

# Detection of Osseous Metastasis by $^{18}\text{F-NaF}/^{18}\text{F-FDG}$ PET/CT Versus CT Alone

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**Purpose:** Sodium fluoride PET ( $^{18}\text{F-NaF}$ ) has recently reemerged as a valuable method for detection of osseous metastasis, with recent work highlighting the potential of coadministered  $^{18}\text{F-NaF}$  and  $^{18}\text{F-FDG}$  PET/CT in a single combined imaging examination. We further examined the potential of such combined examinations by comparing dual tracer  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT with CT alone for detection of osseous metastasis.

**Patients and Methods:** Seventy-five participants with biopsy-proven malignancy were consecutively enrolled from a single center and underwent combined  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT and diagnostic CT scans. PET/CT as well as CT only images were reviewed in blinded fashion and compared with the results of clinical, imaging, or histological follow-up as a truth standard.

**Results:** Sensitivity of the combined  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT was higher than that of CT alone (97.4% vs 66.7%). CT and  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT were concordant in 73% of studies. Of 20 discordant cases,  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT was correct in 19 (95%). Three cases were interpreted concordantly but incorrectly, and all 3 were false positives. A single case of osseous metastasis was detected by CT alone, but not by  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT.

**Conclusions:** Combined  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT outperforms CT alone and is highly sensitive and specific for detection of osseous metastases. The concordantly interpreted false-positive cases demonstrate the difficulty of distinguishing degenerative from malignant disease, whereas the single case of metastasis seen on CT but not PET highlights the need for careful review of CT images in multimodality studies.

**Key Words:** NaF, FDG, PET/CT, metastasis, bone

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Bone is among the most common sites of cancer metastasis, and osseous metastases are an ominous indicator of cancer progression, carrying a substantially worsened prognosis.<sup>1,2</sup> Clinical decision making is therefore often tied to the presence or absence of metastasis, including to the skeleton.  $^{18}\text{F-FDG}$  PET/CT is widely used for the initial detection and staging of various cancers and for monitoring response to therapy. Despite the known advantages of PET in comparison to planar imaging or SPECT, the most widely used imaging modality for the detection of bone metastases remains planar or SPECT imaging using  $^{99\text{m}}\text{Tc-MDP}$ . Current clinical practice therefore often requires separate  $^{18}\text{F-FDG}$  PET/CT and  $^{99\text{m}}\text{Tc-MDP}$  bone scans.<sup>3</sup>

Sodium Fluorine-18 ( $^{18}\text{F-NaF}$ ) is a positron-emitting agent that was historically used as a skeletal tracer for planar scintigraphy before the advent of  $^{99\text{m}}\text{Tc}$ -based agents such as MDP.  $^{18}\text{F-NaF}$  behaves as an analog of the hydroxyl group of hydroxyapatite, the mineral component of bone, and provides a molecular contrast mechanism distinct from the glucose metabolism-dependent uptake of  $^{18}\text{F-FDG}$ . The widespread adoption of  $^{18}\text{F-FDG}$  PET/CT has made  $^{18}\text{F-NaF}$  PET imaging feasible using available equipment and has led to a resurgence of interest in this tracer, with recent data suggesting that  $^{18}\text{F-NaF}$  PET/CT has higher sensitivity and specificity than  $^{18}\text{F-FDG}$  PET/CT or  $^{99\text{m}}\text{Tc-MDP}$  bone scintigraphy for the diagnosis of sclerotic osseous metastatic disease.<sup>4,5</sup>

Given that  $^{18}\text{F-NaF}$  and  $^{18}\text{F-FDG}$  PET possess unique advantages and limitations for detection of osseous metastasis,<sup>6,7</sup> coadministration of both tracers represents an appealing approach. Indeed, recent work demonstrated the feasibility of sequential administration of both tracers without an intervening delay, followed by a single PET/CT acquisition.<sup>8</sup> This combined scan marries the distinct molecular imaging properties of  $^{18}\text{F-NaF}$  and  $^{18}\text{F-FDG}$  PET, without significantly reducing the performance of either tracer alone for the detection of skeletal metastases.<sup>5,9</sup> Moreover, the combined scan represents a decrease in overall radiation dose in comparison with separate  $^{18}\text{F-NaF}$  and  $^{18}\text{F-FDG}$  PET/CT, and is similar in overall dose to  $^{18}\text{F-FDG}$  PET/CT plus  $^{99\text{m}}\text{Tc-MDP}$  bone scintigraphy.<sup>5</sup> Given the theoretical advantages of such combined single-session imaging, we prospectively examined the utility of  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT versus CT alone for the detection of osseous metastatic disease.

## PATIENTS AND METHODS

This study was reviewed and approved by the Stanford University institutional review board and the Cancer Institute Scientific Review Committee. We prospectively enrolled 75 consecutive participants at our institution as part of an international multicenter study of combined  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT versus single-tracer  $^{18}\text{F-NaF}$  and  $^{18}\text{F-FDG}$  PET/CT. Data from a single institution were used because clinical and pathology follow-up was not available from all additional study sites. Although the only entry criterion was biopsy-proven malignancy, a nonrandom distribution of histological types was observed due to disproportionate referral for tumor types not typically otherwise reimbursed (eg, prostate cancer and sarcoma). All participants were imaged between September 2007 and July 2013, and each participant provided written informed consent before enrollment. The details of the protocol and image acquisition are as previously reported.<sup>10</sup> Identical doses of  $^{18}\text{F-FDG}$  and  $^{18}\text{F-NaF}$  were given for the combined and individual examinations. Low-dose CT technique was used for PET/CT interpretations, with separately acquired diagnostic quality CT used for CT-only interpretations. No CT contrast material was administered.

Examinations were scored by reviewers blinded to the presence or absence of metastatic disease (if known) and in accordance with standard practice for each individual modality to preserved concordance with prior studies. For purposes of statistical analysis, the scoring scales were reduced to 2 categories (benign or malignant) as described

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**TABLE 1.** Clinical Data of the Studied Population

	Male	Female
n	58	17
Age, y	60 ± 15.7	46.9 ± 11.5
Stage		
I	2	1
II	16	9
III	23	2
IV	17	5
Initial treatment strategy	9	6
Subsequent treatment strategy	49	11
Primary tumor		
Prostate	39	0
Breast	0	6
Sarcoma	12	10
Colorectal	2	0
Bladder	1	0
Lung	1	0
Renal	1	1
NHL	1	0
Paraganglioma	1	0

The initial treatment indicates participants presenting for initial staging, whereas subsequent treatment indicates participants presenting for restaging or surveillance.

NHL, non-Hodgkin lymphoma.

below. For the  $^{18}\text{F-NaF}$  PET/CT, areas of focally increased  $^{18}\text{F-NaF}$  skeletal uptake were read as malignant unless a benign etiology for this uptake was identified at the same location on the corresponding low-dose CT images. Prior work has shown the validity of qualitative assessment of  $^{18}\text{F-FDG}$  uptake in various malignancies.<sup>11–15</sup> For the  $^{18}\text{F-FDG}$  PET/CT, focal  $^{18}\text{F-FDG}$  uptake less than the mediastinal blood pool was considered benign, uptake equal to the mediastinal blood pool was considered uncertain, and uptake greater than the mediastinal blood pool was considered malignant. For the  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT scans, the previously mentioned criteria were combined to define focal uptake as benign, uncertain, or malignant.<sup>10</sup> Only uptake called malignant was considered as such for statistical analysis.

Multiplanar (axial, sagittal, and coronal) CT-only images were reviewed independently on a GE Centricity PACS system by 2 board-certified musculoskeletal radiologists (S.C.S. and S.C.S.). All identified lesions were scored on a scale of 1 to 5 as follows: 1, benign; 2, likely benign; 3, possibly benign; 4, likely malignant; and 5, malignant. Discordances were reconciled by consensus, and another senior musculoskeletal radiologist (A.M.L.) independently reviewed non-reconcilable discordances. Only lesions scoring either 4 or 5 were considered malignant for purposes of statistical analysis.

A direct comparison of the detected lesions was then performed among the scans. A criterion standard diagnosis of metastasis or no metastasis was first established for each patient based on a combination of clinical, radiological, and pathological (biopsy) follow-up from the time of scanning. Overall, follow-up was available for 74 (98.7%) of 75 patients and was clinical or radiological in 67.6% of cases, with the remaining 32.4% established pathologically via biopsy. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CT and  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT were calculated using a  $2 \times 2$  contingency table, and 95% confidence intervals (CIs) were determined. In addition, each participant's stage of disease was reviewed at the time of analysis, as was their status of either "initial treatment" (ie, initial staging) or "subsequent treatment" (ie, restaging, surveillance) as determined using the Center for Medicare and Medicaid Services guidelines for PET.

## RESULTS

The study cohort consisted of 58 men and 17 women ranging from ages 19 to 84 years (average,  $57.1 \pm 15.8$  years). The clinical characteristics of the study participants are shown in Table 1. The most common histologies were prostate cancer and sarcoma (39 and 22 participants, respectively), with 6 or fewer cases each of the remaining tumor types. Of the 75 participants enrolled in the study, 48 were judged to have osseous metastatic disease ("likely malignant" or "malignant") on at least 1 of the tested modalities (64% of total examinations). The sensitivity, specificity, PPV, and NPV of each modality are presented in Table 2.

As expected, the sensitivity of the combined  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT for detection of osseous metastasis was higher than that of CT alone (97.4% and 66.7%, respectively). The specificities were, however, comparable (86.1% and 77.8%, respectively). This is in keeping with previous data demonstrating significantly higher sensitivity of  $^{18}\text{F-FDG}$  PET/CT and  $^{18}\text{F-NaF}$  PET/CT in comparison with conventional imaging for detection of bone metastases in various cancers.<sup>16–18</sup> An analysis of the performance of the 2 modalities with respect to malignancy type demonstrated slightly reduced sensitivity/specificity of CT alone in cases of prostate cancer and slightly reduced  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT sensitivity in sarcoma and specificity in prostate cancer (Table 2).

In 55 (73%) of 75 studies, there was concordance between CT and  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT. The distribution of these concordant cases followed the overall frequency of tumor types in the study population, with 45% prostate, 31% sarcoma, and 24% of all other tumor types (25, 17, and 13 cases, respectively). Of the concordant cases, 27 (49%) of 55 were concordantly positive, with 28 cases (51%) judged concordantly negative. The concordant positive cases were found to be correct 89% of the time (24 of 27 cases), whereas the concordant negative cases were 100% correct (28 of 28 cases). An example of concordantly positive findings confirmed as osseous metastases on follow-up is shown in Figure 1. A left acetabular lesion

**TABLE 2.** Performance of the CT and the Combined  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT, Assessed by Sensitivity, Specificity, PPV, and NPV

	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %
CT (all cases; n = 74)	66.7 (54.8–75.9)	77.8 (64.9–87.8)	76.5 (62.9–87.1)	68.3 (57.0–77.1)
Prostate (n = 38)	60.9 (45.6–72.9)	68.8 (46.9–86.1)	73.7 (55.3–88.3)	55.0 (37.5–68.9)
Sarcoma (n = 22)	66.7 (36.9–84.2)	84.6 (64.0–96.8)	75.0 (41.5–94.7)	78.6 (59.5–89.9)
All other (n = 14)	85.7 (52.4–98.7)	85.7 (52.4–98.7)	85.7 (52.4–98.7)	85.7 (52.4–98.7)
$^{18}\text{F-NaF}/^{18}\text{F-FDG}$ PET/CT (all cases; n = 74)	97.4 (88.2–99.9)	86.1 (76.1–88.7)	88.4 (80.0–90.6)	96.9 (85.6–99.8)
Prostate (n = 38)	100 (87.2–100)	75.0 (56.7–85.2)	85.2 (74.3–90.6)	100 (75.5–100)
Sarcoma (n = 22)	88.9 (59.6–99.0)	92.3 (72.0–99.3)	88.9 (59.6–99.0)	92.3 (72.0–99.3)
All other (n = 14)	100 (68.5–100)	100 (68.5–100)	100 (68.5–100)	100 (68.5–100)



**FIGURE 1.** A 64-year-old man with prostate cancer. A left acetabular metastasis (arrowhead) is seen on both the combined  $^{18}\text{F}\text{-NaF}/^{18}\text{F}\text{-FDG}$  PET (A) and on the CT (B). Fused PET/CT images are also shown (C).

is seen on both the combined  $^{18}\text{F}\text{-NaF}/^{18}\text{F}\text{-FDG}$  PET and on the CT in a patient with prostate cancer.

Of the 3 cases that were concordant between the 2 modalities but incorrect, all 3 represented false positives. A single site of disease was identified in 2 of 3 cases, whereas symmetric bilateral lesions were seen in the third. In the first case, both modalities incorrectly identified a lesion within the T11 vertebral body in a patient with prostate cancer. The second case was read positive for destructive-appearing lesions associated with the bilateral sacroiliac joints in another patient with prostate cancer. In the third case (Fig. 2), both modalities incorrectly identified a lesion within the left tibial diaphysis in a male patient with sarcoma.

Of 20 discordant cases, CT was judged negative, and  $^{18}\text{F}\text{-NaF}/^{18}\text{F}\text{-FDG}$  PET/CT was positive in 14 (70%), with the converse being true in 6 cases (30%). Overall,  $^{18}\text{F}\text{-NaF}/^{18}\text{F}\text{-FDG}$  PET/CT was correct in 19 (95%) of 20 discordant cases. An example is given in Figure 3A of metastases within a sarcoma patient, identified by  $^{18}\text{F}\text{-NaF}/^{18}\text{F}\text{-FDG}$  PET/CT but missed by CT alone. Interestingly, of the 14 examinations that were incorrectly interpreted as negative for metastatic disease by CT alone (false negative), CT in 3 cases demonstrated at least 1 of the metastatic lesions, which was, however, incorrectly interpreted as benign (Fig. 3B, C). These include an L2 vertebral body and a T9 vertebral body lesion, both of which were incorrectly scored as 2 (“probably benign”) on CT.

Among the 20 discordant cases, 5 were incorrectly interpreted as positive on CT only (CT false positive). Multiple suspicious lesions were identified in 3 of the 5 cases, and in all 5 cases, the maximum lesion score was 4 (likely malignant). Overall, there was

only 1 participant in which a lesion was scored 5 (malignant) on CT and ultimately proven incorrect. Of note, this case was scored malignant by  $^{18}\text{F}\text{-NaF}/^{18}\text{F}\text{-FDG}$  PET/CT as well.

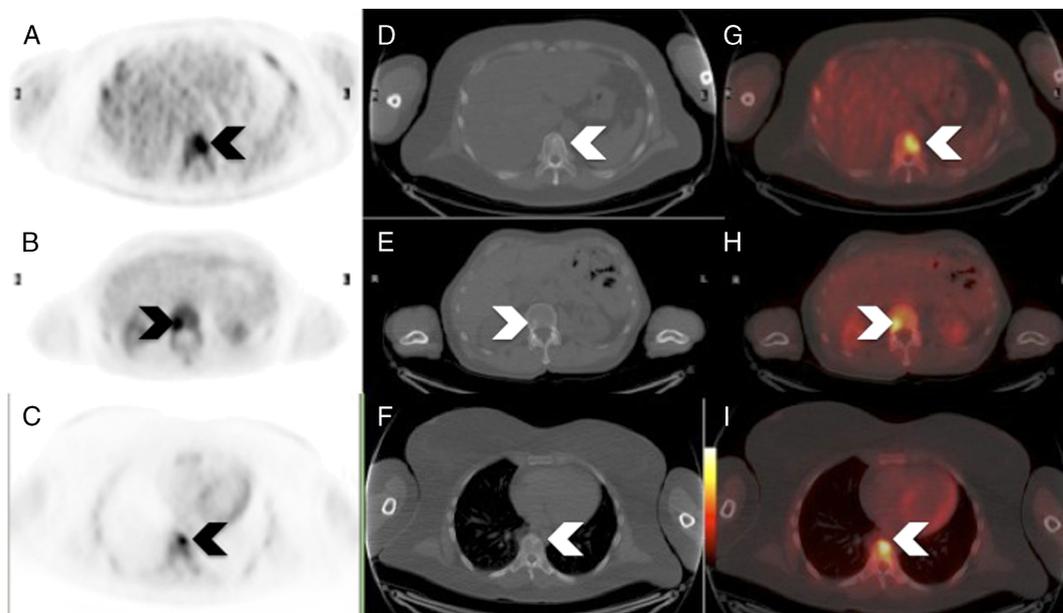
Finally, a single case was identified in which osseous metastasis was correctly detected by CT alone, but not by  $^{18}\text{F}\text{-NaF}/^{18}\text{F}\text{-FDG}$  PET/CT (Fig. 4). In this 30-year-old man with metastatic sarcoma, numerous lesions were seen on CT diffusely involving the axial skeleton and bilateral iliac bones. Despite the widespread metastasis, no metabolically active disease was seen on  $^{18}\text{F}\text{-NaF}/^{18}\text{F}\text{-FDG}$  PET/CT, possibly representing sequela of treated disease.

## DISCUSSION

The presence or absence of metastases is a critical issue in clinical decision making, and numerous methods are employed for the detection of metastatic disease. These range from CT alone to more advanced modalities that increase sensitivity for detection of soft tissue and bony lesions. Although  $^{18}\text{F}\text{-FDG}$  PET/CT represents an excellent modality for the detection of soft tissue metastases, it is known to have variable accuracy for the detection of skeletal metastasis and is particularly poor for blastic lesions.<sup>19–21</sup>  $^{18}\text{F}\text{-NaF}$  PET, although superior to the currently preferred modality for detecting osseous metastasis,  $^{99\text{m}}\text{Tc}\text{-MDP}$  bone scintigraphy<sup>6,22</sup> has not come into widespread use. This is due largely to logistical and financial considerations.<sup>23</sup> The wider availability of PET/CT scanners made it technically feasible to incorporate  $^{18}\text{F}\text{-NaF}$  into routine oncologic imaging algorithms, and recent data have demonstrated the clinical feasibility of combined  $^{18}\text{F}\text{-NaF}/^{18}\text{F}\text{-FDG}$  PET/CT.<sup>8–10</sup> Here we further demonstrate by direct comparison with CT alone that



**FIGURE 2.** A 60-year-old man with sarcoma. Both the combined  $^{18}\text{F}\text{-NaF}/^{18}\text{F}\text{-FDG}$  PET (A) and the CT (B) incorrectly identified as a malignant lesion within the left tibial diaphysis (arrowhead), possibly related to prior trauma/surgery in this region. Fused PET/CT images are also shown (C).

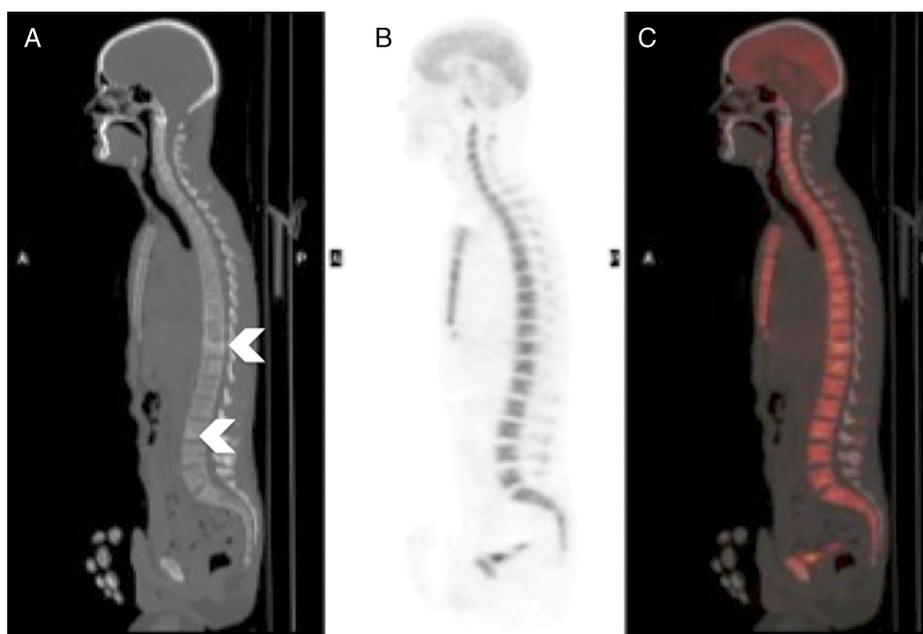


**FIGURE 3.** A, Bone metastasis (arrowhead) in a 45-year-old man with sarcoma identified by  $^{18}\text{F}$ -NaF/ $^{18}\text{F}$ -FDG PET (A) but missed by CT alone (D). Fused PET/CT images are also shown (G). B, The combined  $^{18}\text{F}$ -NaF/ $^{18}\text{F}$ -FDG PET (B) allowed for the correct classification as metastatic lesion (arrowhead) in a patient with prostate cancer, whereas on CT (E), the findings were incorrectly interpreted as benign. Fused PET/CT images are also shown (H). C, Similarly, the combined  $^{18}\text{F}$ -NaF/ $^{18}\text{F}$ -FDG PET (C) allowed for the correct classification as metastatic lesion (arrowhead) in a patient with breast cancer, whereas on CT (F), the findings were incorrectly interpreted as benign. Fused PET/CT images are also shown (I).

combined  $^{18}\text{F}$ -NaF/ $^{18}\text{F}$ -FDG PET/CT is a highly sensitive and specific method for detection of osseous metastatic disease.

Comparison with CT alone was chosen in the current study because this is a very common method for staging cancer patients, and the appearance of bone lesions on CT is critically important in

distinguishing benign from malignant etiologies. Indeed, CT alone demonstrated a substantial degree of concordance with  $^{18}\text{F}$ -NaF/ $^{18}\text{F}$ -FDG PET/CT and had similar specificity. Although the a priori assumption might be that the degree of concordance would largely reflect overlap on negative studies, we did not find this to be the case. In fact,



**FIGURE 4.** A 30-year-old man with metastatic sarcoma. CT (A) showed multiple metastases (arrowheads) involving the axial skeleton. These lesions were not noted prospectively on the  $^{18}\text{F}$ -NaF/FDG PET (B). Fused PET/CT images are also shown (C).

concordant studies were nearly equally distributed between positive and negative cases.

Despite similar specificities, the sensitivity of  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT was, as expected, higher than that of CT alone. This in part reflects a failure of interpretation and not simply detection because 3 of the 14 cases of “false negative” by CT-alone demonstrated lesions that were seen but incorrectly interpreted as likely benign. Although it is true that PET images were interpreted by more experienced readers than the CT images, which could be regarded as a limitation of the study, this reflects the local practice. In addition, an experienced senior musculoskeletal radiologist judged cases with disagreements.

Although combined  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT clearly outperformed CT, it is instructive to take note of the 3 cases, which were read concordantly but incorrectly. Interestingly, all 3 of these were false positives, in retrospect likely representing advanced degenerative change. Moreover, 1 of these cases could likely have been dismissed as unlikely metastatic on both studies in light of the symmetric nature of the lesions. The remaining 2 cases demonstrate the challenge of distinguishing degenerative from metastatic signal on PET and highlight the need for future development of more specific PET tracers. Conversely, the single case in which multiple metastatic foci were seen on CT only, possibly representing sequela of previously treated disease, emphasizes the need for careful and dedicated scrutiny of cross-sectional images in combined molecular and anatomic imaging studies.

It should be noted that conclusions regarding the relative strengths of various imaging modalities are strongly dependent on the case mix within the study population. This represents a potentially significant limitation of the current analysis, which was substantially overrepresented for some tumor types (prostate cancer, sarcoma) and underrepresented for others (lung and breast cancer). Moreover, the single-institution accrual, although allowing more controlled interpretation of the images, may overstate the reproducibility of results where a greater variety of equipment, imaging protocols, diagnoses, and readers are concerned. These limitations could be addressed by similar analysis in larger multicenter cohorts.

## CONCLUSIONS

Dual tracer  $^{18}\text{F-NaF}/^{18}\text{F-FDG}$  PET/CT improves sensitivity and specificity for the detection of skeletal malignancy when compared with CT alone, supporting its clinical use in selected cancer patients. Additional practical benefits of this approach include patient convenience, efficiency of scanner usage, and possible improvements in overall cost,<sup>5,9</sup> all of which may also support combined tracer injection strategies in emerging clinical imaging applications such as PET/MRI.<sup>24</sup>

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