ORIGINAL ARTICLE

Observational Study

Comparisons between glucose analogue 2-deoxy-2-(18F)fluoro-D-glucose and 18F-sodium fluoride positron emission tomography/computed tomography in breast cancer patients with bone lesions

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Abstract

AIM: To compare 2-deoxy-2-(^{18}F)fluoro-D-glucose(^{18}F-FDG) and ^{18}F-sodium (^{18}F-NaF) positron emission tomography/computed tomography (PET/CT) accuracy in breast cancer patients with clinically/radiologically suspected or known bone metastases.

METHODS: A total of 45 consecutive patients with breast cancer and the presence or clinical/biochemical or radiological suspicion of bone metastatic disease underwent ^{18}F-FDG and ^{18}F-fluoride PET/CT. Imaging results were compared with histopathology when available, or clinical and radiological follow-up of at least 1 year. For each technique we calculated: Sensitivity (Se), specificity (Sp), overall accuracy, positive and negative predictive values, error rate, and Youden's index. McNemar's χ^2 test was used to test the difference in sensitivity and specificity between the two diagnostic methods. All analyses were computed on a patient basis, and then on a lesion basis, with consideration of the density of independent lesions on the co-registered CT (sclerotic, lytic, mixed, no-lesions) and the divergent site of disease (skull, spine, ribs, extremities, pelvis). The impact of adding ^{18}F-NaF PET/CT to the work-up of patients was also measured in terms of change in their management due to ^{18}F-NaF PET/CT findings.

RESULTS: The two imaging methods of ^{18}F-FDG and ^{18}F-fluoride PET/CT were significantly different at the patient-based analysis: Accuracy was 86.7% and 84.4%, respectively (McNemar's χ^2 = 6.23, df = 1, P = 0.01). Overall, 244 bone lesions were detected in our analysis. The overall accuracy of the two methods was significantly different at lesion-based analysis (McNemar's χ^2 = 93.4, df = 1, P < 0.0001). In the lesion density-based and site-based analysis, ^{18}F-FDG PET/CT provided more accurate results in the detection of CT-negative metastasis (P < 0.002) and vertebral localizations (P < 0.002); ^{18}F-NaF PET/CT was more accurate in detecting sclerotic (P < 0.005) and rib lesions (P < 0.04). ^{18}F-NaF PET/CT led to a change of management in 3 of the 45 patients (6.6%) by revealing findings that were not detected at ^{18}F-FDG PET/CT.

CONCLUSION: ^{18}F-FDG PET/CT is a reliable imaging tool in the detection of bone metastasis in most cases, with a diagnostic accuracy that is slightly, but significantly, superior to that of ^{18}F-NaF PET/CT in the general population of breast cancer patients. However, the extremely high sensitivity of ^{18}F-fluoride PET/CT can exploit its diagnostic potential in specific clinical settings (*i.e.*, small CT-evident sclerotic lesions, high clinical suspicious of relapse, and negative ^{18}F-FDG PET and conventional imaging).

Core tip: ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and ^{18}F-sodium positron (^{18}F-NaF) positron emission tomography/computed tomography (PET/CT) is undoubtedly an accurate and validated imaging tool in the general population of breast cancer patients for the detection of bone metastasis in most cases. However, thanks to its extremely high sensitivity, ^{18}F-NaF PET/CT could have an adjunctive value in selected patients, significantly impacting their management (*i.e.*, small CT-evident sclerotic lesions, high clinical suspicious of relapse, and negative ^{18}F-FDG PET and conventional imaging). This sensitivity might be particularly relevant for patients who are candidates for surgery or radiotherapy.

INTRODUCTION

Breast cancer is the most prevalent form of cancer in women of Western countries[1-3], with the skeleton being the most common site of distant metastases. Presence, distribution, and type of bone localizations have relevant prognostic implications[4,5]. In particular, with the growing availability of new therapeutic strategies which could potentially improve survival, the early detection of bone metastases has gained pivotal importance[6,7].

Conventional bone scintigraphy (BS) remains the most suitable technique for whole-body screening of bone metastasis due to its low cost and high availability. However, BS has several important limitations, and so additional imaging procedures are often necessary to determine the real significance of scintigraphic abnormalities[8].

During the last decade, positron emission tomography (PET) has evolved from a research tool to an established imaging modality for the staging of different types of malignant tumors, owing to its better spatial resolution and superior image quality with respect to conventional single-photon imaging. Among PET tracers, glucose analogue 2-deoxy-2-(^{18}F)fluoro-D-glucose (^{18}F-FDG) has become the most widely used in clinical routine, resulting in a major impact on the practice of oncology[9]. In breast cancer patients, ^{18}F-FDG-PET enables the detection

of neoplastic lesions on the basis of their increased glucose metabolism, potentially allowing for an accurate assessment of local disease, lymph nodes, and visceral metastases in a single imaging study. Furthermore, by directly reflecting tumor cell viability in bone metastases, this technique can potentially be used for therapy response assessments. In fact, changes in 18F-FDG activity after therapy may reflect an early response to therapy that could be potentially prognostic[10].

Characterization of bone metastases is also possible with 18F-sodium fluoride (18F-NaF), which reflects the increased regional blood flow and osteoblastic bone reaction[8]. Specifically, greater activity of remodeling and bone turnover determines greater blood flow and exchange surface for 18F-fluoride ion absorption and subsequent irreversible incorporation into the bone matrix as fluorapatite[11-13].

Both PET tracers have shown a better diagnostic value compared to BS in detecting bone metastases in patients with breast cancer and several other malignancies[14-20]. Conversely, very limited and controversial information exists in comparing the diagnostic accuracy of 18F-FDG and 18F-NaF PET[19,21,22]. The different uptake mechanisms of these two tracers might be complementary in the context of evaluating lytic and sclerotic lesions, which can both coexist in bone localizations of breast cancer patients[23].

Furthermore, it has been suggested[24] that anatomical localization of the lesions could also influence the accuracy of each technique; this finding is likely to be related to the morphology of bone metastasis. In fact, the involvement of different skeletal segments could determine different degrees of osteoblastic reaction[25,26]. At the time of writing, controversial results have been reported about the accuracy of these two tracers in breast cancer patients[19,21,22], with some authors even proposing their combined use[27,28]. In particular, 18F-FDG PET/computed tomography (CT) can provide information about the presence/absence of disease in the skeleton, as well as in non-skeletal districts. In this context, it not been clearly investigated whether 18F-NaF PET/CT can provide incremental information for the management of breast cancer patients that have already been evaluated by means of 18F-FDG PET/CT.

The current study aims to evaluate the role of the two imaging modalities in the restaging of breast cancer patients with clinically/radiologically suspected or known metastatic bone lesions. In particular, we planned to verify whether the accuracy of the two imaging methods could be influenced by lesion density and location.

MATERIALS AND METHODS

Patient population
Between January 2010 and June 2012, 45 breast cancer patients were referred to our institutions for the execution of both 18F-NaF and 18F-FDG PET/CT for the restaging of clinically/radiologicallysuspected or proven metastatic bone lesions. All study participants, or their legal guardians, provided informed written consent prior to study enrollment, and practices were performed in accordance with the ethical standards laid down in the Declaration of Helsinki. We included only patients who performed the two PET scans within 1 mo and did not received chemotherapy or radiotherapy between the two examinations. By contrast, chemotherapy administration in the month before the two PET/CT exams was not an exclusion criterion. Patient characteristics are listed in Table 1.

PET/CT protocols
Image acquisition was performed according to standard procedures and international guidelines[29,30].

Patients were submitted to 18F-NaF PET/CT using two 16 slices PET/CT hybrid systems: (1) Biograph 16 (Siemens Medical Solutions, Knoxville TN, United States); and (2) Discovery LS (GE Medical Systems, Milwaukee, WI, United States) according to the standard procedure as previously detailed[31].

Image interpretation
Each 18F-FDG-PET/CT and 18F-NaF-PET/CT scan were independently evaluated by two nuclear medicine physicians aware of the patient's clinical history but blinded to the results of the other PET/CT scan and that of other cross-sectional morphological imaging modalities [magnetic resonance imaging (MRI)/CT]. In cases of disagreement,a consensus obtained among readers was used for the final decision. For both 18F-NaF and 18F-FDG PET/CT, scans were interpreted as negative for bone lesions when no pathologic tracer uptake was present within the skeleton. In cases of increased uptake within the joints, the exam was also considered negative. Similarly, for both 18F-NaF and 18F-FDG, avid lesions were diagnosed as benign when degenerative changes or fractures were detected on non-diagnostic CT. Conversely, the presence of focal tracer uptake associated with suspicious or indeterminate morphological changes on non-diagnostic CT were considered as positive. Similarly, for both 18F-NaF and 18F-FDG, high and focal uptake in the absence of lesions on the non-diagnostic CT was considered likely to be "micro-scleroses", and thus classified as positive/malignant.

For each lesion, density on the co-registered CT was recorded and lesions were divided into four groups: Sclerotic, lytic, mixed, and no-lesions. Similarly, lesion localizations were also recorded to assess the impact of the divergent disease sites (skull, spine, ribs, extremities, and pelvis).

Standard references
Since a bone biopsy of all lesions for histology was not considered appropriate for obvious ethical reasons, the radiological and clinical follow-up at 12 mo served as the standard of reference for the final evaluation of the results as true-positive, true-negative, false-positive, and false-negative. Follow-up information included physical examination, laboratory tests, tumor markers,

Table 1 Patient characteristics (*n* = 45)	
Demography	
Age (yr)	61 ± 10
Stage at diagnosis	
I	5
II	21
III	14
IV	5
Histology	
Ductal	35
Lobular	8
Other	2
Tumor receptor (+/-/unknown)	
Estrogen receptor	39/2/4
PgR	29/11/5
c-erb B2	14/24/7
Site of metastatic disease other than bone	
Lung	27%
Liver	20%
Lymph nodes	30%
Systemic therapy	
First-line	81%
Second-line	62%
Third-line	36%
Bisphosphonates	22%
Follow-up (mean 28 mo range 22-39)	
Patients with disease progression	58%
Patients dead from disease	30%

Table 2 Patient-based analysis: Performance comparisons between 2-deoxy-2-(^{18}F)fluoro-D-glucose and ^{18}F-sodium positron emission tomography/computed tomography		
	^{18}F-FDG	**^{18}F-NaF**
Sensitivity (%)	75.00 (55.10-88.00)	91.67 (74.15-97.68)
Specificity (%)	99.00 (84.54-100)	76.19 (54.91-89.37)
Positive predictive value (%)	99.00 (82.41-100)	81.48 (63.3 91.82)
Negative predictive value (%)	77.78 (59.24-89.39)	88.89 (67.2-96.90)
Error rate (%)	13.33 (6.26-26.18)	15.56 (7.75-28.78)
Accuracy (%)	86.67 (73.82-93.74)	84.44 (71.22-92.25)
Youden's index	0.75 (0.75-0.74)	0.6786 (0.68-0.6718)

Estimated parameters corresponding to each technique are presented with 95%CI between square brackets. ^{18}F-FDG: 2-deoxy-2-(^{18}F)fluoro-D-glucose; ^{18}F-NaF: ^{18}F-sodium.

The two imaging methods were significantly different in the patient-based analysis, with an accuracy of 86.7% and 84.4%, respectively (McNemar's χ^2 = 6.23, df = 1, *P* = 0.01.). See Table 2 for details on sensitivity, specificity, and predictive values of the two PET/CT modalities.

Overall lesion-based analysis
Overall, 244 bone lesions were detected in our analysis. The overall accuracy of the two methods was significantly different in the lesion-based analysis (McNemar's χ^2 = 93.4, df = 1, *P* < 0.0001). ^{18}F-NaF showed high sensitivity (90.5%), but a very low specificity (17.5%). By contrast, although ^{18}F-FDG PET/CT showed a lower sensitivity (66%), it was characterized by a significantly higher specificity (96.2%).

Lesion density- and site-based analysis
Significant differences were highlighted in the lesion density- and site- based analysis, as ^{18}F-FDG PET/CT was more accurate in the detection of CT-negative metastasis (*P* < 0.002), vertebral localizations (*P* < 0.002), and sclerotic (*P* < 0.005) and rib lesions (*P* < 0.04). No significant differences were highlighted with respect to accuracy in evaluating lytic and mixed lesions, or in lesions localized in the skull, distal extremities or pelvis. See Table 3 for details on sensitivity, specificity, and accuracy. Figures 1-3 show representative examples of the different performance of the two imaging modalities.

Impact on patient management
Findings that were found only in ^{18}F-NaF PET/CT imaging led to a change of management for 3 of the 45 patients (6.6%). In particular, two patients underwent chemotherapy rather than targeted radiotherapy due to the detection of further skeletal lesions. One patient was excluded from surgical treatment of lung metastasis due to the presence of bone involvement.

DISCUSSION
In this study, we aimed to elucidate the role of ^{18}F-FDG and ^{18}F-NaF PET/CT in restaging breast cancer patients

and other independent imaging studies (CT, MRI, ^{18}F-FDG PET/CT, X-ray studies, and bone scans).

Statistical analysis
For statistical analysis we used the "R" software program[32] and DiagnosisMed software package[33]. We compared ^{18}F-NaF PET/CT and ^{18}F-FDG PET/CT results through patient-, lesion density-, and site-based analyses.

Cochran *Q* test followed by multiple comparisons using McNemar's test with continuity correction and Bonferroni adjustment were used in order to assess differences among imaging modalities. *P* values less than 0.05 were considered statistically significant. The impact of adding ^{18}F-NaF PET/CT to the work-up of patients was also measured in terms of changes to their management due to findings related to this functional imaging.

The statistical methods of this study were reviewed by a biomedical statistician.

RESULTS
Overall diagnostic accuracy and patient-based analysis
Sixteen patients were negative and 16 patients were positive at both imaging modalities. Eleven and two patients were positive only at a single tracer (^{18}F-FDG and ^{18}F-NaF, respectively). Histology was used as standard references in two patients (specifically in one patient who was true positive for bone marrow involvement at ^{18}F-FDG PET and in one patient who was true positive for the presence of an osteosclerotic lesion in the ribs detected by ^{18}F-NaF only).
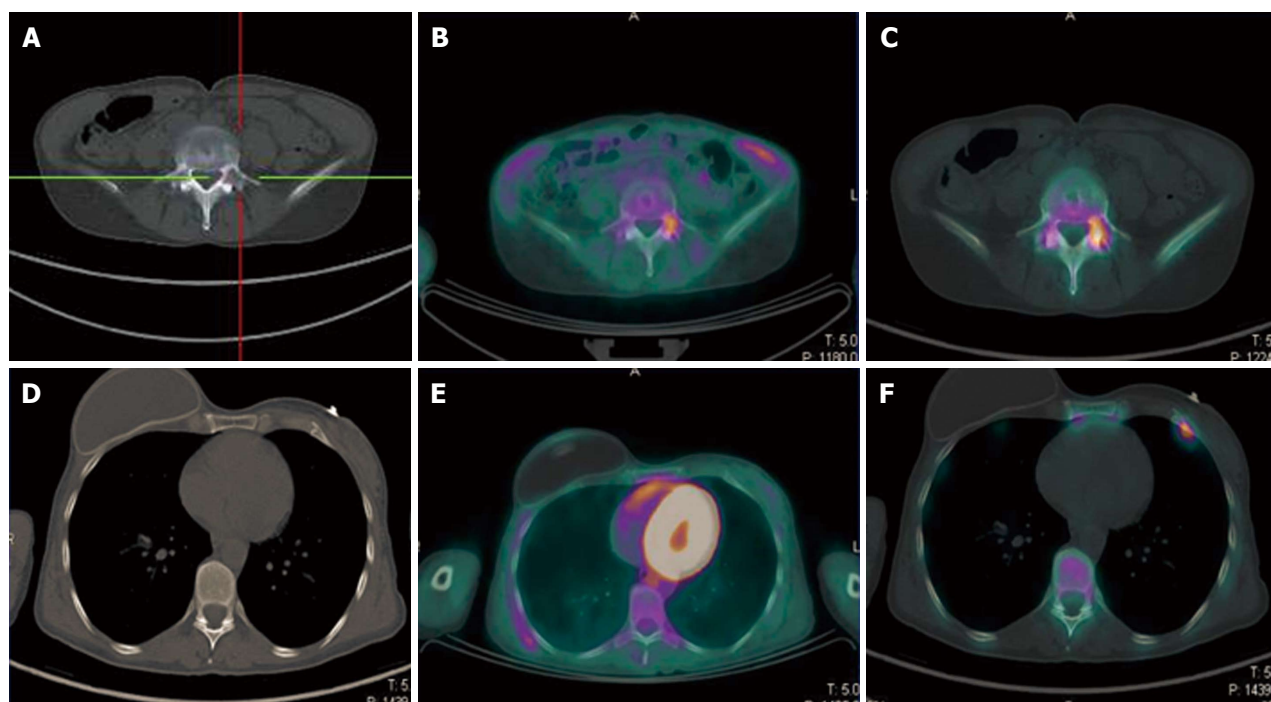
Figure 1 A 49-year-old breast cancer patient with bone relapse. A lytic lesion on the fifth lumbar vertebra was detected with computed tomography in absence of local pain (A). The lesion showed high uptake both at ^{18}F-FDG PET/CT (B) and ^{18}F-NaF PET/CT (C), thus confirming its malignant nature. No further ^{18}F-FDG avid metastasis was highlighted (E). By contrast a focal area of high ^{18}F-NaF uptake was evident in the anterior branch of the seventh rib on the left side (F). This area was indeed corresponding to a small sclerotic indeterminate lesion on the CT and was considered as a further site of disease (D). The patient started systemic therapy rather than a targeted radiotherapy on the fifth lumbar vertebra. ^{18}F-FDG: 2-deoxy-2-(^{18}F)fluoro-D-glucose; ^{18}F-NaF: ^{18}F-sodium; PET/CT: Positron emission tomography/computed tomography.

Table 3 Sites and density characteristics showing different performance between 2-deoxy-2-(^{18}F)fluoro-D-glucose and ^{18}F-sodium positron emission tomography/computed tomography

	n	^{18}F-FDG	^{18}F-NaF	P
Density				
Osteosclerotic	89			0.005
Sensitivity (%):		42.86 (15.82-74.95)	99.00 (64.57-99.00)	
Specificity (%):		97.00 (60.97-97.00)	48.15 (35.39-61.15)	
No lesion/bone marrow	29			0.002
Sensitivity(%):		100.00 (60.97-100.00)	48.15 (30.74-66.01)	
Specificity(%):		100.00 (34.24-100.00)	100.00 (34.24-100.00)	
Site				
Spine	81			0.002
Sensitivity (%):		65.38 (51.80-76.85)	100.00 (93.12-100.00)	
Specificity (%):		98.00 (88.30-98.00)	13.45 (0.61-27.18)	
Ribs	118			0.04
Sensitivity (%):		83.96 (75.81-89.74)	96.23 (90.70-98.52)	
Specificity (%):		78.37 (52.33-92.50)	78.57 (52.41-92.43)	

^{18}F-FDG: 2-deoxy-2-(^{18}F)fluoro-D-glucose; ^{18}F-NaF: ^{18}F-sodium.

with bone lesions by means of patient-, density-, and site-based analyses.

Slight, but significant, differences were highlighted between ^{18}F-FDG and ^{18}F-NaF in the patient-based analysis, with the former showing higher specificity and the latter being characterized by higher sensitivity. These differences were more markedly evident at the lesion-based analysis, where ^{18}F-FDG showed higher accuracy for detecting CT-negative (likely bone marrow confined)

metastasis and lesions located in the spine, while ^{18}F-NaF PET/CT performed better with respect to osteosclerotic and rib lesions. Our results support the view that, when a functional method is needed, information derived by ^{18}F-FDG can correctly classify most breast cancer patients with suspected or known bone metastasis. However, the lesion-based analysis highlighted significant differences between the two imaging methods, which emphasize the different complementary information provided by
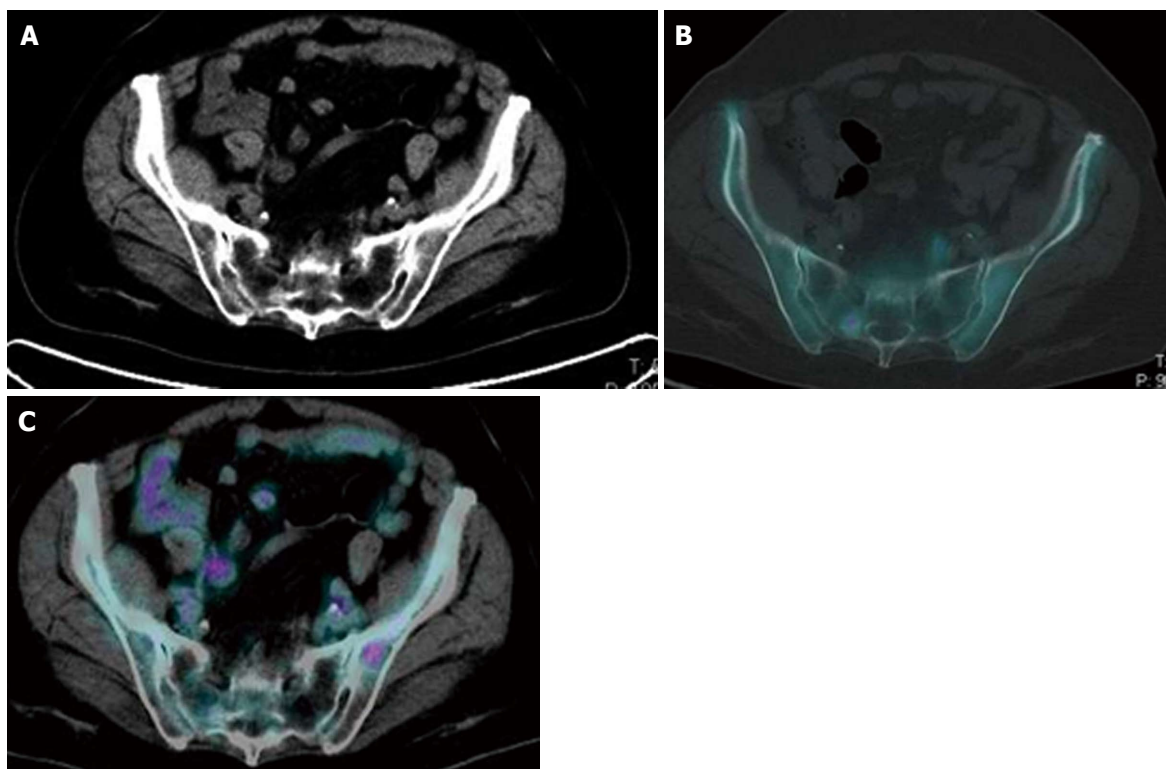
Figure 2 Evidence of the complementary features of 2-deoxy-2-(18F)fluoro-D-glucose and 18F-sodium positron emission tomography/computed tomography in the pelvis of the same breast cancer patient. An 18F-NaF avid sclerotic lesion was detected in the right sacrum in absence of significant 18F-FDG uptake. By contrast high uptake of 18F-FDG was present in a small lytic lesion in the left iliac bone. Due to the absence of a significant local bone reaction, this small lesion did not show any uptake of 18F-NaF. Both lesions corresponded to metastatic sites of disease and disappeared after chemotherapy. 18F-FDG: 2-deoxy-2-(18F)fluoro-D-glucose; 18F-NaF: 18F-sodium; PET/CT: Positron emission tomography/computed tomography.
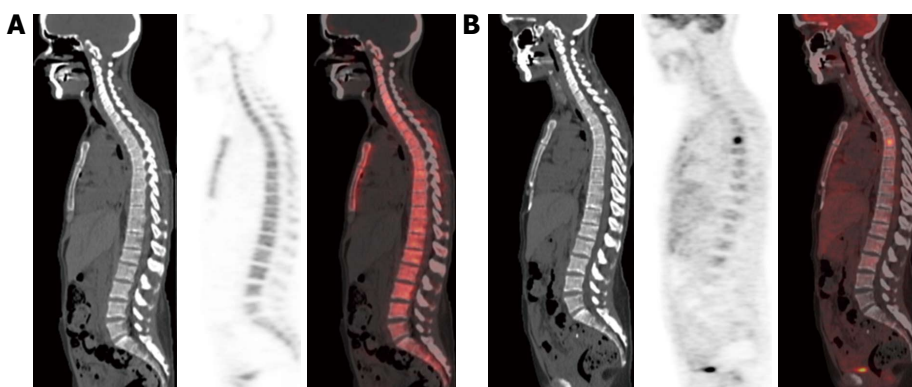

Figure 3 This area is likely to correspond to a bone marrow-confined metastasis not yet characterized by bone remodeling and thus falsely negative in both multidetector computed tomography and 18F-sodium positron emission tomography/computed tomography. No structural lesions or area of 18F-NaF uptake are evident in the vertebral column of this breast cancer patient (A); by contrast an area of high focal 18F-FDG uptake was present in the sixth dorsal vertebra (B). 18F-NaF: 18F-sodium; 18F-FDG: 2-deoxy-2-(18F)fluoro-D-glucose.

the two tracers. In fact, these data fit with the different distribution mechanisms of the two tracers into bone metastases. More specifically, 18F-FDG accumulates into viable, metabolically-active tumor cells[34,35], while 18F-NaF is incorporated into bone crystals within the forming fluorapatite matrix, and thus tends to preferentially accumulate at sites of actively mineralizing bone[36,37]. Osseous metastases seed into the red bone marrow rather than the cortical bone, and this might explain the extremely high accuracy of 18F-FDG PET in detecting metastases confined in the bone marrow, especially at an earlier stage before the occurrence of bone reaction[38,39]. Accordingly, it has been suggested that 18F-FDG PET/CT can be assensitive as magnetic resonance imaging in this setting[40,41]. The relatively poor cellularity that may characterize sclerotic metastases, with relatively smaller volumes of tumor tissue in individual lesions, may influence the degree of 18F-FDG uptake given the small number of elements able to trap it[42].

These findings are thus coherent with the fact

that ^{18}F-FDG uptake is more specific for malignant lesions than bone metabolism tracers, while ^{18}F-NaF is characterized by an extremely high sensitivity, rather than specificity, for both sclerotic and lytic lesions[43]. Surprisingly, both radiotracers showed high accuracy in the detection of lytic localizations, and no differences were highlighted between the accuracy of ^{18}F-FDG or ^{18}F-NaF in the evaluation of this type of lesion. Previous studies compared the accuracy of ^{18}F-FDG PET/CT and BS with respect to lytic lesions and found that ^{18}F-FDG PET/CT is superior to BS in this setting[42,44]. Accordingly, the present findings support the concept that, although ^{18}F-NaF and BS highlight the same pathophysiological mechanisms (increased osteoblastic activity), the greater spatial resolution of PET accounts for the better diagnostic accuracy of ^{18}F-NaF with respect to BS[24,43,45]. In fact, thanks to its better spatial resolution, this tracer is even capable of capturing the increased mineral metabolism related to the thin reactive border that may surround a lytic lesion. By contrast, this subtle reaction is generally too small to be detected by the limited spatial resolution of BS. However, it must be underlined that the extremely high sensitivity of ^{18}F-NaF PET/CT in the detection of both lytic and sclerotic metastases is paralleled by a relatively low specificity[30].

This behavior might represent an important limitation in the use of ^{18}F-NaF PET and strongly advise in favor of the use of hybrid PET/CT imaging, thus increasing the specificity of ^{18}F-NaF PET thanks to the CT-based characterization of bone remodeling (i.e., exclusion of clearly degenerative lesions)[31].

Significant differences between the two tracers were also found in the site-based analysis. In particular, the ^{18}F-FDG results were more accurate in detecting lesions located in the spine, while ^{18}F-NaF provided a more accurate characterization of rib lesions. This could be related to the different structural modification induced by metastases as a function of their anatomical localization. Small lesions in the ribs can show an intense osteoblastic response, even in the presence of poor cellularity, and can therefore be easily identified by means of ^{18}F-NaF[25]. By contrast, the highlighted superiority of ^{18}F-FDG PET in the evaluation of spine lesions can be explained by the fact that many lesions located in the spine were, in this study, characterized by an absence of structural correlates in the co-registered CT. On the other hand, the age of our patient population (mean 60 years) may have also influenced the low accuracy of ^{18}F-NaF for spine lesions. In fact, the presence of areas of non-specific ^{18}F-NaF uptake due to age-related degenerative changes may partially explain the relatively lower accuracy of ^{18}F-NaF in this site. This finding is in line with the notion that ^{18}F-NaF is more accurate than BS, especially for evaluating vertebral localizations[46]. In fact, thanks to the greater resolution and fusion with CT, ^{18}F-NaF can reduce the number off alse positive/indeterminate findings due to degenerative lesions. Although ^{18}F-FDG can also be influenced by degenerative changes, the intensity and focality of these uptakes are lower with respect to bone metastasis; the glucose analogue is thus superior to both bone metabolism tracers in this setting.

Finally, when the specific influence of ^{18}F-NaF was evaluated with respect to patient management, we found that adding ^{18}F-NaF PET to patient work-up led to a change in management in 3 out of 45 patients, due to it revealing metastases undetected by ^{18}F-FDG scan. These findings may underline that the extremely high sensitivity of ^{18}F-NaF uptake can be useful in evaluating patients who are candidates for regional therapy (i.e., surgery or radiotherapy) with the aim of excluding patients with further occult metastases.

The present study has some limitations. It is a two center, retrospective study whose results may have been influenced by its patient population's high pre-test probability of bone metastasis. Although the number of included patients was relatively small, it was comparable, or even higher, with respect to similar studies on the impact of different functional imaging techniques in breast cancer patients with bone metastasis[47,48]. Histological confirmation of metastases was not obtained in the majority of patients, for both practical and ethical reasons. A clinical, biochemical, and radiological follow-up of 12 mo was used as the standard of reference. Obviously, 12-mo follow-up findings might not be sufficient to exhaustively depict disease status. However, sclerotic and/or lytic bone lesions on CT are mostly accepted as metastases[49,50]. Additionally, in many other studies, clinical biopsy was performed only in a minority of patients and comparative imaging modalities were used as standard in order to assess metastatic bone involvement[51].

In conclusion, ^{18}F-FDG PET/CT is a reliable imaging tool in the detection of bone metastasis in most cases, with a high diagnostic accuracy and superior specificity with respect to ^{18}F-NaF PET/CT in the general population of breast cancer patients. However, the extremely high sensitivity of ^{18}F-NaF PET/CT can exploit its diagnostic potential in specific clinical settings, such as small CT-evident sclerotic lesions, possibly changing patient staging or management. Similarly, given the hereby proven complementary role of the two tracers, breast cancer patients could be candidates for ^{18}F-NaF when, despite negative results in ^{18}F-FDG and other imaging methods, they have suggestive clinical and biochemical sign of disease. Therefore ^{18}F-NaF PET/CT emerges as a powerful "second-line" functional imaging tool, which may be of use in selected patients on the basis of their specific clinical history, in order to identify a priori in those patients in which ^{18}F-NaF PET/CT may significantly impact their management.

COMMENTS

Background
Early detection of bone metastases is of pivotal importance in breast cancer patients. To this purpose, besides conventional bone scintigraphy, positron emission tomography has become an established imaging modality, with better spatial resolution and superior image quality. Among positron emission tomography (PET) tracers, 2-deoxy-2-(^{18}F)fluoro-D-glucose (^{18}F-FDG)

represents the most widely used tracer in clinical routine, and can provide information about the presence or absence of disease in the skeleton, as well as in non-skeletal districts. However, characterization of bone metastases is also possible with ^{18}F-sodium fluoride (^{18}F-NaF). In this context, it has not yet been clearly investigated whether ^{18}F-NaF PET/computed tomography (CT) can provide incremental information concerning breast cancer patients that have already been evaluated by means of FDG PET/CT.

Research frontiers
To date, controversial results have been reported about the accuracy of the two PET tracers in breast cancer patients,with some authors even proposing their combined use. This work aims to clarify whether, at least in specific conditions, these two tracers could be complementary in order to improve diagnostic accuracy in bone lesion characterization.

Innovations and breakthroughs
This work aims to compare the role of ^{18}F-FDG and ^{18}F-NaF PET/CT in re-staging breast cancer patients with bone lesions through patient-, lesion density-, and site-based analyses. A more prompt and accurate characterization of bone alterations could lead to more accurate patient management.

Applications
Besides ^{18}F-FDG, ^{18}F-NaF PET/CT emerges as a powerful "second-line" functional imaging tool, which may be useful in selected patients on the basis of their specific clinical history.

Terminology
Glucose analogue ^{18}F-FDG PET enables the detection of neoplastic lesions on the basis of their increased glucose metabolism directly reflecting tumor cell viability, thereby allowing forthe characterization of skeletal and extra-skeletal lesions. On the other hand, ^{18}F-NaF reflects the increased regional blood flow and osteoblastic bone reaction being irreversibly incorporated into the bone matrix as fluorapatite.

Peer-review
An agreement on which is the best PET tracer in the characterization of bone lesions has not been yet been reached. In this study, the authors compared ^{18}F-FDG and ^{18}F-NaF PET/CT accuracy in the restaging of breast cancer patients. They observed that, despite ^{18}F-FDG PET/CT possibly being considered the most reliable tool in the general population of breast cancer patients, it can exploit its diagnostic potential in specific clinical settings. These results were interesting and provided important information concerning the most appropriate management of breast cancer patients with suspected bone metastases.

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