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

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Institutional review board statement: The Internal Review Board (Comitato Etico Regionale della Liguria) evaluated and approved this retrospective study.

Informed consent statement: All study participants, or their legal guardians, provided informed written consent prior to study enrollment. We did not report any details that might disclose the identity of the subjects under study.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: No additional data are available.

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Received: May 28, 2015
Peer-review started: May 31, 2015
First decision: September 18, 2015
Revised: October 23, 2015
Accepted: December 9, 2015
Abstract

AIM: To compare 2-deoxy-2-(18F)fluoro-D-glucose (18F-FDG) and 18F-sodium (18F-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 18F-FDG and 18F-fluoride-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 χ² 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 18F-NaF PET/CT to the work-up of patients was also measured in terms of change in their management due to 18F-NaF PET/CT findings.

RESULTS: The two imaging methods of 18F-FDG and 18F-fluoride-CT were significantly different at the patient-based analysis: Accuracy was 86.7% and 84.4%, respectively (McNemar’s χ² = 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 χ² = 93.4, df = 1, P < 0.0001). In the lesion density-based and site-based analysis, 18F-FDG PET/CT provided more accurate results in the detection of CT-negative metastasis (P < 0.002) and vertebral localizations (P < 0.002); 18F-NaF PET/CT was more accurate in detecting sclerotic (P < 0.005) and rib lesions (P < 0.04). 18F-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 18F-FDG PET/CT.

CONCLUSION: 18F-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 18F-NaF PET/CT in the general population of breast cancer patients. However, the extremely high sensitivity of 18F-fluoride-CT can exploit its diagnostic potential in specific clinical settings (i.e., small CT-evident sclerotic lesions, high clinical suspicious of relapse, and negative 18F-FDG PET and conventional imaging).

Key words: 18F-sodium positron emission tomography/computed tomography; Breast cancer; Bone lesion; 2-deoxy-2-(18F)fluoro-D-glucose

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INTRODUCTION

Breast cancer is the most prevalent form of cancer in women of Western countries[4,5], with the skeleton being the most common site of distant metastases. Presence, distribution, and type of bone localizations have relevant prognostic implications[3,5]. 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[6].

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-(18F)fluoro-D-glucose (18F-FDG) has become the most widely used in clinical routine, resulting in a major impact on the practice of oncology[6]. In breast cancer patients, 18F-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 $^{18}$F-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 $^{18}$F-sodium fluoride ($^{18}$F-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 $^{18}$F-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 $^{18}$F-FDG and $^{18}$F-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, $^{18}$F-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 has been clearly investigated whether $^{18}$F-NaF PET/CT can provide incremental information for the management of breast cancer patients that have already been evaluated by means of $^{18}$F-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. 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 receive 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 $^{18}$F-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 $^{18}$F-FDG-PET/CT and $^{18}$F-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 $^{18}$F-NaF and $^{18}$F-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 $^{18}$F-NaF and $^{18}$F-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 $^{18}$F-NaF and $^{18}$F-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,
and other independent imaging studies (CT, MRI, \(^{18}\text{F}\)-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 \(^{18}\text{F}\)-NaF PET/CT and \(^{18}\text{F}\)-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 \(^{18}\text{F}\)-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 (\(^{18}\text{F}\)-FDG and \(^{18}\text{F}\)-NaF, respectively). Histology was used as standard references in two patients (specifically in one patient who was true positive for bone marrow involvement at \(^{18}\text{F}\)-FDG PET and in one patient who was true positive for the presence of an osteosclerotic lesion in the ribs detected by \(^{18}\text{F}\)-NaF only).

**DISCUSSION**

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

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

<table>
<thead>
<tr>
<th>Site</th>
<th>n</th>
<th>$^{18}$F-FDG</th>
<th>$^{18}$F-NaF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosclerotic</td>
<td>89</td>
<td>42.86 (15.82-74.95)</td>
<td>99.00 (64.57-99.00)</td>
<td>0.005</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td></td>
<td>97.00 (60.97-97.00)</td>
<td>48.15 (35.39-61.15)</td>
<td></td>
</tr>
<tr>
<td>Specificity (%)</td>
<td></td>
<td>100.00 (60.97-100.00)</td>
<td>48.15 (30.74-66.01)</td>
<td></td>
</tr>
<tr>
<td>No lesion/bone marrow</td>
<td>29</td>
<td>100.00 (60.97-100.00)</td>
<td>100.00 (34.24-100.00)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td></td>
<td>100.00 (60.97-100.00)</td>
<td>100.00 (34.24-100.00)</td>
<td></td>
</tr>
<tr>
<td>Specificity (%)</td>
<td></td>
<td>100.00 (34.24-100.00)</td>
<td>100.00 (34.24-100.00)</td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>81</td>
<td>65.38 (51.80-76.85)</td>
<td>100.00 (93.12-100.00)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td></td>
<td>98.00 (88.30-98.00)</td>
<td>13.45 (6.61-27.18)</td>
<td></td>
</tr>
<tr>
<td>Specificity (%)</td>
<td></td>
<td>83.96 (75.81-89.74)</td>
<td>96.23 (90.70-98.52)</td>
<td></td>
</tr>
<tr>
<td>Ribs</td>
<td>118</td>
<td>78.37 (52.33-92.50)</td>
<td>78.57 (52.41-92.43)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

$^{18}$F-FDG: 2-deoxy-2-($^{18}$F)fluoro-D-glucose; $^{18}$F-NaF: $^{18}$F-sodium.
the two tracers. In fact, these data fit with the different distribution mechanisms of the two tracers into bone metastases. More specifically, $^{18}$F-FDG accumulates into viable, metabolically-active tumor cells,[34,35] while $^{18}$F-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 $^{18}$F-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 $^{18}$F-FDG PET/CT can be as sensitive 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 $^{18}$F-FDG uptake given the small number of elements able to trap it.[42].

These findings are thus coherent with the fact
that 18F-FDG uptake is more specific for malignant lesions than bone metabolism tracers, while 18F-NaF is characterized by an extremely high sensitivity, rather than specificity, for both sclerotic and lytic lesions\textsuperscript{[43]}\textsuperscript{[43]}. Surprisingly, both radiotracers showed high accuracy in the detection of lytic localizations, and no differences were highlighted between the accuracy of 18F-FDG or 18F-NaF in the evaluation of this type of lesion. Previous studies compared the accuracy of 18F-FDG PET/CT and BS with respect to lytic lesions and found that 18F-FDG PET/CT is superior to BS in this setting\textsuperscript{[42,44]}\textsuperscript{[44]}. Accordingly, the present findings support the concept that, although 18F-NaF and BS highlight the same pathophysiological mechanisms (increased osteoblastic activity), the greater spatial resolution of PET accounts for the better diagnostic accuracy of 18F-NaF with respect to BS\textsuperscript{[44,43,43]}\textsuperscript{[44]}. 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 18F-NaF PET/CT in the detection of both lytic and sclerotic metastases is paralleled by a relatively low specificity\textsuperscript{[30]}\textsuperscript{[30]}. This behavior might represent an important limitation in the use of 18F-NaF PET and strongly advise in favor of the use of hybrid PET/CT imaging, thus increasing the specificity of 18F-NaF PET thanks to the CT-based characterization of bone remodeling (i.e., exclusion of clearly degenerative lesions)\textsuperscript{[31]}.\textsuperscript{[31]}

Significant differences between the two tracers were also found in the site-based analysis. In particular, the 18F-FDG results were more accurate in detecting lesions located in the spine, while 18F-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 18F-NaF\textsuperscript{[25]}.\textsuperscript{[25]} By contrast, the highlighted superiority of 18F-FDG PET in the evaluation of spine lesions can be explained by the fact that many lesions located in the spine, 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 18F-NaF for spine lesions. In fact, the presence of areas of non-specific 18F-NaF uptake due to age-related degenerative changes may partially explain the relatively lower accuracy of 18F-NaF in this site. This finding is in line with the notion that 18F-NaF is more accurate than BS, especially for evaluating vertebral localizations\textsuperscript{[46]}\textsuperscript{[46]}. In fact, thanks to the greater resolution and fusion with CT, 18F-NaF can reduce the number off also positive/indeterminate findings due to degenerative lesions. Although 18F-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 18F-NaF was evaluated with respect to patient management, we found that adding 18F-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 18F-FDG scan. These findings may underlie that the extremely high sensitivity of 18F-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\textsuperscript{[47,48]}\textsuperscript{[47]}. 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\textsuperscript{[49,50]}\textsuperscript{[49]}. 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\textsuperscript{[51]}.\textsuperscript{[51]}

In conclusion, 18F-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 18F-NaF PET/CT in the general population of breast cancer patients. However, the extremely high sensitivity of 18F-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 18F-NaF when, despite negative results in 18F-FDG and other imaging methods, they have suggestive clinical and biochemical sign of disease. Therefore 18F-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 18F-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-(18F)fluoro-D-glucose (18F-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 diagnosed 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 restaging 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 for the 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 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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