

Superiority of 18F-FNa PET/CT for Detecting Bone Metastases in Comparison with Other Diagnostic Imaging Modalities



Superioridade da PET/CT com FNa-F18 na Detecção de Metástases Ósseas quando Comparada com Outros Métodos de Diagnóstico por Imagem

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Acta Med Port 2017 Jan;30(1):53-60 • <http://dx.doi.org/10.20344/amp.7818>

ABSTRACT

Introduction: The 18F-NaF positron emission tomography/computed tomography is being considered as an excellent imaging modality for bone metastases detection. This ability was compared with other imaging techniques.

Material and Methods: We retrospectively evaluated 114 patients who underwent 18F-NaF positron emission tomography/computed tomography. Of these, 49 patients also had bone scintigraphy, 61 18F-FDG positron emission tomography/computed tomography and 10 18F-FCH positron emission tomography/computed tomography. We identified the technique that detected the largest number of bone metastases. For the detection of skeletal metastases with the 18F-NaF positron emission tomography/computed tomography study, the contribution of the positron emission tomography component was compared with the contribution of the computed tomography component. Cases in which 18F-NaF positron emission tomography/computed tomography and bone scintigraphy required further additional tests for diagnosis clarification were registered.

Results: The 18F-NaF positron emission tomography/computed tomography was superior to bone scintigraphy in 49% of the patients ($p < 0.001$); it was superior to 18F-FDG positron emission tomography/computed tomography in 59% of the patients ($p < 0.001$) and it was superior to 18F-FCH positron emission tomography/computed tomography in 40% of the patients ($p < 0.001$). None of the compared imaging techniques were superior to 18F-NaF positron emission tomography/computed tomography. The positron emission tomography component was superior to computed tomography in 35% of the cases ($p < 0.001$). Further investigation was suggested in only 3.5% of patients who underwent 18F-NaF positron emission tomography/computed tomography (45% for bone scintigraphy) ($p < 0.001$).

Discussion: As with other authors, our experience also confirms that 18F-NaF positron emission tomography/computed tomography is an excellent imaging modality for the detection of bone metastases, detecting lesions in more patients and more lesions per patient.

Conclusion: The 18F-NaF positron emission tomography/computed tomography showed a superior ability for the detection of bone metastases when compared with bone scintigraphy, 18F-FDG positron emission tomography/computed tomography and 18F-FCH positron emission tomography/computed tomography.

Keywords: Bone Neoplasms/diagnostic imaging; Bone Neoplasms/secondary Fluorodeoxyglucose F18; Positron-Emission Tomography; Radionuclide Imaging

RESUMO

Introdução: A tomografia por emissão de positrões/tomografia computadorizada - FNa-F18 vem sendo considerada como uma modalidade imagiológica com vantagens na pesquisa de metastização óssea. Comparámos a sua capacidade para deteção de metástases ósseas com a de outras técnicas imagiológicas.

Material e Métodos: Avaliámos retrospectivamente 114 doentes que realizaram tomografia por emissão de positrões/tomografia computadorizada - FNa-F18. Destes, 49 realizaram também cintigrafia óssea, 61 tomografia por emissão de positrões/tomografia computadorizada - FDG-F18 e 10 tomografia por emissão de positrões/tomografia computadorizada - FCH-F18. Identificámos a técnica que detetou um maior número de metástases ósseas. Comparámos ainda a tomografia por emissão de positrões com a componente tomografia computadorizada da tomografia por emissão de positrões/tomografia computadorizada - FNa-F18. Registámos as situações nas quais a tomografia por emissão de positrões/tomografia computadorizada FNa-F18 e a cintigrafia óssea necessitaram de exames adicionais para esclarecimento complementar.

Resultados: A tomografia por emissão de positrões/tomografia computadorizada - FNa-F18 foi superior à cintigrafia óssea em 49% dos doentes ($p < 0,001$); foi superior à tomografia por emissão de positrões/tomografia computadorizada - FDG-F18 em 59% dos doentes ($p < 0,001$) e foi superior à tomografia por emissão de positrões/tomografia computadorizada - FCH-F18 em 40% dos doentes ($p < 0,001$). Nenhuma das técnicas imagiológicas avaliadas lhe foi superior. Na tomografia por emissão de positrões/tomografia computadorizada - FNa-F18 a componente tomografia por emissão de positrões foi superior à tomografia computadorizada em 35% dos casos ($p < 0,001$). Foi sugerida investigação complementar em apenas 3,5% dos doentes que realizaram tomografia por emissão de positrões/tomografia computadorizada - FNa-F18 (45% para a cintigrafia óssea) ($p < 0,001$).

Discussão: Em conformidade com o referido por outros autores, a nossa experiência confirma que a tomografia por emissão de positrões/tomografia computadorizada - FNa-F18 tem excelente desempenho na deteção de metástases ósseas, sendo capaz de identificar

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Recebido: 03 de maio de 2016 - Aceite: 13 de setembro de 2016 | Copyright © Ordem dos Médicos 2017



lesões em mais doentes, e em maior número, quando comparada com outras técnicas imagiológicas.

Conclusão: A tomografia por emissão de positrões/tomografia computadorizada - FNa-F18 revelou superioridade na deteção de metástases ósseas comparativamente à cintigrafia óssea, à tomografia por emissão de positrões/tomografia computadorizada - FDG-F18 e à tomografia por emissão de positrões/tomografia computadorizada - FCH-F18.

Palavras-chave: Cintigrafia; Neoplasias Ósseas/diagnóstico por imagem; Neoplasias Ósseas/secundário; Tomografia por Emissão de Positrões

INTRODUCTION

Malignant bone involvement affects 30-70% of cancer patients, with breast cancer as the leading cause in women and prostate cancer in men, followed by lung cancer in both genders.^{1,2} Bone metastases are classified as lytic, with an aggressive and rapid-growth behaviour or blastic, with a slower course and each tumour follows a trend towards showing a specific type of lesion. Early diagnosis is crucial as bone involvement leads to relevant symptoms and complications, with a relevant impact in staging, therapeutic approach, outcome and patient's quality of life.¹

Plain radiography (XR), computed tomography (CT), magnetic resonance imaging (MRI), 99m-Tc bone scintigraphy (BS) and positron emission tomography / computed tomography (PET/CT) scan are imaging modalities with the capability for the assessment of bone metastases.^{2,3} XR is no longer recommended due to its low sensitivity. An estimated 30-75% reduction in bone density is required so that a bone metastasis may be visualized in XR. CT has a higher sensitivity when compared to XR, even though a significant reduction in bone density is still needed; for this reason, it is not recommended for an early detection of bone metastases, apart from showing low sensitivity for the identification of intramedullary lesions. MRI allows for the early detection of intramedullary lesions, although with a lower sensitivity for the detection of cortical metastases when compared to CT.³ BS has been recommended as the first choice for the detection of bone metastases and it has been estimated that it can detect malignant bone lesions approximately 2 to 18 months earlier than CT. However, radiotracer uptake in BS occurs in areas of increased osteoblast activity, allowing for the identification of blastic metastases; the presence of osteolytic metastases is therefore an important cause for false negative results. In addition, benign conditions with increased bone turnover such as fractures or degenerative and inflammatory diseases of the bone are an important cause for false positive results.² BS is a highly sensitive test for the identification of osteoblastic metastases located at the peripheral skeleton and low sensitive for the spine and the pelvis, showing an extremely low specificity.⁴ Sensitivity and specificity have been increased to values slightly over 90% with the use of single-photon emission computed tomography (SPECT) and mainly SPECT/CT. Unlike PET/CT, SPECT/CT is not a whole-body scan and those values are only obtained within each body section under assessment.⁵

PET/CT imaging has been increasingly used for the identification of malignant bone involvement, using different radiotracers as biomarkers for different molecular behaviours of these lesions, as for instance 18F-fluorodeoxyglucose (18F-FDG), which is used for the identification of areas with

an increased glycolytic activity, mapping tumour's specific characteristics using 18F-fluoromethylcholine (18F-FCH) for the identification of an increased choline uptake by prostate carcinoma cells and somatostatin analogues in neuroendocrine tumours⁶ as well as the 18F-sodium fluoride (18F-NaF) for the identification of areas with an increased osteoblast activity.⁷

This study aimed at showing a higher detection capability of 18F-NaF PET/CT imaging when compared to BS, 18F-FDG PET/CT and 18F-FCH PET/CT for the identification of skeletal abnormalities consistent with malignant bone involvement and requiring less additional diagnostic tests when compared to BS.

Finally, it also aimed at showing a higher detection capability of the molecular component of PET vs. smart dose CT (sdCT) imaging component of hybrid 18F-NaF PET/CT scanning technique.

MATERIAL AND METHODS

Population and methodology

In total, 114 patients (65 female, mean age 62 ± 10, range 16-82) underwent 18F-NaF PET/CT imaging for the identification of malignant bone involvement between March 2009 and March 2016 and clinical records were analysed, including 58 (51%) patients diagnosed with breast carcinoma, 41 (36%) with prostate carcinoma, eight (7%) with lung carcinoma and seven (6%) with other clinical conditions (two patients with suspicious CT images of bone metastases of unknown primary origin, one with paraneoplastic syndrome, one with colon carcinoma, one with bladder carcinoma, one with pyriform sinus carcinoma and one diagnosed with a sarcoma).

All the patients underwent other nuclear medicine testing over a 6-month period of time, also considered due to its detection capability of malignant bone involvement (BS, 18F-FDG PET/CT and 18F-FCH PET/CT) and with an indication for the different clinical situations and no significant clinical or laboratorial change occurred over that period of time, nor any modification in management occurred. 18F-NaF PET/CT imaging was compared to each of these imaging modalities. Those considered as positive for the presence of secondary malignant bone involvement were recorded and the percentages of positive results were compared. The performance of the different imaging techniques was also assessed, regarding the identification of the highest number of lesions per patient.

Out of the 114 patients who underwent 18F-NaF PET/CT imaging, 49 also underwent BS. Mean (± SD) length of time between both tests was 68 ± 62 (2 - 176) days. In this subgroup of 49 patients, 32 (65.3%) were diagnosed with

breast carcinoma, 10 (20.5%) with prostate carcinoma, six (12.2%) with lung carcinoma and one (2%) with suspicious CT images of bone metastases from an unknown-origin tumour.

Out of the 114 patients who underwent 18F-NaF PET/CT, 61 also underwent 18F-FDG PET/CT. Mean (\pm SD) length of time between both tests was 35 ± 50 (1 - 181) days. In this subgroup of 61 patients, 49 (80.4%) were diagnosed with breast carcinoma, six (10%) with lung carcinoma, one (1.6%) with colon carcinoma, one (1.6%) showed suspicious CT images of bone metastases of an unknown primary origin, one (1.6%) with paraneoplastic syndrome, one (1.6%) with piriform sinus carcinoma, one (1.6%) with bladder carcinoma and one (1.6%) diagnosed with a sarcoma.

Out of the 114 patients who underwent 18F-NaF PET/CT, 10 patients with prostate carcinoma also underwent 18F-FCH PET/CT. Mean (\pm SD) length of time between both tests was 44 ± 70 (3 - 181) days.

PET imaging results in the 114 patients who underwent the 18F-NaF PET/CT were compared to sdCT images and the detection capability of malignant bone involvement regarding each physiological imaging component of the hybrid technique (molecular vs. morphological) was assessed.

Clinical situations in which additional tests were suggested for further diagnosis clarification in the 49 patients who underwent BS and in the 114 patients who underwent 18F-NaF PET/CT imaging were recorded.

18F-NaF PET/CT protocol

All the patients with an indication for 18F-NaF PET/CT imaging were previously informed about the aims and procedures of the test and a written informed consent has been obtained.

The acquisition protocol of the test involved whole-body images obtained 60 minutes upon the intravenous administration of 370 MBq of 18F-NaF. The patients were placed lying in dorsal decubitus position with the arms extended by the sides in a GE PET/CT Discovery ST scanner. The following CT acquisition parameters for attenuation correction and anatomical mapping were used: 120 kV, smart mA: noise index of 35 with current values ranging between 10 - 200 mA, pitch 1.5:1, rotation 0.5 s and 3.75 mm slice thickness. A 3D PET emission test was obtained with a 70 cm field of view (FOW) diameter and a 3 minute emission duration per each table position. Data were collected in list mode and were reconstructed using an ordered subset expectation maximization (OSEM) iterative 3D reconstruction algorithm with 20 subsets per each two iterations, 128 x 128 matrix and a post-reconstruction full width at half maximum (FWHM) 5mm filter.

18F-NaF PET/CT image interpretation

18F-NaF PET/CT images were consensually interpreted by two nuclear medicine specialists previously knowing patient's clinical records and with access to the available lab

and imaging tests.

A semi-quantitative analysis was made by obtaining the value of maximum standardized uptake (SUV_{max}) for each lesion. SUV_{max} determination was based on the creation of a volume of interest encompassing the lesion and was considered as an indicator of the intensity of tracer uptake by the lesions.

Malignant bone involvement was diagnosed based on the intensity of 18F-NaF uptake and on CT tomodensitometric characteristics.

An abnormal 18F-NaF uptake with an intensity over the one obtained in normal skeleton suggested the presence of malignant bone involvement. Structural characterisation and anatomical location of the lesions was obtained by the CT imaging component and allowed for the identification of any benign pathology, such as an inflammatory or degenerative articular disorder as well as other benign situations involving an increased osteoblast activity.

Statistical analysis

SPSS (version 23) was used and a p -value <0.05 was considered as significant for all the tests. Quantitative values were expressed as mean \pm standard deviation (SD) and qualitative as n (%). McNemar test was used for the comparison between positive results of the tests and binomial test was used for the performance assessment. Chi-square test was used for the comparison between 18F-NaF PET/CT and BS as well as for any additional testing required for diagnosis clarification.

RESULTS

The frequency of positive results for the presence of malignant bone involvement was obtained for each subgroup of patients and the comparative assessment of the results was obtained. The reference to the technique with the highest performance for the identification of the highest number of lesions consistent with bone metastases was also recorded.

18F-NaF PET/CT versus bone scintigraphy

18F-NaF PET/CT showed positive findings of the presence of malignant bone involvement in 33 (67%) patients and negative in 16 (33%) out of the 49 patients in the subgroup of those having undergone 18F-NaF PET/CT and BS. Positive BS findings were found in 28 (57%) patients, negative in 16 (33%) and equivocal in five (10%). Even though more positive findings with 18F-NaF PET/CT were found when compared to BS, no statistically significant differences were found ($p = 0.063$). 18F-NaF PET/CT and BS showed overlapping performances in 25 (51%) of the patients and the former showed higher performance in 24 (49%) patients, in whom a higher number of lesions were identified. A higher number of lesions were detected by 18F-NaF PET/CT imaging in a significantly higher percentage of patients when compared to BS ($p < 0.001$). These results are shown in Table 1.

Table 1 - 18F-NaF PET/CT imaging versus Bone Scintigraphy (49 patients)

Imaging Technique	Positive n (%)	Negative n (%)	Equivocal n (%)	Overlapping Performance	Higher Performance
18F-NaF PET/CT	33 (67%)	16 (33%)	0 (0%)	25 (51%)	24 (49%)
Bone scintigraphy	28 (57%)	16 (33%)	5 (10%)	25 (51%)	0 (0%)

Table 2 - 18F-NaF PET/CT imaging versus 18F-FDG PET/CT (61 patients)

Imaging Technique	Positive n (%)	Negative n (%)	Equivocal n (%)	Overlapping Performance	Higher Performance
18F-NaF PET/CT	41 (67%)	20 (33%)	0 (0%)	25 (41%)	36 (59%)
18F-FDG PET/CT	27 (44%)	33 (54%)	1 (2%)	25 (41%)	0 (0%)

Tabela 3 - PET/CT com FNa-F18 versus PET/CT com FCH-F18 (10 doentes)

Imaging Technique	Positive n (%)	Negative n (%)	Equivocal n (%)	Overlapping Performance	Higher Performance
18F-NaF PET/CT	5 (50%)	5 (50%)	0 (0%)	6 (60%)	4 (40%)
18F-FCH PET/CT	2 (20%)	7 (70%)	1 (10%)	6 (60%)	0 (0%)

18F-NaF PET/CT versus 18F-FDG PET/CT

18F-NaF PET/CT showed positive findings of the presence of malignant bone involvement in 41 (67%) patients and negative in 20 (33%) out of the 61 patients in the subgroup of those having undergone 18F-NaF PET/CT and 18F-FDG PET/CT. Positive 18F-FDG PET/CT findings were found in 27 (44%), negative in 33 (54%) and equivocal in one (2%) patient. 18F-NaF PET/CT showed significantly higher performance when compared to 18F-FDG PET/CT ($p < 0.001$).

18F-NaF PET/CT and 18F-FDG PET/CT showed overlapping performances in 25 (41%) and the former showed higher performance in 36 (59%) patients. A higher number of lesions were detected by 18F-NaF PET/CT in a significantly higher percentage of patients when compared to 18F-FDG PET/CT ($p < 0.001$). These results are shown in Table 2.

18F-NaF PET/CT versus 18F-FCH PET/CT

18F-NaF PET/CT showed positive findings of the presence of malignant bone involvement in five (50%) patients and negative in five (50%) out of the 10 patients in the subgroup of those having undergone 18F-NaF PET/CT and the 18F-FCH PET/CT. Positive 18F-FCH PET/CT findings were found in two (20%), negative in seven (70%) and equivocal in one (10%) patient. 18F-NaF PET/CT showed higher performance when compared to 18F-FCH PET/CT, with no statistically significant differences ($p < 0.250$) in a group of only 10 patients.

18F-NaF PET/CT and 18F-FCH PET/CT showed overlapping performances in six (60%) and the former showed higher performance in four (40%) patients. A higher number of lesions was found in 18F-NaF PET/CT in a significantly higher number of patients when compared to 18F-FCH PET/CT ($p < 0.001$). These results are shown in Table 3.

PET molecular component versus CT morphological component

Positive findings of the presence of malignant bone involvement were found with 18F-NaF PET/CT molecular component in 64/114 (56%) patients, negative in 49/114 (43%) and equivocal in 1/114 (1%). Positive findings were found with sdCT component in 48/114 (42%) and negative in 66/114 (58%) patients. Significantly higher positive findings were shown with 18F-NaF PET/CT when compared to sdCT imaging ($p < 0.001$).

PET and sdCT components showed an overlapping performance in 74/114 (65%) of the patients and the former showed higher performance in 40/114 (35%). A higher number of lesions was found in PET in a significantly higher number of patients when compared to sdCT component ($p < 0.001$).

None of the imaging techniques showed higher performance in our group of patients when compared to the 18F-NaF PET/CT as regards the number of lesions detected per patient.

Different clinical situations showing higher detection capability of 18F-NaF PET/CT when compared to BS and to sdCT, 18F-FDG PET/CT and 18F-FCH PET/CT are shown in Fig 1, 2 and 3, respectively.

Additional diagnosis clarification requirement was described in 22/49 (45%) patients who underwent BS and in only 4/114 (3.5%) patients who underwent 18F-NaF PET/CT imaging, which was a significant difference ($p < 0.001$).

DISCUSSION

18F-NaF is available for PET imaging of the skeleton. It was first used in 1962 even though it had a limited use due to the technical characteristics of the detection equipment available at the time. With the emergence of PET devices, the 18F-NaF tracer was reintroduced into the clinical practice and its use for the detection of malignant bone involvement is still under evaluation,⁸ sharing the uptake mechanism with the agents used for BS. After diffusion through capillaries into the bone tissue, fluoride ions exchange with hydroxyl groups in hydroxyapatite crystals of bone producing fluorapatite which is deposited at the surface of bone where

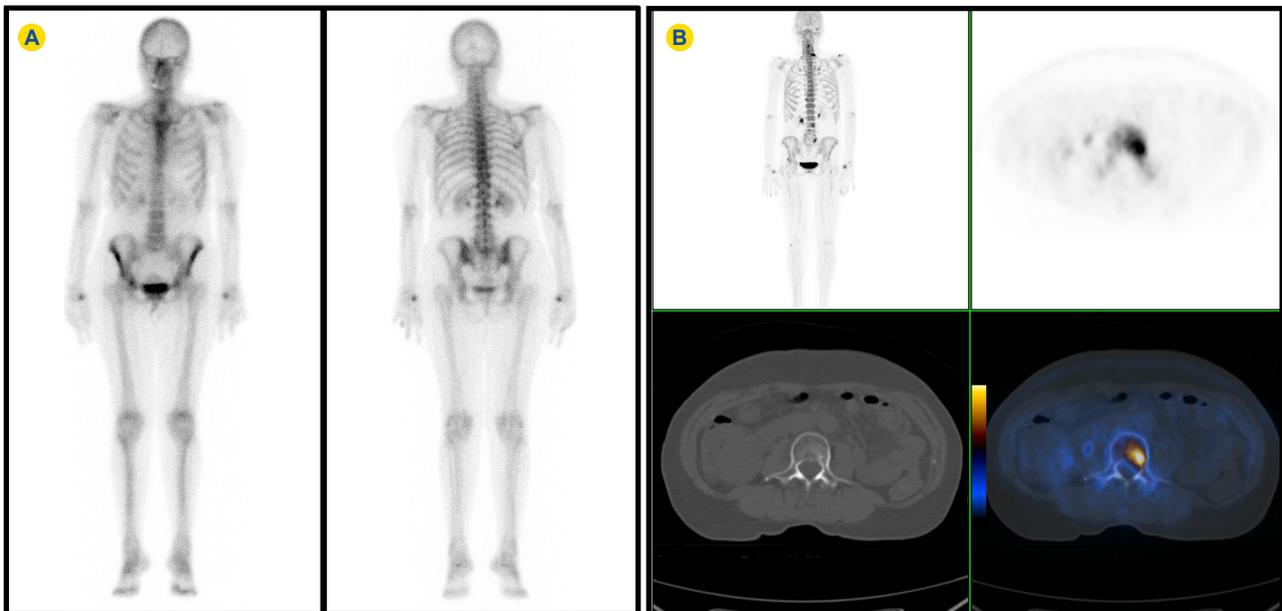


Figure 1 - Patient with breast carcinoma treated 10 years ago, showing elevated levels of the tumour marker and 18F-FDG PET/CT imaging showing no evidence of the disease. Bone scintigraphy (A) did not show any abnormalities and abnormal images were found in the 18F-NaF PET/CT imaging (B) suggesting the presence of bone metastases affecting the spine and the ribs, with no abnormalities in CT imaging component.

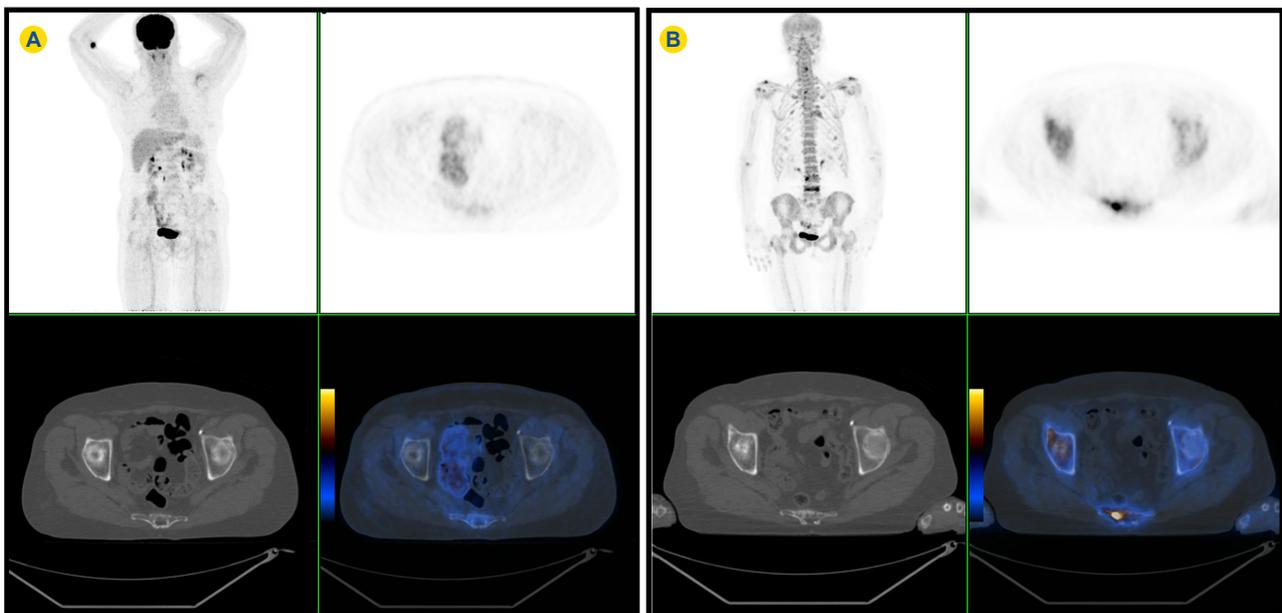


Figure 2 - Patient with a breast carcinoma treated 6 years ago, showing elevated levels of the tumour marker. 18F-FDG PET/CT imaging showing no suspicious abnormality (A) and 18F-NaF PET/CT imaging showing multiple bone metastases (B).

turnover and remodelling is greatest.⁹ 18F-NaF PET/CT is advantageous when compared to BS due to procedure and tracer's better characteristics. PET/CT imaging is technically helpful due to the fact that it is a tomographic and hybrid imaging modality, with higher sensitivity and spatial resolution when compared to planar BS, even when additional SPECT or SPECT/CT slice images are obtained. 18F-NaF has advantageous pharmacokinetic characteristics due to its negligible plasmatic protein binding unlike diphosphonates and to faster and almost complete blood clearance. In addition, bone uptake is two to three times higher. These characteristics allow for better quality

images, with increased lesion-to-background and lesion-to-normal bone tissue ratios.¹⁰ 18F-NaF and diphosphonate dosimetry is similar and the excess absorbed dose due to CT has been considered as negligible. The new technologies associated to PET, such as time of flight (TOF) allowed for the administration of lower activity concentrations, approximately half of those usually used, corresponding to similar or even lower doses to those involved in BS.¹¹ Total time of acquisition in 18F-NaF PET/CT imaging is lower than in BS, leading to improved patient convenience.¹² Comparative studies have shown that 18F-NaF PET/CT vs. BS allows for earlier detection of malignant

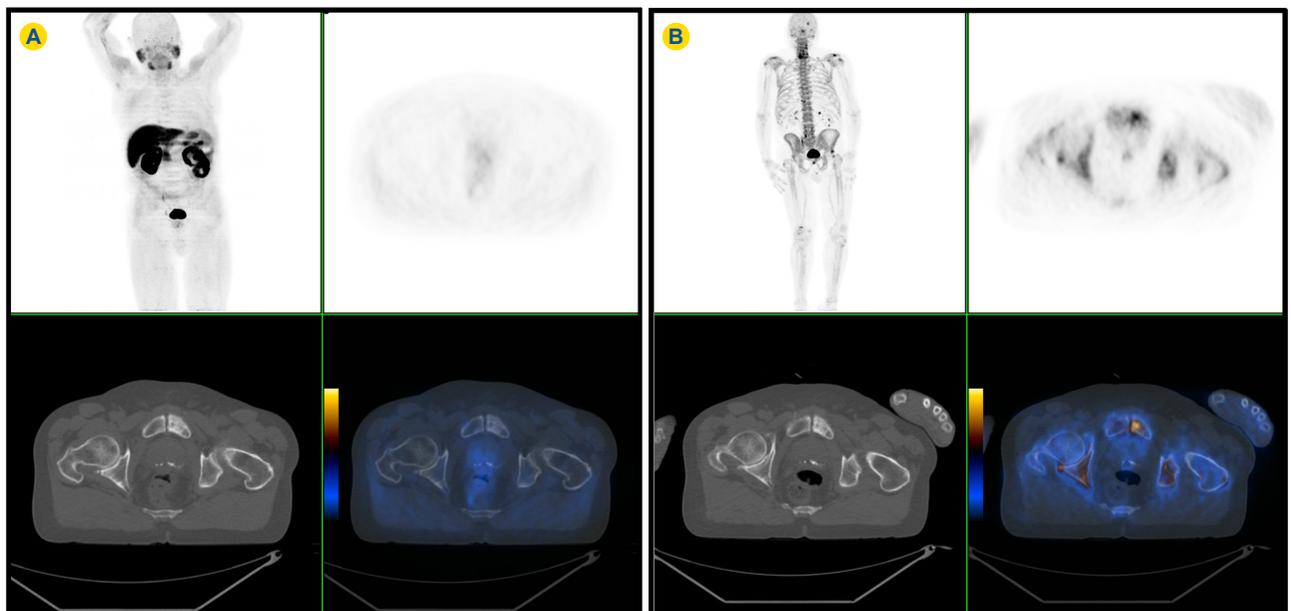


Figure 3 - Patient with a prostate carcinoma in biochemical recurrence. PET/CT with FCH-F18 with no suspicious abnormalities (A) and PET/CT with FNa-F18 suggestive of bone metastasis in the basin and skull (B).

bone involvement,¹³ with higher sensitivity, acuity and reliability.¹⁴⁻¹⁶ The lack of any histological gold standard for every bone lesion was a limitation to this study and therefore the characteristics of sensitivity, specificity and diagnostic acuity of the compared techniques were not assessed. The presence of an undetermined number of false positive and false negative results has been considered with any of the techniques included in the study. Some studies have found values of sensitivity and specificity close to 100% with 18F-NaF PET/CT imaging and have considered this imaging modality as first-choice for the detection of malignant bone involvement,^{16,17} with a high specificity due to the fact that CT component of PET/CT imaging has a contribution to the differentiation of benign lesions from bone metastases, morphologically defining any functional abnormalities¹⁰ and allowing for staging optimization as well as for the selection of the best management at the most adequate timing¹⁸ and being more efficient for monitoring treatment response,¹⁹ with a better impact on the approach to cancer patients with bone involvement.^{20,21}

According to our experience, 18F-NaF PET/CT imaging also showed higher detection capability when compared to BS (in 49% of the patients) in a more assertive way, requiring less additional tests for diagnosis clarification (3.5% vs. 45%); this may represent another advantage of 18F-NaF PET/CT imaging to be confirmed with larger studies and including cost-effectiveness analysis.

18F-FDG PET/CT imaging allows for the simultaneous detection of malignant skeletal and extra-skeletal involvement, corresponding to an advantage for the overall assessment of cancer patients. There is a current agreement that 18F-FDG PET/CT has significantly higher sensitivity when compared to BS for the detection of lytic and intra-medullary bone involvement.²² Different comparative studies involving 18F-FDG PET/CT, CT, MRI

and BS found that 18F-FDG PET/CT and whole-body MRI had similar diagnostic performance and both showed significantly higher performance when compared to CT and BS.^{2,23} Even though 18F-FDG PET/CT imaging has shown high sensitivity for the detection of osteolytic metastases, it showed low sensitivity for the detection of osteoblastic metastases²⁴ and even lower for the detection of skull lesions, due to the physiological brain activity.²⁵ An imaging technique as 18F-NaF PET/CT, capable of identifying both types of malignant bone involvement is therefore advantageous.²⁶ 18F-NaF PET/CT imaging allows for the identification of osteoblastic metastases and indirectly of osteolytic metastases, showing even the minimal osteoblastic reaction produced in the surrounding healthy bone by this type of metastasis. However, it is recognized that 18F-FDG PET/CT imaging has a higher impact on the outcome due to the identification of osteolytic metastases, more aggressive and with higher metabolic activity, associated with poorer outcome, with lower average and overall disease-free survival times.²⁷ Igaru *et al.* carried out a prospective pilot study in which the assessment capability of the extension of bone disease with 18F-NaF PET/CT imaging was compared to BS, 18F-FDG PET/CT and whole-body MRI and found that 18F-NaF PET/CT has a higher performance than any other technique.²⁸ A meta-analysis of 20 studies involving 1,170 patients compared the diagnostic performance of 18F-NaF PET/CT imaging vs. BS and 18F-FDG PET/CT and also found that 18F-NaF PET/CT has an excellent diagnostic capability for the detection of malignant bone involvement and showed higher diagnostic performance when compared to BS and 18F-FDG PET/CT.²⁹ In this study, we also found a higher detection capability of 18F-NaF PET/CT vs. 18F-FDG PET/CT (in 59% of the patients).

18F-NaF PET/CT imaging also showed a higher

detection capability vs. 18F-FCH PET/CT (in 40% of the patients) in our small group of patients with prostate carcinoma. Our results were in line with other studies describing higher specificity values with 18F-FCH PET/CT for the detection of malignant bone involvement associated with prostate carcinoma, even though with lower sensitivity when compared to 18F-NaF PET/CT.³⁰ However, the additional detection capability of extra-skeletal involvement, namely lymph node involvement, is an acknowledged advantage of 18F-FCH PET/CT vs. 18F-NaF PET/CT.

We were also able to find abnormal findings in PET imaging component that were not shown in CT component (in 35% of the patients), explaining for an acknowledged earlier detection capability of PET when compared to CT.³

This study aimed at giving a contribution to the reflection on the best methodology for the identification of malignant bone involvement. Current guidelines still consider BS as gold standard even though the higher detection capability of 18F-NaF PET/CT imaging has been increasingly described in literature.^{20,31} With the widespread use of PET/CT scanners and the optimization of 18F-NaF distribution, it is expectable that it will gradually replace BS in clinical practice, not only in cancer patients¹⁸ but also in patients with benign skeletal pathologies.^{25,32}

Limitations of the study included: a) the fact that this was a retrospective study; b) the length of time between the different imaging tests, even though acceptable in most cases and possible significant clinical impact having been discarded, was above what would be desirable in some patients; c) even though the imaging findings were considered according to patient's clinical and laboratorial context, there was no histological confirmation of the lesions consistent with malignant bone involvement – this was not feasible nor ethical. Therefore, the presence of an undetermined number of false positive and false negative results for any of the techniques has been assumed; d) an heterogeneous group of pathologies were included in the study, leading to different types of bone metastases (blastic, lytic, mixed) with different levels of detection capability by the different techniques; e) the subgroup of patients in whom

18F-NaF PET/CT and 18F-FCH PET/CT imaging were compared corresponded to a small number of patients; f) finally, CT scan was obtained with no intravenous contrast, with optimized acquisition parameters (smart dose) for PET/CT although not usually used in standard CT scan.

CONCLUSION

In our group of patients, a high number of abnormal findings were shown by 18F-NaF PET/CT imaging which were still not shown in CT imaging component. When compared to BS, it showed higher detection capability of lesions consistent with malignant bone involvement and requiring less additional tests for diagnosis clarification. In addition, a higher performance was found, when compared to 18F-FDG PET/CT and 18F-FCH PET/CT. These results explain for the use of 18F-NaF PET/CT imaging as gold standard for the detection of malignant bone involvement. However, this indication needs further confirmation with prospective studies designed for each pathology and including cost-effectiveness analysis.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

FINANCIAL SUPPORT

The authors declare that there was no financial support in writing this manuscript.

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