Original article

Nuclear Medicine Communications

^{18}F-fluoride PET/CT for assessing bone involvement in prostate and breast cancers

Nadia Withofs[a], Benjamin Grayet[b], Tino Tancredi[b], Andrée Rorive[c], Christine Mella[e], Fabrice Giacomelli[e], Frédéric Mievis[e], Joël Aerts[e], David Waltregny[d], Guy Jerusalem[c] and Roland Hustinx[a]

Objective **To evaluate the accuracy of ^{18}F-fluoride PET/computed tomography (CT) to detect bone metastases (BMs) in a breast and prostate cancer population, using magnetic resonance imaging (MRI) or thin-slice CT as a gold standard.**

Methods **We have prospectively included 34 patients with breast ($N=24$) or prostate cancer ($N=10$) at high risk of BMs. Whole-body PET/CT (low-dose CT) and bone scintigraphy (BS) with single photon emission CT were obtained for all 34 patients and the results compared with a radiological gold standard.**

Results **Out of the 386 foci detected by PET/CT, 219 (56.7%) could be verified by CT or MRI. Eighty-six additional foci were detected by BS ($n=46$) or seen only by CT ($n=9$), MRI ($n=23$), or both CT and MRI ($n=8$). The total number of verified lesions was therefore 274 (58.1%), including 119 (43.4%) benign and 155 (56.6%) BM. The sensitivity, specificity, and accuracy of ^{18}F-fluoride PET/CT were 76, 84.2, and 80%, respectively. For BS, they were 44.8, 79.2, and 60%, respectively. Sensitivity significantly decreased for the lytic lesions. The accuracy of PET/CT was significantly superior to BS for pelvic and lumbar lesions. PET/CT provided a correct diagnosis (M+/M0) in 32 of 33 patients (one false positive) compared with 28 of 33 with BS (four false positive, one false positive).**

Conclusion **^{18}F-fluoride PET/CT is significantly more accurate than BS for detecting BMs from breast and prostate cancers.** ***Nucl Med Commun*** **32:168–176 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Nuclear Medicine Communications 2011, **32**:168–176

Keywords: bone metastases, breast cancer, ^{18}F-fluoride, PET/computed tomography, prostate cancer

[a]Division of Nuclear Medicine, [b]Department of Medical Imaging, [c]Division of Medical Oncology, [d]Division of Urology, CHU Liège and [e]Cyclotron Research Center, University of Liège, Liège, Belgium

Correspondence to Dr Roland Hustinx, MD, PhD, Division of Nuclear Medicine, Centre Hospitalier Universitaire de Liège, Sart Tilman B35, Liège I 4000, Belgium
Tel: +32 43667199; fax: +32 43668257;
e-mail: rhustinx@chu.ulg.ac.be

Received 11 July 2010 **Revised** 4 September 2010
Accepted 5 October 2010

Introduction

Prostate and breast cancers are the most common malignancies worldwide, with a high incidence of bone metastases (BMs). Early detection and accurate assessment of bone involvement is needed to optimize treatment and therefore reduce or delay skeletal-related events. Currently, whole-body bone scintigraphy (BS) is only recommended in selected patients at high risk of BM and not for routine breast or prostate cancer surveillance [1,2]. Computed tomography (CT) and magnetic resonance imaging (MRI) are sensitive and specific modalities for the diagnosis of BM, but are limited to an anatomical region [3,4]. MRI is superior to CT for detecting early intramedullary lesions [5]. Newer whole-body techniques of MRI acquisition are promising but are not fully validated for routine clinical use [5]. Compared with conventional imaging, 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) positron emission tomography (PET) seems to exhibit higher specificity and accuracy to detect BM in breast cancer [6]. The results of studies comparing FDG-PET to BS are conflicting but the latter is generally considered the best option for assessing the entire skeleton [7]. In contrast, the contribution of FDG PET in prostate cancer is limited. Indeed, FDG uptake can be low especially in well-differentiated tumors limiting the sensitivity of FDG-PET for the staging or follow-up of prostate cancer [8]. Alternative PET tracers are under investigation for prostate cancer imaging. Recent studies evaluating ^{18}F-choline PET/CT showed promising result for the detection of early prostate cancer BM [9,10].

Blau *et al.* [11] first imaged the skeleton with ^{18}F-fluoride in the early 1960s. ^{18}F-fluoride is easily produced in high specific activity. Its pharmacokinetic properties are superior to those of technetium-99m (^{99m}Tc) methylene diphosphonate (MDP) used for BS resulting in a higher bone uptake and faster blood clearance [12,13]. As current PET systems combine high sensitivity and spatial resolution with reduced acquisition time, ^{18}F-fluoride is being actively re-evaluated. Compared with BS, all studies showed higher sensitivity of ^{18}F-fluoride PET to detect BM, even for lytic lesions [14–18]. Only few data suggest a higher accuracy of PET/CT with ^{18}F-fluoride to detect BM compared with conventional techniques [19,20].

0143-3636 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/MNM.0b013e3283412ef5

The aim of this study was to evaluate, in a population of breast and prostate cancers, the accuracy of ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS for detecting BMs, using full diagnostic CT or MRI as a gold standard (GS).

Methods

Patients

We prospectively included 34 patients with breast ($n = 24$) or prostate ($n = 10$) cancer at a high risk of BM (mean age ± standard deviation: 60.2 ± 12.3 years). The protocol was approved by the ethics committee of our institution and all patients gave informed consent to participate in the study. We included patients with asymptomatic suspect bone lesion on BS (15 female patients) or elevated cancer antigen CA 15-3 greater than or equal to 45 UI/ml ($N = 3$) or prostate-specific antigen greater than 20 ng/ml ($N = 9$) or clinical suspicion of bone involvement (one female; one male). Finally, five breast cancer patients with known BM were included for restaging during treatment (tamoxifen citrate, $N = 2$; aromatase inhibitor, $N = 2$; weekly paclitaxel, $N = 1$).

Twenty-three patients (18 females; five males) were on antihormone therapy before PET/CT imaging and 16 patients with breast cancer received chemotherapy in the course of the disease. Out of these 16 patients who received chemotherapy, one received paclitaxel 15 days before PET/CT, one received neoadjuvant chemotherapy (FEC 100: epirubicin, 5-fluorouracil, and cyclophosphamide) 20 days before PET/CT and 14 received chemotherapy but not recently (median time: 659.5 months; minimum: 20 months; maximum: 1235. 2 months). Ten patients received biphosphonates (oral biphosphonate: five female patients; intravenous zoledronic acid: five female patients administered to all at least 1 month before PET/CT imaging).

^{18}F-fluoride PET/computed tomography

^{18}F-fluoride was prepared by proton irradiation of water enriched in oxygen-18 with an IBA 18/9 cyclotron (Ion Beam Applications, Louvain-La-Neuve, Belgium) using targets made of niobium or silver and windows made of Havar with a usual beam of 30 min. The radioactive solution was then transferred to a GE MX synthesizer (General Electric, Loncin, Belgium) modified to accept a tuned kit that contained all the raw materials needed. After adsorption on an anion exchange resin and washing with water for injection, the ^{18}F-fluoride was eluted with a sterile physiological solution. The solution was then dispensed with sterilizing filtration according to European cyclic GMP. Quality control of the sodium ^{18}F-fluoride solution was done as described in the *European Pharmacopoeia* (01-2008 : 2100). All patients received 300 MBq of ^{18}F-fluoride through an indwelling catheter. We asked the patients to walk and drink 1 l of water during the uptake time of 45–60 min. Thirty-one PET/CT studies were undertaken using a Gemini Dual system (Philips, Cleveland, Ohio, USA), which combines a GSO crystal-based PET and a dual-slice CT scanner. Three were acquired using a Gemini TF (Philips, 16-slice CT). A whole-body low-dose CT acquisition (5 mm slice thickness; tube voltage: 120 kV and tube current–time product: 80 mAs) was followed by a PET scan. PET acquisition time in the Gemini Dual system was 2 min per bed position (pbp) from the skull to the upper thighs and then 1 min pbp to the toes. In the Gemini TF system, it was 1.5 min pbp for the axial skeleton and 1 min for lower limbs. Data were corrected for decay, scatter, random, attenuation and were reconstructed using an iterative three-dimensional row-action maximum likelihood algorithm; CT data were used for attenuation correction.

^{99m}Tc-methylene diphosphonate bone scintigraphy

Whole-body planar BS (PBS) was performed 3–4 h after an injected dose of 1000 MBq ^{99m}Tc-MDP using a double-headed γ-camera (e.cam; Siemens, Erlangen, Germany), fitted with low-energy high-resolution collimators, 1024×256 matrix, acquisition speed of 15 cm/min. Thirty-four single field-of-view (FOV) single-photon emission computed tomography (SPECT) scans were done using the same machine (same collimators, 128/128 matrix, step-and-shoot method with a 180° rotation, non-circular orbit, without zoom, 32 steps of 20 s). Twenty were centered on the thoracic region and 14 on the lumbar spine and pelvis. Data were reconstructed on a Mirage workstation (Segami Corporation, Columbia, USA) using an iterative algorithm (ReSpect).

Computed tomography and MRI

Thin-slice CT images (limited to a region of high ^{18}F-fluoride uptake) were acquired using standard clinical parameters, directly after the PET/low-dose CT on the Gemini Dual system ($N = 39$; maximum three regions per patient) or in the Department of Radiology with a multislice spiral CT ($N = 1$; Siemens Somaton Sensation 16).

Twenty-two MRI were taken using three different systems (Harmony 1 Tesla, Symphony 1.5 Tesla, and Trio 3.0; Siemens). Acquisition sequences were similar for each studied region: T1-weighted sequence [repetition time (TR), 550 ms; echo time (TE), 15 ms; flip angle (FA), 903°], short TI inversion recovery sequences (TR, 4000 ms; TE, 63 ms; FA, 180°) and T1-weighted fat saturation sequences (TR, 550 ms; TE, 15 ms; FA 90°) after an intravenous injection of 20 ml gadolinium.

Image analysis

Two nuclear medicine physicians interpreted whole-body PET/CT images (corrected and not corrected for attenuation). They were not aware of the indication of the PET/CT (symptoms, biological markers, or suspicious lesion on BS). All foci of ^{18}F-fluoride increased uptake were recorded. A radiologist analyzed the low-dose CT

images in parallel. A consensus was then established to classify each lesion as malignant (score 4), most likely malignant (score 3), equivocal (score 2), most likely benign (score 1), or benign (score 0). The radiologist characterized the lytic, sclerotic, or mixed patterns of malignant lesions. The choice of the GS was based on the localization of lesions. When the lesions were localized on the skull, thoracic cage, or long bone, a centered diagnostic CT scan was performed directly after the PET/CT acquisition in the hybrid system. For the vertebral column or the pelvic lesions, an MRI scan was planned in the department of radiology. We did not consider CT or MRI confirmation for joint lesions or lesions located on hands, feet, or knee except when any doubt on malignancy existed. All diagnostic CT scans were taken in the hybrid system directly after the PET/CT except for one acquired 13 days later. The median time interval between PET/CT imaging and MRI acquired in the radiology department was 6 days (range: 0–28 days). A second radiologist independently visualized thin-slice CT and MRI and categorized each lesion as benign or malignant. BS imaging was performed before or after PET/CT with a median time interval of 14 days (range: 1–35 days). An experimented nuclear medicine physician blindly reviewed BS images, the lesion classes being the same as for the PET/CT.

Data analysis

In a lesion-based analysis, we confronted the diagnosis obtained with ^{18}F-fluoride PET/CT and BS with the conclusions of the diagnostic CT or MRI scans. Second, we separated the lesions with regard to their localization: skull and cervical spine, dorsal or lumbar spine, pelvis, thoracic cage, and long bones. In the third analysis, we considered the sclerotic, lytic, or mixed characteristics of metastases.

In a patient-based analysis, we considered the final diagnosis (metastatic or not) of the PET/CT and BS compared with the GS for each patient.

Statistical analysis

Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated at the lesion and patient levels for each PET/CT and BS technique.

We compared the different imaging techniques using the area under the curves obtained with receiver operating characteristic analysis. A P value inferior to 0.05 was considered statistically significant.

The ability of each technique to detect BM was also compared using the McNemar statistical hypothesis tests with a P value of less than 0.05 defined as being statistically significant.

Results

Lesion-based analysis

Three hundred and eighty-six foci of ^{18}F-fluoride increased uptake were detected, and 219 (56.7%) of them were verified by either MRI ($N = 121$) or CT scanning ($N = 76$) or both ($N = 22$). ^{18}F-fluoride PET/CT described 136 BM, 62 benign lesions, and 21 equivocal lesions. There was a total of 274 (58.1%) verified lesions including additional foci detected on BS and verified by a GS ($N = 15$) and lesions seen on CT and/or MRI only ($N = 40$). According to diagnostic CT or MRI, 119 lesions (43.4%) were benign and 155 (56.6%) were BM. Out of 53 breast cancer metastases specified with thin-slice CT, 24 were sclerotic (45.3%), 12 lytic (22.6%), and 17 were mixed (32.1%).

Considering inconclusive lesions as benign, the sensitivity of ^{18}F-fluoride PET/CT and BS was 76 and 44.8%, respectively. Table 1 summarizes the results in the two populations considering an inconclusive lesion as benign or malignant. Specificity for each technique was 84.2 and 79.2%, respectively. Receiver operating characteristic

Table 1 Sensitivity, specificity, PPV, NPV, and accuracy of ^{18}F-fluoride (^{18}F-NaF) PET/CT, ^{99m}Tc-MDP BS with SPECT

Population	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy
^{18}F-NaF PET/CT					
Breast	73.9/81.0	79.3/68.3	86.1/81.6	63.7/67.5	0.76/0.76
Prostate	100.0/100.0	94.7/89.5	85.7/75.0	100.0/100.0	0.96/0.92
Total	76.0/82.5	84.2/75.0	86.0/80.9	73.2/76.9	0.80/0.79
BS					
Breast	43.0/43.0	76.8/70.7	76.3/71.8	43.8/41.7	0.55/0.53
Prostate	66.7/66.7	84.2/81.6	57.1/53.3	88.9/88.6	0.80/0.78
Total	44.8/44.8	79.2/74.2	73.4/69.0	52.8/51.1	0.60/0.58

Inconclusive lesions considered benign/malignant.
BS, bone scintigraphy; CT, computed tomography; MDP, methylene diphosphonate; NPV, negative predictive value; PPV, positive predictive value; SPECT, single photon emission computed tomography.

Table 2 Sensitivity, specificity and accuracy of ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS in the various regions of the skeleton

Region	Sensitivity (%)	Specificity (%)	Accuracy
Skull and cervical spine			
PET/CT	66.7	86.7/80.0	0.83/0.78
BS	33.3	93.3/86.7	0.83/0.78
Dorsal spine			
PET/CT	71.4/74.3	85.0/80.0	0.76/0.76
BS	51.4	90.0/85.0	0.65/0.64
Lumbar spine			
PET/CT	73.1/84.6	82.6/82.6	0.78/0.84
BS	34.6	69.6/60.9	0.51/0.47
Pelvis			
PET/CT	74.1/82.8	68.4/68.4	0.73/0.79
BS	31.0	73.7	0.42
Thorax			
PET/CT	95.5	87.5/81.3	0.92/0.89
BS	81.8	61.9	0.72
Long bones			
PET/CT	63.6/72.7	92.3/61.5	0.84/0.65
BS	45.5	90.5	0.75

Equivocal lesions considered benign/malignant (when it differed).
BS, bone scintigraphy; CT, computed tomography; MDP, methylene diphosphonate.

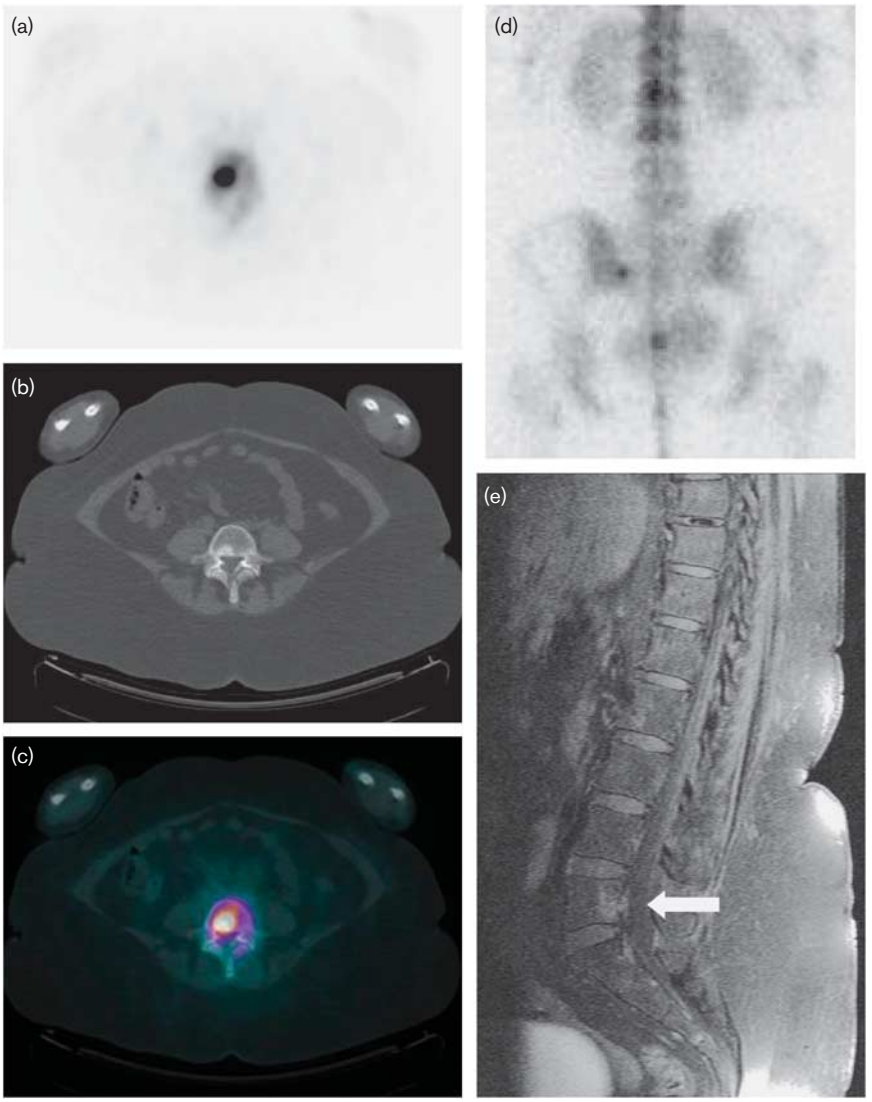
analysis showed that the ability of ^{18}F-fluoride PET/CT to detect BM was significantly superior to BS ($P < 0.0001$). When analyzing PBS and SPECT, it seemed that the contribution of SPECT to PBS was not significant ($P = 0.3124$). Table 2 summarizes sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ^{18}F-fluoride PET/CT and PBS in different locations of the skeleton. Compared with BS, the sensitivity of PET/CT was higher in all locations. The accuracy of PET/CT was significantly superior to BS for pelvic and lumbar spine locations ($P < 0.05$). Figure 1 illustrates an osteoblastic BM located on a lumbar vertebra identified with PET/CT and overlooked with BS.

The sensitivity of PET/CT and PBS was related to the heterogeneity of presentation of BM. Table 3 shows the sensitivity of each technique for detecting lytic, sclerotic, or mixed BM.

Patient-based analysis

For this analysis we excluded one patient with prostate cancer. He was claustrophobic and refused MRI; a thin-slice CT scan verified only one of 43 detected lesions. Thirty-two patients out of the 33 (97%) were correctly diagnosed (M +/M0: 20/12) with ^{18}F-fluoride PET/CT. PET/CT erroneously characterized only one patient as being metastatic. All patients with BM were identified with PET/CT.

Fig. 1



An osteoblastic bone metastasis (breast cancer) located on the fifth lumbar vertebra was identified with ^{18}F-fluoride PET/computed tomography (CT) (transverse sections; a: PET; b: low-dose CT; c: fused PET/CT) and overlooked with bone scintigraphy (d). MRI (e: T1-weighted fat saturation sequences after intravenous injection of gadolinium, sagittal view) confirmed the malignant character of the lesion (arrow).

The extent of the disease was correctly estimated in seven patients, overestimated in three, and underestimated in 10 patients. BS identified 19 of the 20 metastatic patients (95%); the extent of the disease was correctly estimated in three patients, overestimated in three, and underestimated in 13 patients. BS was false positive (FP) for four patients and false negative (FN) for one patient. The final diagnosis by PET/CT and BS was concordant for 29 (87.9%) patients (19 true positive; nine true negative, and one FP) and discordant for four (12.1%) patients. ^{18}F-fluoride PET/CT correctly estimated these four patients (one true positive; three true negative); BS missed one metastatic patient and falsely diagnosed metastases for three patients. Three patients showed equivocal lesions with PET/CT, none of them had shown BM on the basis of MRI or thin-slice CT scanning. Two patients showed equivocal lesions with BS and none of them had shown BM on the basis of MRI or thin-slice CT scanning. At the level of the patient, the difference between PET/CT and BS was not statistically significant ($P > 0.05$).

Table 3 Results of ^{18}F-fluoride PET/CT and ^{99m}Tc-MDP BS in the three types of BM in breast cancer

Metastases	TP	FN	Sensitivity (%)
Osteolytic			
PET/CT	7	5	58.3
BS	4	8	33.3
Osteoblastic			
PET/CT	20/22	2/0	90.9
BS	16	6	72.7
Mixed			
PET/CT	14	3	82.4
BS	8	9	47.1

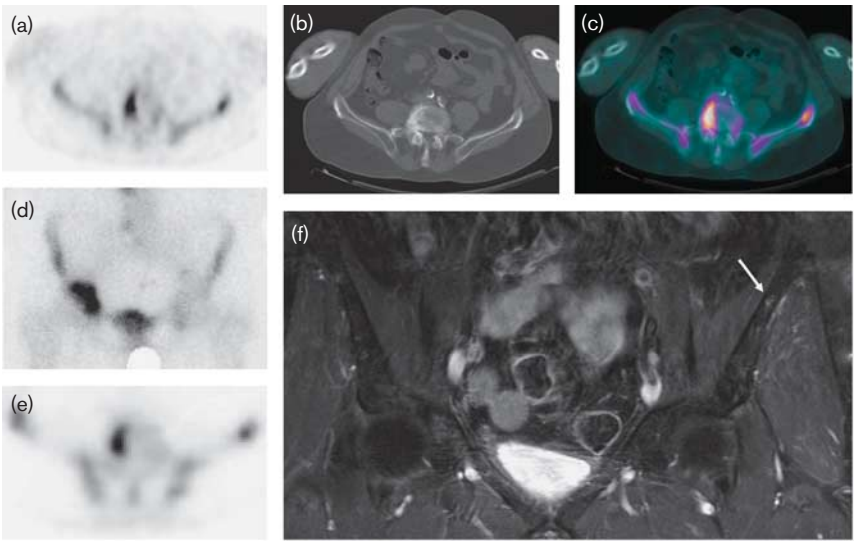
Inconclusive lesions are considered benign/malignant (when it differed).
BM, bone metastases; BS, bone scintigraphy; CT, computed tomography; FN, false negative; MDP, methylene diphosphonate; TP, true positive.

Discussion

Bone involvement is frequent in breast and prostate cancers, particularly in cases of recurrence. Because of its ability to detect BM several months before plain radiography, ^{99m}Tc-MDP BS is the technique of choice for screening. Nevertheless, the limited specificity of BS often requires confirmation with CT scanning or MRI. SPECT increases the sensitivity of the technique and the new SPECT/CT hybrid system improves the ability to distinguish BM from a benign lesion [21]. The availability of SPECT/CT is growing but is not widespread yet and planar imaging with a single FOV SPECT remains the mainstay in many institutions.

Since the 1990s, few studies have evaluated the ability of ^{18}F-fluoride PET to detect BM. In a prospective study including five patients with multiple skeletal metastases from breast cancer, Petren-Mallmin *et al.* [14] reported a high tracer uptake in both sclerotic and lytic breast cancer BMs. The investigators suggested a dual tracer approach combining FDG and ^{18}F-fluoride with encouraging results [22,23]. All the initial studies comparing BS with ^{18}F-fluoride PET showed a higher accuracy of PET in diagnosing bone involvement [16–18]. More recently, Kruger *et al.* [24] compared the diagnostic accuracy of FDG-PET/CT with ^{18}F-fluoride PET in a population of 68 patients with nonsmall cell lung carcinoma. All BMs

Fig. 2

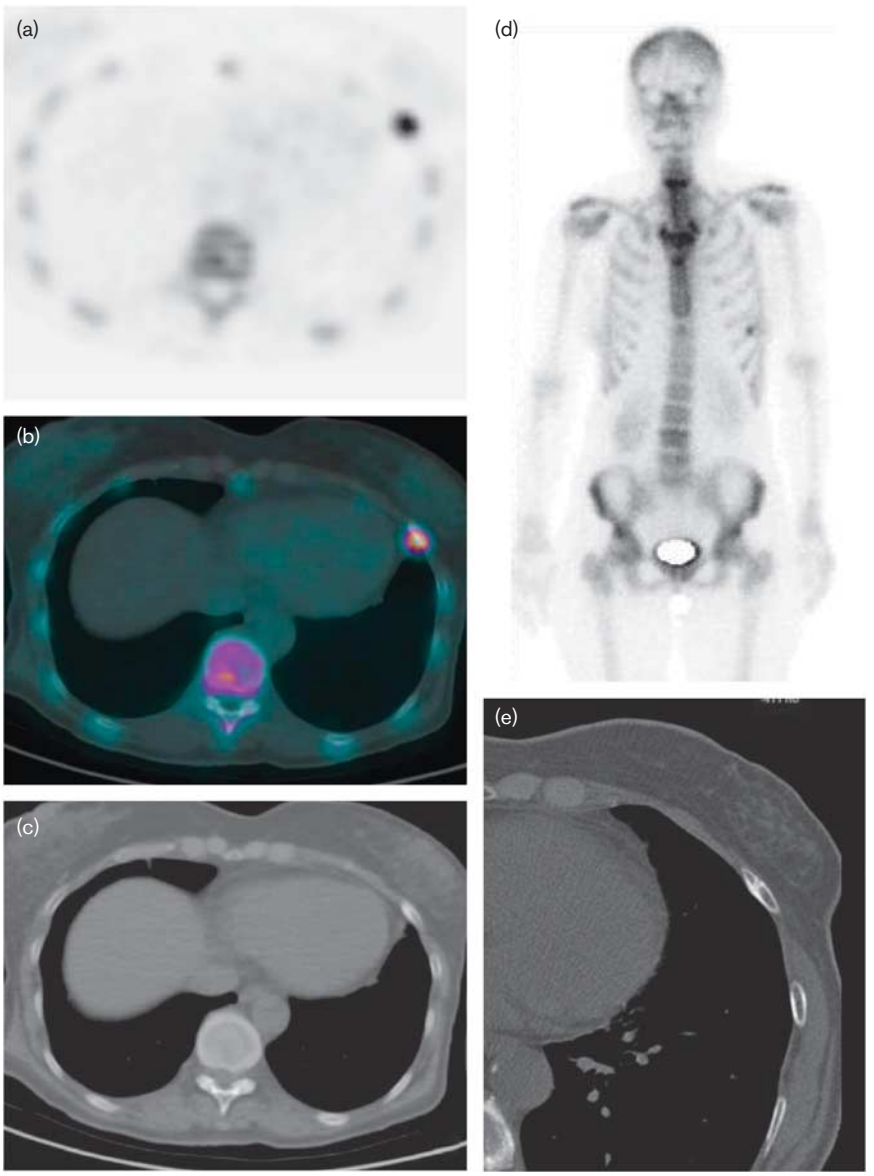


A bone metastasis (prostate cancer) was detected with ^{18}F-fluoride PET/computed tomography (CT) in the left hip-bone (transverse sections; a: PET; b: low-dose CT; c: fused PET/CT images). There was no lesion individualized with ^{99m}Tc-methylene diphosphonate planar bone scintigraphy (d), single photon emission computed tomography (e) only showed a slight asymmetry that was overlooked. MRI (f: T1-weighted fat saturation sequences after intravenous injection of gadolinium, coronal view) confirmed the malignant character of the lesion (arrow).

were osteolytic. ^{18}F-fluoride PET correctly diagnosed 67 of 68 patients (one FN) and correctly identified four patients with BM missed with FDG-PET/CT.

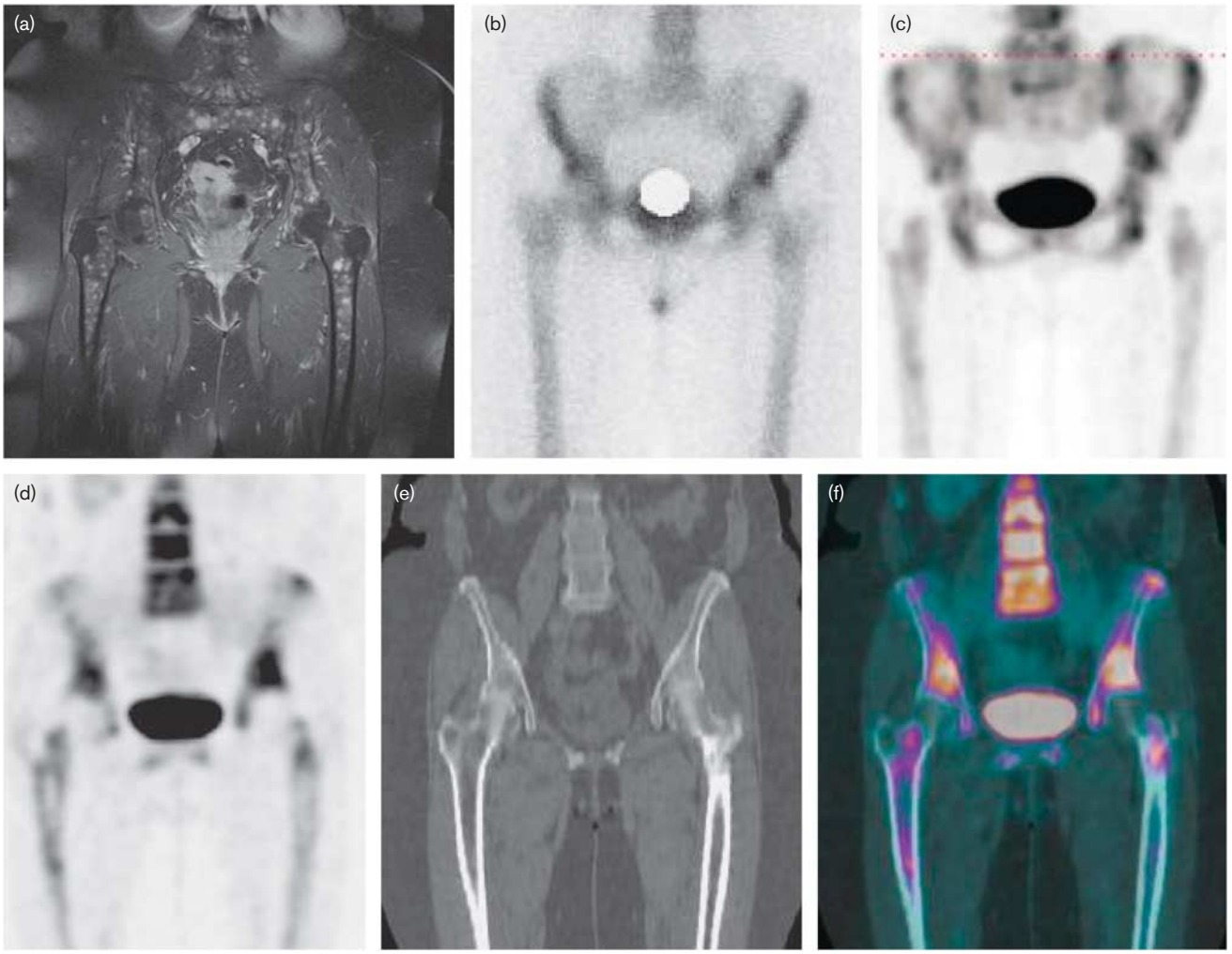
Only three studies assessed current PET/CT systems to detect BM with ^{18}F-fluoride [10,19,20]. The first study suggested that ^{18}F-fluoride PET/CT was more sensitive than PET for detecting BM. Combined with PET, low-dose CT scanning improved accuracy by better characterizing the malignant or benign character of a region of abnormal ^{18}F-fluoride uptake [19]. In a second study, the same group compared the accuracy of ^{18}F-fluoride PET/CT, PET, ^{99m}Tc-MDP PBS, and multi-FOV SPECT in 44 patients with prostate cancer at high risk of BM [20]. The third study evaluated ^{18}F-fluoride PET/CT in parallel with ^{18}F-fluorocholine without a comparison with BS [10]. In all three studies, the final diagnosis of lesions was mostly based on the findings of the low-dose CT part of PET/CT or clinical follow-up. Given the somewhat perfectible GS used in these papers, we wanted to assess the accuracy of ^{18}F-fluoride PET/CT for detecting BM by using MRI or a CT scan as a reference.

Fig. 3



PET/CT images illustrate foci of high ^{18}F-fluoride uptake in the sixth left rib (transverse sections; a: PET; b: fused PET/CT). On the basis of the sclerotic lesion described by the radiologist on the low-dose CT (c), this lesion was classified as most likely metastatic. (e) The thin-slice CT performed in the PET/CT system clearly shows a fracture. This patient with a breast cancer was falsely classified positive not only with ^{18}F-fluoride, but also with technetium-99m (^{99m}Tc)-methylene diphosphonate bone scintigraphy (d: anterior planar image).

Fig. 4



MRI (a: T1-weighted fat saturation sequences after intravenous injection of gadolinium, coronal view) shows multiple bone metastases (BMs) (breast cancer) disseminated on the pelvis and femurs. Technetium-99m (^{99m}Tc)-methylene diphosphonate planar bone scintigraphy (PBS) (b) overlooked BM and was considered normal; the single field-of-view single photon emission computed tomography acquired (not shown) did not change PBS diagnosis (c). ^{18}F-fluoride PET/computed tomography (CT) (coronal sections; d: PET; e: low-dose CT; f: fused PET/CT) detected some BM and correctly modified the final diagnosis of BS.

Our results confirm the significantly higher sensitivity of ^{18}F-fluoride PET/CT to detect BM in breast and prostate cancers compared with BS with SPECT. The contribution of a single FOV SPECT to PBS was not significant and PBS + SPECT remained less sensitive than PET/CT (Fig. 2). The sensitivity of both PET/CT and BS depended on the location of the lesions and was particularly higher for lesions located on the thoracic cage. The sensitivity of both PET/CT and BS also depended on the subtype (osteolytic, osteoblastic, or mixed) of BM. We only detected 58.3% of the lytic metastases with PET/CT. At the level of the patient, all 20 metastatic patients were identified with PET/CT. The final diagnosis made with PET/CT and BS was discordant for four of the 33 patients (12.1%). ^{18}F-fluoride PET/CT correctly modified (considering inconclusive lesions as benign) the diagnosis of BS of all these four patients (M→B: 3; B→M: 1). Although this study was not designed to estimate the real impact on the patient's clinical management, these results should be considered as highly encouraging.

In contrast to earlier studies, we described more equivocal lesions with PET/CT ($N = 21$) than with BS ($N = 6$) and more often for breast cancer lesions ($N = 19$) than prostate cancer lesions (PET/CT: $N = 2$). The inconclusive lesions described with PET/CT were located on the thoracic cage ($N = 6$), spine ($N = 5$), pelvis ($N = 5$), long bones ($N = 4$), or skull ($N = 1$). Seven of the 21 inconclusive lesions described with PET/CT were verified with MRI, all were BM. The 13 remaining inconclusive lesions verified with a diagnostic CT scan were defined as BM for two lesions and as benign for 11

lesions. For one inconclusive lesion for which both MRI and diagnostic CT were performed, the final diagnosis was discordant: MRI described a BM and the CT scan did not show anything. These observations could reflect the higher sensitivity of MRI to detect early BM compared with CT scanning. The follow-up of these lesions would have been interesting but most patients were treated so that a final diagnosis is not available. The low-dose CT scan did not help to characterize most inconclusive foci described with PET.

In our study, a low-dose CT scan did not improve the specificity of ^{18}F-fluoride PET/CT with regard to PBS. One study already mentioned the limits of a low-dose CT scan acquired with FDG-PET for the detection of BM [25]. In our population, the low-dose CT scan did not show any abnormal findings for 24.5% of the 155 foci detected on PET/CT and corresponding to BM on the GS. Moreover, for 14 of the 19 FP (73.7%) lesions reported with the PET/CT, the radiological findings were considered as malignant or probably malignant. In these cases, a low-dose CT scan misguided our final judgment on the reading of PET and contributed to lowering the specificity of PET/CT. One such case is illustrated in Fig. 3. The low-dose CT scan is helpful to better localize foci detected with PET but has limited diagnostic value. Furthermore, for the only patient falsely classified as malignant with PET/CT (and BS), the diagnostic CT scan was negative. In this case, the GS was in fact, as the follow-up confirmed BM. This shows an obvious limitation of our study, that is, the constraints of the GS. First, not all foci could be imaged with the radiological GS because of temporal scheduling constraints in clinical practice. Second, the choice of a CT scan over an MRI as a reference for rib lesions was guided by general guidelines in clinical practice [5]. To estimate the potential impact of the choice of the GS on our results, we estimated the performance of PET/CT considering lesions verified only with MRI or diagnostic CT scans. The difference in the performance of PET/CT, considering MRI or CT as GS, was significant ($P = 0.002$) only when inconclusive lesions were considered malignant. Figure 4 illustrates the superiority of MRI in detecting BM.

In this study, the sensitivity and specificity of ^{18}F-fluoride PET/CT are both lower than those described by Even-Sapir *et al.* [19,20]. In these studies, the GS was mainly the CT part of the PET/CT, which could contribute to explaining the near-perfect accuracy of PET/CT. We elected to compare nuclear medicine results with the radiological techniques that are both recognized as reference methods for assessing BM and used in the day-to-day clinical practice of oncology. We feel that this radiological GS is an improvement compared with available data, albeit imperfect. Methodological hurdles abound when assessing the diagnostic performance of imaging methods for detecting BM. Pathological verification is not an option for obvious reasons. Long-term follow-up might be an alternative but it has its own limitations as most patients will receive systematic treatment that will both alter the radiological appearance of the lesions and modify the oncological status of the patients. Nonetheless, we detected all prostate cancer BM with PET/CT. In the breast cancer population, the 27 FN lesions did not show any increased ^{18}F-fluoride uptake and could not be explained by any specific characteristics such as clinical presentation or history of chemotherapy or antihormone therapy.

In conclusion, ^{18}F-fluoride PET/CT is more accurate and, in particular, more sensitive than BS for detecting bone involvement in breast and prostate cancers. Low-dose CT scanning did not improve specificity of PET compared with BS, but greatly improved the localization of the lesions. PET/CT imaging with ^{18}F-fluoride correctly modified the BS results in 12.1% (four patients) of our population and should be considered as an alternative for staging high-risk patients.

Acknowledgements

The authors express their appreciation to the oncologists who participated to the recruitment of the patients. Part of this study was presented at the 55th Annual Meeting of the Society of Nuclear Medicine, New Orleans, Louisiana, June 14–18, 2008. They also thank Laurence Seidel for providing statistical data.

This study was supported by a FIRS Grant from the University hospital of Liège.

References

1 Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, *et al.* American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. *J Clin Oncol* 2006; **24**:5091–5097.
2 Walsh PC, DeWeese TL, Eisenberger MA. Clinical practice. Localized prostate cancer. *N Engl J Med* 2007; **357**:2696–2705.
3 Hamaoka T, Madewell JE, Podoloff DA, Hortobagyi GN, Ueno NT. Bone imaging in metastatic breast cancer. *J Clin Oncol* 2004; **22**:2942–2953.
4 Ghanem N, Uhl M, Brink I, Schafer O, Kelly T, Moser E, *et al.* Diagnostic value of MRI in comparison to scintigraphy, PET, MS-CT and PET/CT for the detection of metastases of bone. *Eur J Radiol* 2005; **55**:41–55.
5 Costelloe CM, Rohren EM, Madewell JE, Hamaoka T, Theriault RL, Yu TK, *et al.* Imaging bone metastases in breast cancer: techniques and recommendations for diagnosis. *Lancet Oncol* 2009; **10**:606–614.
6 Radan L, Ben-Haim S, Bar-Shalom R, Guralnik L, Israel O. The role of FDG-PET/CT in suspected recurrence of breast cancer. *Cancer* 2006; **107**:2545–2551.
7 Hodgson NC, Gulenchyn KY. Is there a role for positron emission tomography in breast cancer staging? *J Clin Oncol* 2008; **26**:712–720.
8 Schoder H, Larson SM. Positron emission tomography for prostate, bladder, and renal cancer. *Semin Nucl Med* 2004; **34**:274–292.
9 Beheshti M, Langsteger W, Fogelman I. Prostate cancer: role of SPECT and PET in imaging bone metastases. *Semin Nucl Med* 2009; **39**:396–407.
10 Beheshti M, Vali R, Waldenberger P, Fitz F, Nader M, Loidl W, *et al.* Detection of bone metastases in patients with prostate cancer by ^{18}F fluorocholine and ^{18}F fluoride PET-CT: a comparative study. *Eur J Nucl Med Mol Imaging* 2008; **35**:1766–1774.
11 Blau M, Nagler W, Bender MA. Fluorine-18: a new isotope for bone scanning. *J Nucl Med* 1962; **3**:332–334.

12 Blake GM, Park-Holohan SJ, Cook GJ, Fogelman I. Quantitative studies of bone with the use of ^{18}F-fluoride and ^{99m}Tc-methylene diphosphonate. *Semin Nucl Med* 2001; **31**:28–49.
13 Grant FD, Fahey FH, Packard AB, Davis RT, Alavi A, Treves ST. Skeletal PET with ^{18}F-fluoride: applying new technology to an old tracer. *J Nucl Med* 2008; **49**:68–78.
14 Petren-Mallmin M, Andreasson I, Ljunggren O, Ahlstrom H, Bergh J, Antoni G, *et al.* Skeletal metastases from breast cancer: uptake of ^{18}F-fluoride measured with positron emission tomography in correlation with CT. *Skeletal Radiol* 1998; **27**:72–76.
15 Schirrmeister H, Guhlmann A, Kotzerke J, Santjohanser C, Kuhn T, Kreienberg R, *et al.* Early detection and accurate description of extent of metastatic bone disease in breast cancer with fluoride ion and positron emission tomography. *J Clin Oncol* 1999; **17**:2381–2389.
16 Schirrmeister H, Guhlmann A, Elsner K, Kotzerke J, Glatting G, Rentschler M, *et al.* Sensitivity in detecting osseous lesions depends on anatomic localization: planar bone scintigraphy versus ^{18}F PET. *J Nucl Med* 1999; **40**:1623–1629.
17 Schirrmeister H, Glatting G, Hetzel J, Nussle K, Arslandemir C, Buck AK, *et al.* Prospective evaluation of the clinical value of planar bone scans, SPECT, and (18)F-labeled NaF PET in newly diagnosed lung cancer. *J Nucl Med* 2001; **42**:1800–1804.
18 Hetzel M, Arslandemir C, Konig HH, Buck AK, Nussle K, Glatting G, *et al.* F-18 NaF PET for detection of bone metastases in lung cancer: accuracy, cost-effectiveness, and impact on patient management. *J Bone Miner Res* 2003; **18**:2206–2214.
19 Even-Sapir E, Metser U, Flusser G, Zuriel L, Kollender Y, Lerman H, *et al.* Assessment of malignant skeletal disease: initial experience with ^{18}F-fluoride PET/CT and comparison between ^{18}F-fluoride PET and ^{18}F-fluoride PET/CT. *J Nucl Med* 2004; **45**:272–278.
20 Even-Sapir E, Metser U, Mishani E, Lievshitz G, Lerman H, Leibovitch I. The detection of bone metastases in patients with high-risk prostate cancer: ^{99m}Tc-MDP planar bone scintigraphy, single- and multi-field-of-view SPECT, ^{18}F-fluoride PET, and ^{18}F-fluoride PET/CT. *J Nucl Med* 2006; **47**:287–297.
21 Ndlovu X, George R, Ellmann A, Warwick J. Should SPECT-CT replace SPECT for the evaluation of equivocal bone scan lesions in patients with underlying malignancies? *Nucl Med Commun* 2010; **31**:659–665.
22 Hoegerle S, Juengling F, Otte A, Altehoefer C, Moser EA, Nitzsche EU. Combined FDG and [F-18]fluoride whole-body PET: a feasible two-in-one approach to cancer imaging? *Radiology* 1998; **209**:253–258.
23 Iagaru A, Mittra E, Yaghoubi SS, Dick DW, Quon A, Goris ML, *et al.* Novel strategy for a cocktail ^{18}F-fluoride and ^{18}F-FDG PET/CT scan for evaluation of malignancy: results of the pilot-phase study. *J Nucl Med* 2009; **50**:501–505.
24 Kruger S, Buck AK, Mottaghy FM, Hasenkamp E, Pauls S, Schumann C, *et al.* Detection of bone metastases in patients with lung cancer: (99m)Tc-MDP planar bone scintigraphy, (18)F-fluoride PET or (18)F-FDG PET/CT. *Eur J Nucl Med Mol Imaging* 2009; **36**:1807–1812.
25 Nakamoto Y, Cohade C, Tatsumi M, Hammoud D, Wahl RL. CT appearance of bone metastases detected with FDG PET as part of the same PET/CT examination. *Radiology* 2005; **237**:627–634.