

Prevalence of exclusive lower extremity metastases at $^{18}\text{F-NaF}$ PET/CT*

Prevalência de metástases exclusivas em membros inferiores em exames de PET/TC com $^{18}\text{F-NaF}$

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Abstract Objective: To evaluate the prevalence of exclusive lower extremity metastases, specifically in the femur and below the knee, observed at $^{18}\text{F-NaF}$ PET/CT.

Materials and Methods: One thousand consecutive PET/CT studies were retrospectively evaluated for the presence of exclusive uptake in lower extremities suggesting metastatic involvement. The presumptive diagnoses based on such uptakes were subsequently obtained by evaluation of other imaging studies.

Results: No exclusive uptake suggestive of metastasis below the femur was observed in the present series. Exclusive uptake was observed in the proximal femur with a presumptive diagnosis of metastasis in two patients.

Conclusion: The prevalence of exclusive metastasis below the femur is low and scanning from head to knees is appropriate in most cases.

Keywords: PET/CT; $^{18}\text{F-NaF}$; Scintigraphy; Bone; Metastasis.

Resumo Objetivo: Avaliar a prevalência de metástases exclusivas em membros inferiores, subdivididas em lesões femorais e abaixo dos joelhos, em exames de PET/TC com $^{18}\text{F-NaF}$.

Materiais e Métodos: Mil exames consecutivos foram retrospectivamente avaliados para a presença de captações exclusivas em membros inferiores sugestivas de comprometimento metastático. Os diagnósticos presuntivos dessas captações foram posteriormente obtidos pela avaliação de outros exames realizados.

Resultados: Não foram observadas captações exclusivas sugestivas de metástases abaixo dos fêmures na nossa casuística. Foi observada captação exclusiva no terço superior do fêmur com diagnóstico de metástase em dois pacientes.

Conclusão: A prevalência de metástase exclusiva abaixo dos fêmures é baixa e a realização do exame da cabeça até os joelhos é adequada na maioria dos casos.

Unitermos: PET/TC; $^{18}\text{F-NaF}$; Cintilografia; Osso; Metástase.

INTRODUCTION

Bone scintigraphy is one of the most utilized nuclear medicine imaging methods, offering the advantages of whole-body assessment at a single scanning session, relatively low cost and high sensitivity^(1–3). Currently, technetium-99m-

methylene diphosphonate ($^{99\text{m}}\text{Tc-MDP}$) is the main radiopharmaceutical utilized in most imaging centers, but other radiopharmaceuticals may be utilized in the assessment of bone alterations. In this context, the increasing utilization of F-18 sodium fluoride is highlighted ($^{18}\text{F-NaF}$)^(2–4).

$^{18}\text{F-NaF}$, a positron emitter whose half life is 110 minutes, was the first tracer utilized for skeleton images acquisition, introduced by Blau et al. in 1962 and approved for clinical utilization by the U.S. Food and Drug Administration in 1972^(5,6). In the mid-1970s, fluoride was replaced by $^{99\text{m}}\text{Tc}$ -polyphosphonate, both due the wider availability of $^{99\text{m}}\text{Mo}/^{99\text{m}}\text{Tc}$ generators and the more appropriate characteristics of $^{99\text{m}}\text{Tc}$ -polyphosphonates for utilization in gamma chambers. The $^{18}\text{F-NaF}$ uptake mechanism is similar to that of $^{99\text{m}}\text{Tc-MDP}$, with $^{18}\text{F-}$ ions exchange with OH- on the surface of the bone hydroxyapatite matrix, but with better

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pharmacokinetic characteristics, including rapid blood clearance and greater fluoride uptake by the bone (about two-fold greater than that of $^{99\text{m}}\text{Tc}$ -MDP), resulting in a better target to non-target ratio in a short time interval^(7,8). The pharmacokinetic superiority of fluoride associated with a higher spatial resolution and higher sensitivity of PET/CT allows for the formation of better quality images as compared with planar scintigraphy and single-photon emission tomography.

In Brazil, ^{18}F -NaF is produced since 2008 by Instituto de Pesquisas Energéticas e Nucleares, and the scan modality has been performed at several Brazilian institutions. Thus, a more appropriate evaluation of the utilization of this technique is indispensable and undoubtedly there is a necessity for definition of the better imaging protocol, in order to reduce costs, allowing for a more rapid dissemination of the method in the country. In the literature, there is no protocol defining the body extent to be studied, so frequently whole-body images are acquired similarly to bone scintigraphy. On the other hand, the investigation of metastases by ^{18}F -FDG PET/CT or with other radiopharmaceuticals is frequently performed only up to the distal portion of the lower limbs because of the low prevalence of exclusive lower extremity tumors in most cases. Due to the short half life of the radiopharmaceutical, the reduction of the acquisition time resulting from the smaller scan extent may imply an increase in the number of scans performed with a same radiopharmaceutical activity and, consequently, a reduction of involved costs.

Objective

To evaluate the prevalence of exclusive lower-extremity metastases, more specifically those below the femur, at ^{18}F -NaF PET/CT.

MATERIALS AND METHODS

One thousand consecutive ^{18}F -NaF PET/CT studies were retrospectively reviewed. The scans were performed in the period from June 2011 to January 2013. The images with

exclusive uptake in lower limbs were initially classified into three categories, as follows: poorly suggestive of metastasis; undefined; suggestive of metastasis. The presumptive diagnoses based on such exclusive peripheral uptakes were later established either by means of evaluation of other studies or by reanalysis of the PET/CT images by a radiologist with experience in musculoskeletal system images. On the basis of such presumptive diagnoses, the patients were divided into two categories, as follows: probably malignant uptake and probably benign uptake. On its turn, probably malignant uptakes were classified into femoral and below-the-femur.

The PET/CT images were acquired in a Discovery GE 690 apparatus. Each patient received a ^{18}F -NaF activity corresponding to 185 MBq (5 mCi) and the acquisitions occurred about 60 minutes after the radiopharmaceutical administration. The 3D time-of-flight whole-body PET images were acquired with one minute per bed position, slice thickness = 15 cm and 3 cm slices overlapping (corresponding to 13 to 15 bed positions, depending on the patient's height). Whole body CT was performed with 120 kVp, 30 mAs, 0.5 second/rotation, pitch = 1.0, and slice thickness = 3.75 mm.

RESULTS

Twenty-six patients presented exclusive lower extremity uptake. In two patients, such uptakes were initially classified as metastases, in 13, as undefined, and in 11, as poorly suggestive of metastasis. Later, one of the cases of exclusive uptakes classified as metastasis in the major trochanter of the right femur (Figure 1A) was classified as probably benign, because pelvic CT image acquired after 15 months demonstrated an area of possible heterotopic calcification in this region (Figure 1B); in the other case classified as metastasis, malignancy located in the right femoral neck was confirmed by magnetic resonance imaging (MRI) (Figure 2) – the patients presented with a lung neoplasm. Amongst the 13 patients with exclusive lower limb uptake classified as undefined, two cases were classified as probably malignant

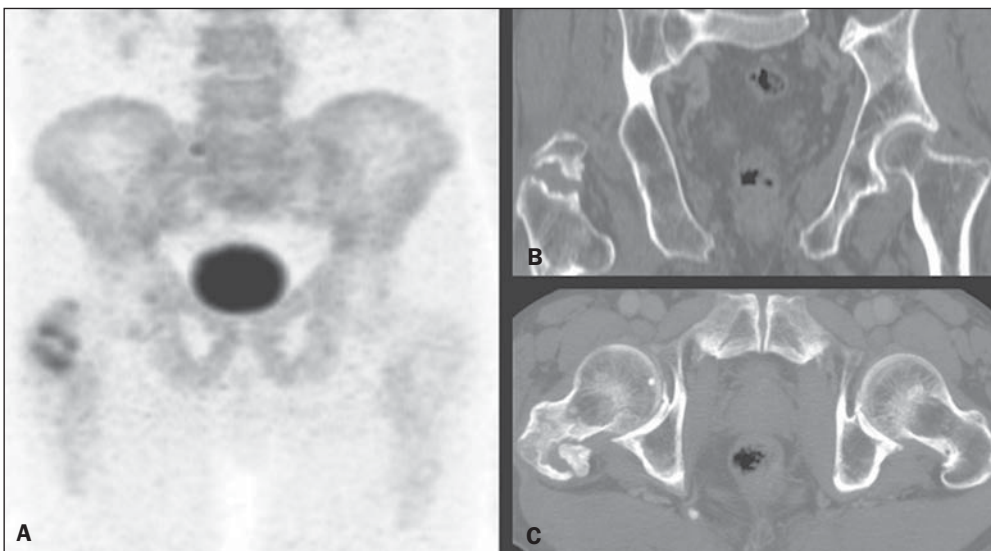


Figure 1. ^{18}F -NaF PET image (A) shows osteogenic reaction in the region of the major trochanter and intertrochanteric sulcus of the right femur, suggesting secondary involvement by the underlying disease. Coronal (B) and axial (C) pelvic CT performed after 15 months revealing possible heterotopic calcification in this region, classified as a probably benign lesion.



Figure 2. Coronal fusion PET/CT (A) and PET (B) with ¹⁸F-NaF show osteogenic reaction at right femoral head and neck, suspicious for bone involvement secondary to the underlying disease. Pelvic MRI coronal section T1-weighted image with fat suppression after intravenous gadolinium injection (C) shows expansile lesion infiltrating the bone marrow of the right femoral head and neck, suggestive of secondary finding. Also a medullary lesion is observed in the femoral diaphysis suspicious for secondary involvement.

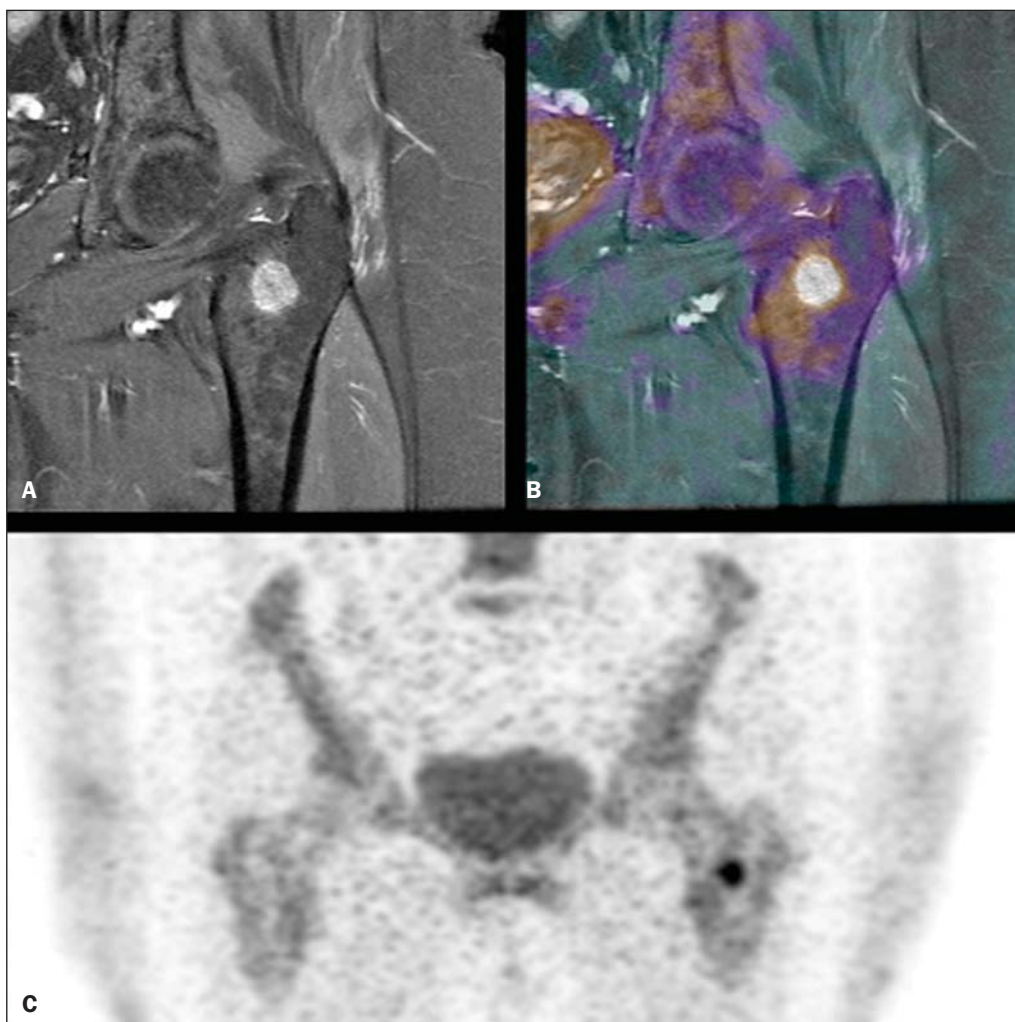


Figure 3. MRI coronal section of left hip – T1-weighted image with fat suppression after intravenous gadolinium injection (A) shows nodular lesion measuring 1.7 cm in the intertrochanteric region. ¹⁸F-NaF PET – coronal section (B) shows focal hyper-uptake in the same region, suspicious for secondary involvement; coronal ¹⁸F-NaF PET and MRI fusion of left hip (C) reveals correspondence of metabolic and anatomic findings.

in the images reanalysis and in the evaluation of other studies. In one of such cases, the uptake was located in the left intertrochanteric region and was considered as suggestive of secondary compromise at MRI (Figure 3) – the patient presented with breast cancer with metastases in the liver and

lung. In the other case, the uptake was located in the distal region of the right femur and the malignancy was confirmed by the PET/CT computed tomography image itself, characterizing bone infiltration by metastasis from melanoma in adjacent soft tissue (Figure 4) – the patient presented with

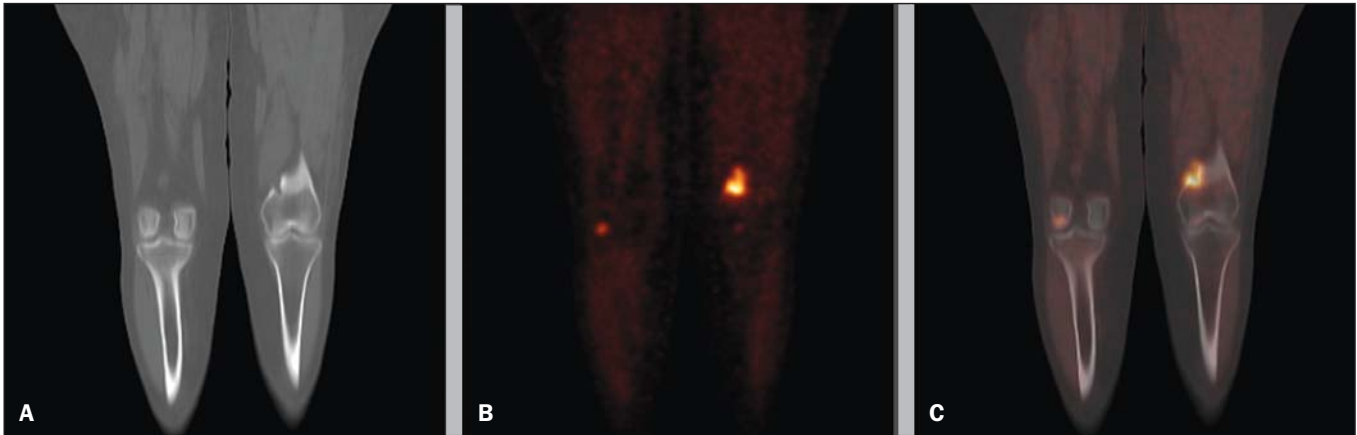


Figure 4. Coronal CT (A), PET (B) and ^{18}F -NaF PET/CT fusion (C) images show osteogenic reaction in the distal metaphyseal region of the left femur, suggestive of metastatic bone infiltration originating from melanoma. Osteogenic reaction of probable osteodegenerative origin is also observed.

multiple nodular areas in soft tissues compatible with involvement by the underlying disease. The other cases of undefined uptake were classified as probably benign by the reanalysis of PET/CT images or by further imaging studies. The 11 cases of uptake originally classified as poorly suggestive of metastasis were classified as benign as follow-up and images reanalysis. Thus, only two out of 1,000 patients presented exclusive lower extremity bone uptake suggesting bone metastasis, both in the proximal third of the femora, and a third patient presented multiple metastases from melanoma in soft tissues, with one of such metastases infiltrating the distal region of the left femur.

DISCUSSION

In spite of the fact that the presence of single metastases in the skeleton is not an uncommon finding, the prevalence of exclusive lower extremity metastasis detected at bone scintigraphy is low^(9,10). Such a prevalence has already been evaluated at scans with $^{99\text{m}}\text{Tc}$ -MDP using a gamma chamber^(9,10), and some case reports describe such finding, that is considered to be rare, principally in cases where the metastasis is located below the femora^(11,12). However, the current protocols for $^{99\text{m}}\text{Tc}$ -MDP bone scintigraphy keep recommending whole-body imaging despite the low prevalence of metastasis in lower extremities^(13,14). With the introduction of ^{18}F -NaF bone scintigraphy performed in a PET/CT apparatus, one has raised the question about the extent of the body segment to be studied, considering that the acquisition of a smaller extent of the body might lead to reduction of the images acquisition time and, consequently, to a higher number of scans to be performed delivering a same radiopharmaceutical activity. In spite of the fact that the Society of Nuclear Medicine protocol on ^{18}F -NaF PET/CT⁽⁸⁾ does not specify the body extent to be assessed, the topic regarding patient's positioning mentions the protocol of that same society on the utilization of ^{18}F -FDG PET/CT, recommending the scanning from the skull base to the root of the thighs⁽¹⁵⁾. Additionally, some services⁽¹⁶⁾ have recommended the scanning to be done from the skull base to the mid thigh, possibly on the basis of

the ^{18}F -FDG PET/TC protocols^(15,17). Despite such a discussion, up to the present moment there is no study in the literature evaluating the prevalence of exclusive bone metastasis in lower extremities, particularly below the femora, detected at ^{18}F -NaF PET/CT. In the present retrospective analysis of 1,000 consecutive scans performed in the authors' institution, only three cases of exclusive bone metastasis in lower extremities were observed, but in one of the patients, the metastasis was actually to soft tissue with extension to the adjacent bone tissue. Thus, in the present series the prevalence of exclusive bone metastasis in lower extremities was of only 0.2%, and the two described metastases occurred in the proximal third of the femora.

Therefore, as demonstrated by previous studies about $^{99\text{m}}\text{Tc}$ -MDP bone scintigraphy^(9,10) and, as confirmed the present results obtained with ^{18}F -NaF PET/CT, the prevalence of exclusive bone metastasis in lower extremities, particularly below the femora, is low, thus the scanning up to the knees might be appropriate in most cases. Such a reduction in the extent of the body to be assessed during scan may reduce the acquisition time in up to about 4 minutes (25%), which implies a higher number of scans to be performed with delivery of a same activity, given the short radiopharmaceutical half life (110 minutes).

Another issue to be taken into consideration in the analysis of the present series is that, although the bone metastases in those two patients were exclusive in lower extremities, in at least one of them this was not the only metastatic site as the patient with breast cancer presented also with lung and liver metastases. Thus, in such a patient the area of bone metastasis is not considered, by definition⁽¹⁸⁾, to be an exclusive metastasis and, therefore, its presence does not change the disease stage. So, as far as the disease stage definition is considered, the imaging of lower extremities could only change such parameter in 0.1% of the patients in the present study.

CONCLUSION

The prevalence of exclusive uptake in lower extremities suggesting metastasis is low, and exclusive bone metastases

predominantly occur in the femora. Thus the ¹⁸F-NaF PET/CT scan on the body segment from the head to the knees is appropriate in most cases where such a scan is requested for investigation of metastases.

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