDG PET and $^{18}$F-NaF PET in a 61-year-old woman with locally advanced invasive ductal carcinoma of the left breast. (a) Initial staging anterior FDG PET MIP image shows hypermetabolic left axillary nodal metastasis (arrow); no additional FDG-avid lesions were depicted. (b) Anterior $^{18}$F-NaF PET MIP image shows malignant osseous involvement of the L2 (black arrow) and C7 (white arrow) vertebral bodies. Note the incidental uptake (arrowheads) bilaterally in the wrists (depicted over the pelvis), a finding that was secondary to arthritis or trauma. No definite CT correlate was identified. (c) However, a coronal STIR MR image shows a hyperintense mass (arrow) in the L2 vertebral body, a finding that helps confirm a metastasis. This example shows that hypometabolic metastases on FDG PET images may be better depicted on $^{18}$F-NaF PET images.

**Image Interpretation**

The mechanism of uptake of $^{18}$F-NaF is similar to the uptake of other skeletal imaging agents because it depends on local osseous blood flow and, more importantly, on regional osteoblastic activity. Normal uptake of $^{18}$F-NaF evenly accumulates throughout the osseous skeleton, with slightly greater deposition in the axial skeleton than in the appendicular skeleton. Elimination of the radiotracer occurs through the urinary tract, and the kidneys and bladder show radiotracer uptake in patients with normal renal function. At least 20% of the radiotracer is cleared from the body within 2 hours after intravenous administration (8). In children, physiologic growth changes within the metaphyses cause increased localization of the radiotracer, which is bilaterally symmetric (12).

$^{18}$F-NaF is deposited at sites of increased bone turnover and remodeling. Metastatic lesions are seen indirectly because of the local bone response to the underlying tumor, and most metastatic lesions show focal $^{18}$F-NaF uptake, whether they are lytic, blastic, or mixed (4,6,19). Detection of malignant lesions with $^{18}$F-NaF has proved highly sensitive, given the optimal pharmacokinetics of the radiotracer in combination with the performance of PET/CT technology. One of the earliest applications of $^{18}$F-NaF was the imaging of pri-
Figure 10. Underestimation of bone metastases in a 53-year-old woman with lung adenocarcinoma. (a) Initial staging anterior FDG PET MIP image shows a hypermetabolic primary lung mass in the right middle lobe, with right hilar nodal metastases (arrows). An equivocal finding in the left iliac crest was depicted with FDG PET (not well shown on MIP image), which led to further workup with $^{18}$F-NaF PET. (b) Anterior $^{18}$F-NaF PET MIP image shows clinically significant metastatic disease in multiple vertebral bodies, including T10 (black arrow) and L1–L3 (circle). The uptake in the left iliac crest (white arrow) helps confirm that the equivocal abnormality depicted at FDG PET is a metastasis. (c) Sagittal reformatted CT image shows the mixed lytic and sclerotic lesion (arrow) in T10, which is at risk for vertebral body collapse. Imaging with $^{18}$F-NaF PET changed the patient management in this case because previously unsuspected bone disease was depicted.

mary bone tumors; however, now its use is primarily in patients at high risk for bone metastases (14).

At our institution, most $^{18}$F-NaF PET/CT examinations are performed for oncologic surveys of the skeletal system, particularly in patients with breast cancer. Bone metastases from breast cancer do not indicate a poor prognosis; instead, their discovery may improve overall patient outcome before the development of associated morbidities. Both osteolytic and osteoblastic metastases from breast cancer can show increased $^{18}$F-NaF uptake (Figs 6, 7) (15,42). Often, osteolytic metastases from breast cancer can be characterized as photopenic lesions with a peripheral rim of radiotracer uptake (Fig 8) (15). $^{18}$F-NaF PET/CT can also be used to confirm clinically suspected bone metastases that are not evident at FDG PET/CT or those that show decreased FDG avidity, such as metastases from renal and thyroid carcinomas and well-differentiated neoplasms (Fig 9) (43).
Figure 11. Metastasis after right nephrectomy in a young 16-year-old female patient who had the translocation variant subtype of renal cell carcinoma. (a) Anterior $^{18}$F-NaF PET MIP image shows a small area of moderate uptake (arrow) in the L2 vertebral body. (b) Axial CT image through the lumbar spine shows a small lytic metastasis (arrow) that corresponds to the area of uptake in a.

In addition to breast cancer, $^{18}$F-NaF PET/CT skeletal surveys have proved advantageous in the detection of malignant metastatic disease from other primary carcinomas such as prostate, renal, and lung cancer (Fig 10). This advantage is particularly evident in the vertebral column, in which improved accuracy in the detection of small lesions compared with $^{99m}$Tc-MDP has been reported (Fig 11) (17,23).

Uptake of $^{18}$F-NaF is not tumor specific, and nonmalignant entities can demonstrate radiotracer uptake, including arthritis, trauma, and bone processes such as fibrous dysplasia and Paget disease. The degree of radiotracer uptake cannot be used to differentiate benign from malignant lesions (12,15). Radiographic correlation and CT correlation are imperative in diagnostic interpretation, and the interpretation of examinations with PET/CT fusion is essential for a correct diagnosis. Many benign bone lesions, including osteophytes and degenerative endplate changes, will show increased $^{18}$F-NaF uptake, and interpretation with PET/CT fusion greatly increases specificity (20). If a stand-alone PET examination is performed, the images can be fused manually to existing CT images to improve specificity. Also, recognizing the pattern of radiotracer uptake can help with differentiation between benign and malignant disease. For example, linear increased uptake along the vertebral body endplates is indicative of degenerative disease and can be used to exclude bone metastasis with a high probability (44). Regional hyperemia with inflammatory arthropathies such as rheumatoid arthropathy may also lead to increased $^{18}$F-NaF uptake in bone and in the surrounding soft tissues (Fig 12) (12,15). Occasionally, it will not be possible to differentiate benign from malignant uptake, and correlation with CT or MR imaging may be necessary for diagnostic accuracy (Figs 13–15).

It is important to review images on a dedicated workstation capable of fusion of PET and CT images and to review any pertinent findings from the patient’s history, including prior trauma, surgery, or other localized conditions that may affect the distribution of $^{18}$F-NaF. Accurate interpretation
Figure 12. Regional hyperemia secondary to rheumatoid arthritis in a 61-year-old woman undergoing $^{18}$F-NaF PET/CT for breast cancer restaging. (a) Anterior $^{18}$F-NaF PET MIP image of the upper portion of the body shows increased accumulation of $^{18}$F-NaF (arrows) in the shoulders, the right elbow, and the right wrist that was related to underlying rheumatoid arthritis. (b) Coronal fused PET/CT image shows increased joint uptake (arrows) that is due to inflammation.
Figure 14. Nonmalignant accumulation of $^{18}$F-NaF in a sacral insufficiency fracture in a 63-year-old woman with breast carcinoma and new pelvic pain. (a) Anterior MIP image of the pelvis depicts intense activity (arrow) in the right sacrum. (b) Coronal oblique multiplanar reformatted CT image through the sacrum shows a nondisplaced fracture (arrow) through the right sacral ala. This example shows the usefulness of CT in lesion characterization.

requires correlation with relevant laboratory test findings, such as the serum alkaline phosphatase and prostate-specific antigen levels, and the findings from prior imaging studies (12).

Standardized uptake values may be calculated with imaging on current PET/CT systems; however, the routine clinical use of these values has not been validated. Brenner and colleagues (45) demonstrated that in areas of low $^{18}$F-NaF uptake, such as in the long bones, the standardized uptake value measurements may not be as reliable as in areas with higher uptake, such as the spine. Therefore standardized uptake value measurements may not be an appropriate tool for the assessment of metabolic changes in long bones (12,45). Further studies are needed to determine whether the standardized uptake value can be used to reliably evaluate regions of bone metabolism.

Extraosseous Uptake of $^{18}$F-NaF

Uptake of $^{18}$F-NaF can sometimes be observed in nonosseous structures such as the arterial vasculature, gastrointestinal tract, and genitourinary tract. Uptake in the vasculature can be seen in major arteries such as the coronary arteries, the carotid arteries, and the aorta of older adults with atherosclerotic calcification and can be used as a marker of active plaque calcification and inflammation (41,46). As a bone-seeking radiopharmaceutical, $^{18}$F-NaF can localize in extraosseous calcifying lesions. Lesions containing dystrophic or microscopic calcification, or calcified visceral metastases can show focal uptake of $^{18}$F-NaF (Figs 16–18) (7). Occasionally, administration of $^{18}$F-NaF may also demonstrate moderate gut uptake, and recognition of this pattern is important for correct interpretation and diagnosis (Fig 19). The exact mechanism of bowel uptake is unknown. We observed that small and large bowel uptake of $^{18}$F-NaF can be variable among patients, with extensive uptake in some patients and minimal uptake in others.

Limitations

Investigators have previously reported that PET/CT imaging with $^{18}$F-NaF is superior to conventional $^{99m}$Tc-MDP bone scintigraphy for the detection of osseous metastases (2,23). However, certain points should be considered before entering into routine clinical use of $^{18}$F-NaF PET/CT (23,24). Various causes of new bone formation will demonstrate increased $^{18}$F-NaF uptake, and there is appropriate concern that this uptake will lead to a higher number of false-positive interpretations. At skeletal PET, a typical pattern is seen for common benign and nonmalignant causes of uptake, such as degenerative disk disease, facet arthropathy, and trauma; and familiarity with these characteristic appearances is imperative for accurate diagnosis. Any spinal lesion not associated with the endplate or joint surface that does not show a typical uptake pattern should be considered as suspicious for metastatic disease (15). Imaging with hybrid PET/CT systems allows CT characterization of equivocal lesions, which improves specificity (12,20,47). The results of $^{18}$F-NaF PET/CT examination are time-consuming to interpret, containing thousands of images. Also, a great amount of detail is obtained with these examinations, and each area of asymmetric ra-
Figure 15. Nonmalignant uptake caused by fibrous dysplasia in a 68-year-old woman. (a) Axial $^{18}$F-NaF PET image shows focal marked uptake (arrow) in the occipital bone. (b, c) Axial CT (b) and fused PET/CT (c) images show an expansile ground-glass lesion (arrow) with well-defined margins, findings that are most compatible with fibrous dysplasia.

Figure 16. Hepatic parenchymal uptake of $^{18}$F-NaF in a 44-year-old woman with breast carcinoma. (a) Axial $^{18}$F-NaF PET image shows localized extraosseous accumulation in the right lobe of the liver (arrow). (b) Correlative axial CT image shows a partially calcified breast cancer metastasis (arrow) that corresponds to the uptake in a.
Figure 17. Unsuspected cardiac uptake in a 47-year-old woman with breast cancer. (a) Axial \(^{18}\)F-NaF PET image shows a round area of intense uptake (arrow) in the region of the right atrium. No other abnormal areas of \(^{18}\)F-NaF uptake were depicted. Cardiac MR imaging was performed for further workup. (b) Axial contrast-enhanced T1-weighted fat-suppressed MR image shows a low-signal-intensity right atrial mass (arrow) with mild enhancement, a finding that corresponds to the abnormal uptake area in (a). The findings at histopathologic evaluation disclosed a heavily calcified organizing thrombus within the right atrium.

diotracer uptake needs to be correlated with the CT fusion images. Readers of \(^{18}\)F-NaF PET/CT must be aware that there is a learning curve with image interpretation.

Another limitation is that small predominantly lytic metastases may show absent or faint \(^{18}\)F-NaF uptake, resulting in a false-negative interpretation (Fig 20). This problem can occur when the metastatic lesion is too small to have excited an underlying osteoblastic reaction (43,48). This phenomenon is particularly true with small spinal lesions, in which there is minimal osteoblastic response, and the FDG PET/CT examination is more likely to identify these purely marrow metastases. Conversely, small lesions in the limb bones are diagnosed easily with \(^{18}\)F-NaF because of an intense osteoblastic response (7,43).

The cost-effectiveness of \(^{18}\)F-NaF PET/CT has not yet been evaluated fully. Despite its superior sensitivity and specificity, the radiotracer is more costly, and PET/CT systems are less available than \(^{99m}\)Tc-MDP bone scintigraphy (20). In a study of lung cancer patients conducted in Germany, investigators demonstrated that \(^{18}\)F-NaF PET is associated with a twofold increase in cost but had better acceptance by patients, given the shorter examination time (49). Therefore in oncologic imaging, \(^{18}\)F-NaF PET may be reserved for selected patient populations deemed at high risk for osseous metastases or those who are clinically suspected of having ma-
lignant skeletal involvement (7,47).

It is well known that a higher radiation dose is associated with $^{18}$F-NaF PET/CT, which requires the judicious use of this modality with regard to more sensitive populations, such as children and adolescents. The risk-benefit ratios should be evaluated before each examination. Additionally, in routine clinical practice, many oncologic patients will be followed with multiple imaging examinations, which contribute to an overall higher radiation exposure.

Comparison of $^{18}$F-NaF PET/CT and FDG PET/CT: Which Examination Should Be Performed?

FDG is a glucose analog that enters cells through glucose membrane transport proteins that are overexpressed in tumor cells, and uptake directly reflects tumor metabolism (47). In contrast, $^{18}$F-NaF is a bone-specific agent, and its uptake reflects increased blood flow and underlying osteoblastic responses to bone destruction by tumor cells (4,24). Because FDG is not limited to the evaluation of bone metabolism, it is advantageous in the detection of both skeletal and soft-tissue malignant sites, including the primary tumor, internal lymph nodes, and visceral metastases (15).

Direct comparison of $^{18}$F-NaF PET/CT and FDG PET/CT with prospective evaluations has not been studied extensively, and future investigations are needed. In one study, investigators compared the diagnostic accuracy of FDG PET/CT with $^{18}$F-NaF PET and $^{99m}$Tc-MDP bone scintigraphy in patients with non–small cell lung cancer (50). The investigators discovered that FDG PET/CT was superior in the detection of lytic metastases, when compared with $^{99m}$Tc-MDP scintigraphy, and $^{18}$F-NaF PET was at least as sensitive as FDG PET/CT (50). FDG appears more effective in the detection of purely marrow metastases, particularly fast-growing lesions, before an underlying osseous reaction can be depicted with $^{18}$F-NaF PET/CT. On the same note, $^{18}$F-NaF PET/CT is more likely to allow identification of osseous metastases of tumors with low FDG avidity, such as thyroid and renal cancers (43).

In a few studies, investigators have proposed combining $^{18}$F-NaF and FDG radiopharmaceuticals by administering the two radiopharmaceuticals at the same time combined into a single injection. Although this combination has not yet been accepted into routine clinical practice, the potential benefits are increased sensitivity for the detection of skeletal metastases when compared with $^{18}$F-NaF alone, improved patient convenience, and more efficient use of PET/CT imaging times (51–53).

Both FDG PET and $^{18}$F-NaF PET have roles in management of bone metastases, and they are complementary, particularly in evaluation of breast cancer metastases, which can be both lytic and sclerotic. Some investigators recommend use of FDG PET/CT as a perioperative initial staging method, and $^{18}$F-NaF PET/CT hybrid fusion imaging is considered the optimal examination for specific evaluation of the skeletal system (54).

Conclusions

$^{18}$F-NaF PET/CT hybrid fusion imaging is an established imaging tool for the localization and characterization of benign and malignant skeletal processes, and it has proved to be more accurate than conventional planar $^{99m}$Tc-MDP bone scintigraphy. The superior image contrast and high spatial resolution of $^{18}$F-NaF PET/CT provide greater anatomic localization of osseous lesions, particularly bone metastases. The favorable kinetics of $^{18}$F-NaF allows accurate imaging of bone blood flow and metabolism. Imaging with $^{18}$F-NaF PET/CT is essential in the
Figure 20. False-negative findings at $^{18}$F-NaF PET in a 43-year-old woman with breast carcinoma. (a, b) Initial staging lateral FDG PET MIP (a) and sagittal fused FDG PET/CT (b) images show a small focus (oval) of increased uptake (standardized uptake value, 2.5) in the T6 vertebral body. No other findings suggestive of distant metastases were depicted at FDG PET/CT. (c) Sagittal reformatted CT image of the thoracic spine shows a corresponding 5-mm lytic lesion (oval). $^{18}$F-NaF PET was performed for further evaluation. (d) Sagittal $^{18}$F-NaF PET image shows no evidence of skeletal metastases. (e) Before therapy, an axial CT image at the level of T6 shows the lytic vertebral body metastasis (arrow). (f) After therapy, an axial CT image shows progressive blastic changes of the lesion (arrow), findings that are indicative of a treated metastasis. As highlighted by this case, small purely lytic metastases may show false-negative findings on $^{18}$F-NaF PET images.
management of cancer patients at risk for bone involvement. Awareness of this PET/CT application will aid in appropriate care for cancer patients, and a thorough knowledge of the imaging appearances of benign and malignant bone processes is invaluable for correct diagnosis.

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References
Uptake of $^{18}$F-NaF is a function of osseous blood flow and reflects bone remodeling, and the uptake indicates osteoblastic activity by identifying reactive changes in the underlying affected bone (8). Abnormal areas of increased $^{18}$F-NaF uptake depicted on PET/CT images are due to processes that increase exposure of the surface of bone and provide a higher availability of binding sites, such as osteolytic and osteoblastic processes.

$^{18}$F-NaF has minimal binding to serum proteins, which allows a rapid single-pass extraction and fast clearance from the soft tissues. Compared with $^{99m}$Tc-MDP, the bone uptake of $^{18}$F-NaF is twice as great (11,13). This greater bone uptake and the faster soft-tissue clearance lead to shorter $^{18}$F-NaF imaging times, as well as increased bone-to-background ratios for $^{18}$F ions, a finding that improves the diagnostic accuracy.

Initially approved for imaging areas of altered osteogenic activity, $^{18}$F-NaF PET/CT is primarily used as a method for the detection of skeletal metastases in cancer patients, including anatomic localization and assessment of the extent of disease (12).

$^{18}$F-NaF is deposited at sites of increased bone turnover and remodeling. Metastatic lesions are seen indirectly because of the local bone response to the underlying tumor, and most metastatic lesions show focal $^{18}$F-NaF uptake, whether they are lytic, blastic, or mixed (4,6,19).

Uptake of $^{18}$F-NaF is not tumor specific, and nonmalignant entities can demonstrate radiotracer uptake, including arthritis, trauma, and bone processes such as fibrous dysplasia and Paget disease. The degree of radiotracer uptake cannot be used to differentiate benign from malignant lesions (12,15).