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Original Article

Early bone marrow metastasis detection: The additional value of FDG-PET/CT vs. CT imaging

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ABSTRACT

Objective: To assess the addition value of ^{18}F-Fluorodeoxyglucose (FDG) PET/computed tomography (FDG-PET/CT) vs. CT in detecting early metastatic deposits in bone marrow (BM).
Methods: From January 2009 to December 2010, 198 consecutive patients (88 male, 110 female; median age: 64 years) were retrospectively examined. All patients underwent ^{18}F-FDG-PET/CT for disease evaluation: 65 for lung cancer, 66 for breast cancer, 57 for lymphoma and 10 for multiple myeloma. All scans were reviewed by a radiologist and a specialist in nuclear medicine for the identification of bone lesions. The presence of BM metastases was confirmed by biopsy, sequential PET/CT scan or magnetic resonance imaging when available. A patient-based analysis was performed.
Results: Investigating the presence of skeletal metastasis, 94 (48%) patients had positive and 104 (52%) negative CT scan whereas 110 (56%) had positive and 88 (44%) negative FDG-PET/CT scan ($P < 0.001$). The two imaging modalities were concordant in 178 (90%) patients for bone lesions; on the contrary 20 (10%) patients had discordant results ($P < 0.001$). In 21 out of 178 concordant patients BM lesions were identified both in CT and FDG-PET, whereas nine out of the 20 discordant patients showed BM involvement at PET/CT only. Overall, PET/CT was able to identify 30 (15%) patients with BM lesions. In these latter patients, the maximum standardized uptake value (SUVmax) for BM metastases was 7.9 ± 4.5 (range: 3.1–19.0), resulting slightly higher in patients with negative than positive CT scan (8.3 ± 5.1 vs. 7.8 ± 4.3, respectively; $P = 0.79$).
Conclusions: FDG-PET/CT resulted more accurate than CT in early detection of BM metastases. The FDG-PET/CT images improve the staging of about 15% of our study population. PET/CT detected BM lesions mainly on the basis of their increased metabolic activity rather than on anatomical alterations. Moreover, it provided an accurate identification of tumour viability that was useful for treatment planning and follow-up.

1. Introduction

The early detection of skeletal involvement at any phase of cancer evolution can significantly change the staging of the disease and thus alter the treatment strategy. The positron emission tomography (PET) contribution, as respect the computed tomography (CT), in the management of cancer patients with skeletal involvement, is still under investigation. The PET images could allow to identify the early changes in medullary and cortical portions of bones, whereas CT images can mainly detect anatomical modifications, i.e. the cortical bone lesions.

In the last years, the role of molecular imaging in bone lesions has been focalized on bone marrow (BM) involvement, including the meaning and the implications on patient management [1–3]. For decades, biopsy of BM has been performed to assess BM infiltration in the initial staging of lymphoma and this practice is still considered as a "gold standard" [3]. Nevertheless, focal malignant infiltration of BM can be missed by biopsy, leading to

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false negative results and negatively affecting clinical management [4]. Several studies on molecular imaging techniques applied to BM lesion investigation reported a high diagnostic accuracy as compared to standard morphologic methods [5,6]. The detection of focal BM uptake in haematolymphoid disorders were extensively reported in literature [2,3,5], while this issue has not been yet investigated for solid tumours. Bone lesions in solid tumours can be accurately detected by magnetic resonance imaging (MRI) during staging and restaging exams for several tumours [7]. However, some studies suggested that also FDG-PET may be useful for the same purpose, with the advantage to offer whole-body investigation. In this regard, in the present study we aimed [1] to evaluate the ability of fluorodeoxyglucose (FDG) PET/CT in detecting bone lesions and [2] to compare FDG-PET/CT with CT bone findings in a sample of patients with haematolymphoid and solid tumours. Furthermore, we provided an effort to clarify these subjects and the controversies reported in the literature.

2. Materials and methods

2.1. Patient population

From January 2009 to December 2010, 198 consecutive patients (88 men; 110 women; median age: 64 years) were retrospectively examined. Fifty-seven (29%) patients referred to or centre for lymphoma, 65 patients (33%) for lung cancer, 66 (33%) for breast cancer and 10 (5%) with multiple myeloma. For the present study we selected patients with solid tumours that often spread to the skeleton (the reported prevalence of skeletal metastases is 70 to 95% for myeloma, 65 to 75% for breast cancer and 30 to 40% for lung cancer).

At the time of FDG-PET/CT, none of the patients were under treatment. Pathologic TNM staging was evaluated according to the criteria of American Joint Committee on Cancer (AJCC).

The indications for the PET/CT examination were:

- suspect of disease relapse;
- doubtful chest and bone radiographs;
- doubtful ^{99m}Tc-disphosfonate bone scan. The characteristics of the study population are resumed in Table 1.

The present study was performed according to the declaration of Helsinki. All patients gave their informed consent for PET/CT examination. The present retrospective analysis did not require Institutional Review Board approval nor informed consent by national institution.

Table 1
Characteristics of patient population.

Patients	*n* (%)
n (total)	198
Sex	
Male	88 (45)
Female	110 (55)
Disease	
Breast cancer	66 (33)
Lymphoma	57 (29)
Lung Cancer	65 (33)
Myeloma	10 (5)
Reason for PET/CT	
Initial staging	48 (24)
Restaging	102 (52)
Follow-up	37 (19)
Post-therapy assessment	11 (6)
Staging (according the Seventh version of AJCC)	
Stage I	38 (19)
Stage II	41 (21)
Stage III	24 (12)
Stage IV	45 (23)
Unknown	50 (25)

AJCC: America Joint Committee on Cancer.

2.2. PET/CT imaging

All PET/CT scans were performed at our institution. Whole-body ^{18}F-FDG-PET/CT exams were performed using the hybrid PET/CT scanner Biograph 16 (Siemens Medical Solutions, Illinois, USA). PET system consists on a high-resolution 3D scanner, with a spatial resolution of 4.7 mm. The integrated CT system consists of a 16-slices scanner (Siemens Somatom Sensation). The CT images were used both for PET attenuation correction and for anatomical localization of areas with high FDG-uptake. All patients were advised to fast for at least 6 hours before PET/CT examination. After injection of 3 MBq/kg/b.w. of ^{18}F-FDG, patients rested for a period of 60 minutes in a comfortable chair. Transmission images were obtained using a low-dose helical CT scan (80 mAs, 80–140 kV, 2-mm slice thickness; 1.35 pitch, 0.5-sec rotation). Emission images ranging from the proximal femur and the base of the skull were acquired in 3D mode for 2 to 3 minutes per bed position. The data were reconstructed by the attenuation weighted-OSEM (ordered subset expectation maximization) iterative method, with two iterations and eight subsets, in a 128 × 128 matrix (5.25 mm pixel size) with slice thickness of 2 mm. A Gaussian filter was applied to the image after reconstruction along the axial and transaxial directions. Processed images were displayed in coronal, transverse, and sagittal planes.

2.2.1. Image analysis

At visual analysis, an increased, non physiological FDG-uptake, was recorded as positive. The absence of uptake was defined as a negative finding.

The maximum standardized uptake value (SUVmax) was determined in regions of interest (ROI) drawn on the attenuation-corrected PET/CT images around suspected lesion sites. SUV calculation for the 3D PET data was performed automatically through the following formula:

$$SUV(g/cc) = K(Bq/cc) \times \left[b.w(kg)/A_{inj}(Bq)\right] \times 1000g/kg$$

where K is the calibrated pixel-value (in Bq/cc), *b.w.* is the body weight of the patient and A_{inj} is the injected activity in Bq corrected for the decay at the time of acquisition.

2.3. Interpretation of PET/CT and CT images

The CT and fused PET/CT images were assessed by four experienced physicians: two radiologists interpreted the CT images, whereas two nuclear medicine specialists interpreted the PET/CT images, for the identification of bone lesions. The presence of BM metastases was confirmed by biopsy, sequential FDG-PET/CT scans or magnetic resonance imaging (MRI), performed during a follow-up of at least 6 months. The final reports of FDG-PET and CT examinations were compared. When non-bone disease was also identified, the diagnosis was verified by clinical follow-up in 79 (40%) patients and through subsequent imaging studies in the remaining population. According to the subsequent follow-up PET/CT scan, all multiple foci of heterogeneous FDG-uptake localized in BM which resolved without performing any therapy were considered benign, whereas the presence of new lesions or an growth of pre-existing ones were considered as metastasis. The metabolic activation after chemotherapy was not considered BM involvement but a physiologic condition. Finally, bone lesion were defined as osteolytic, osteoblastic or mixed according to their morphological characteristics at CT scan.

2.4. Statistical methods

A patient-based analysis was performed. Continuous data are presented as mean ± standard deviation (SD), while categorical data as percentages. The primary endpoint was the comparison of PET/CT and CT findings for BM involvement. Associations for paired samples were assessed using *t*-Student test or Mann–Whitney test depending on the normality of the variable, verified with the Shapiro–Wilk test. Comparisons between dichotomises variables were performed by Chi^2 test, or Fischer exact test, as appropriate. $P < 0.05$ was considered statistically significant. Statistical analysis was performed by SPSS software (SPSS Inc., Advanced Models 15.0, Chicago, Illinois).

3. Results

3.1. Bone marrow involvement at FDG-PET/CT

Out of 198 studied patients, 181 had positive PET/CT results, whereas 17 resulted negative (91% vs. 9%). Among patients with positive PET/CT, 110 had bone lesions, in particular 102 had segmental bone metastasis, and eight patients a diffuse FDG-uptake in all bone segments.

In the subset of 110 patients with bone metabolic lesions, 21 (19%) had associated visceral lesions (liver and lung), 32 (29%) had lymph node disease, and 27 (25%) showed visceral and non visceral metastases, while in the remnant 30 (27%) patients BM involvement was found. In these latter group of patients, the mean SUVmax for BM metastasis was 8.3 ± 4.9 (range: 3.1–19.9). Localisation of BM lesions at FDG-PET was as follow: sternum $n = 2$, ribs $n = 3$, pelvis $n = 7$, humerus $n = 2$, spine $n = 12$, clavicle $n = 1$ and diffuse in backbone and pelvis $n = 3$. An example of a patient with focal BM involvement is depicted in Fig. 1. The PET/CT objectives were: initial staging for 48 patients (24%); restaging for 102 (52%); follow-up for 37 (19%), and assessment of therapy efficacy in 11 (6%) patients. No difference about the distribution of BM in the four subsets of patients was found ($P = 0.774$). Among patients at initial staging ($n = 48$), 9 (19%) had BM metastasis: seven patients with lymphoma, one with lung cancer, and one with multiple myeloma. In patients with lymphoma ($n = 7$), BM metastasis was confirmed by biopsy. In patient with lung cancer and BM foci a MRI examination was performed to confirm them. Finally, in patient with multiple myeloma both a diffuse medullary involvement and visceral metastasis were demonstrated. In the restaging subset, 18/102 patients (18%) had BM metastases; eight patients with breast cancer had also visceral disease thus the management was not changed; in other seven breast cancer patients, BM lesions were associated with non visceral involvement (lymph nodes) and finally one patient had multiple BM foci (Fig. 2) thus a chemotherapy treatment was planned. One out of 18 patients with lung cancer showed both visceral and non visceral involvement, and one patient with multiple myeloma showed both visceral and BM diffusion; thus any change in therapeutic management was made. In the follow-up subset series, 3/37 (8%) patients had BM involvement: one patient with breast cancer, one with lung cancer, and one with multiple myeloma. The first patient had only a focal BM localization and an osteolytic lesion; the BM lesion was confirmed by a followed PET/CT scan. In the patient

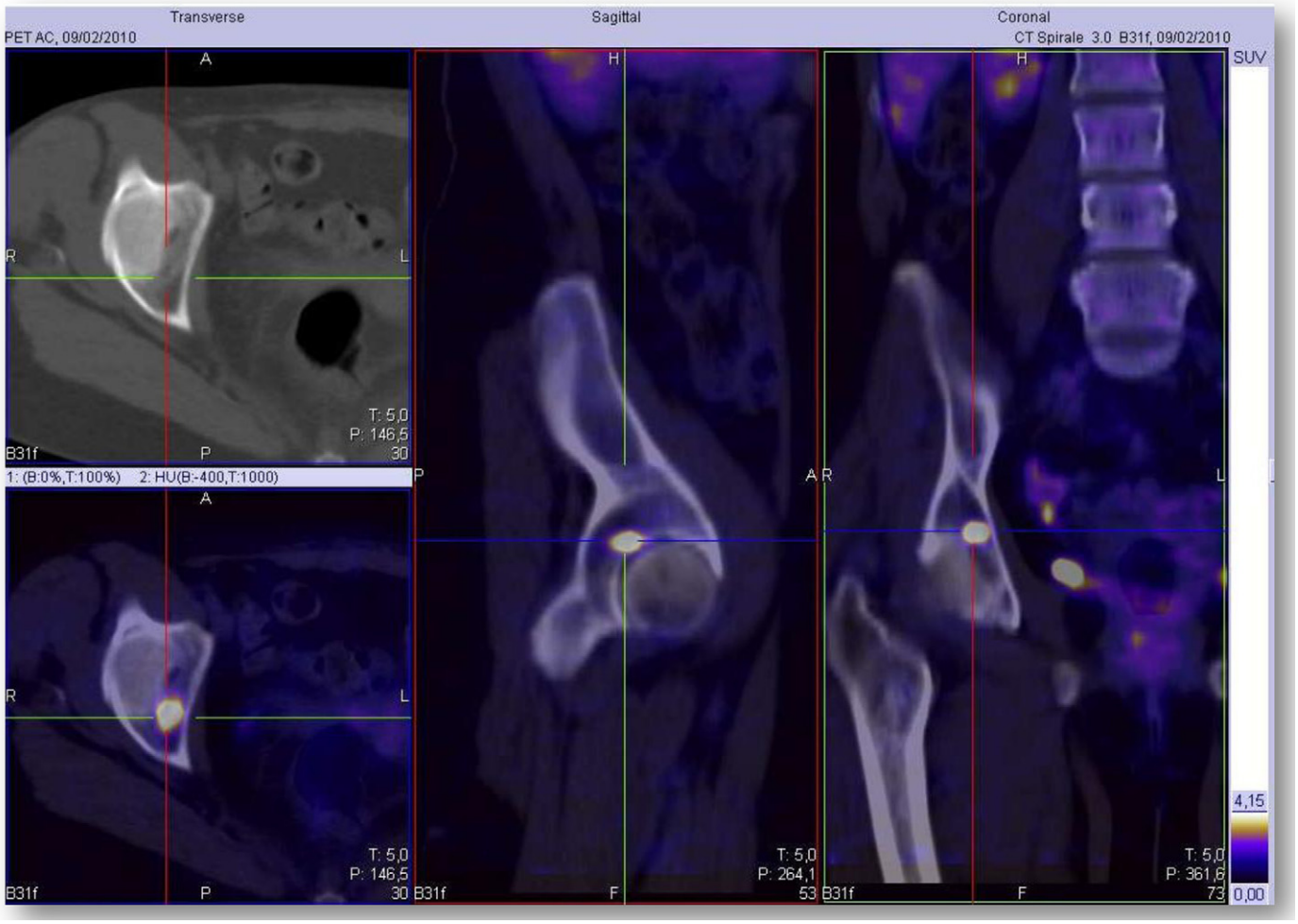

Fig. 1. An example of a patient with a focal FDG-uptake in right ischium, compatible with bone marrow lesion.

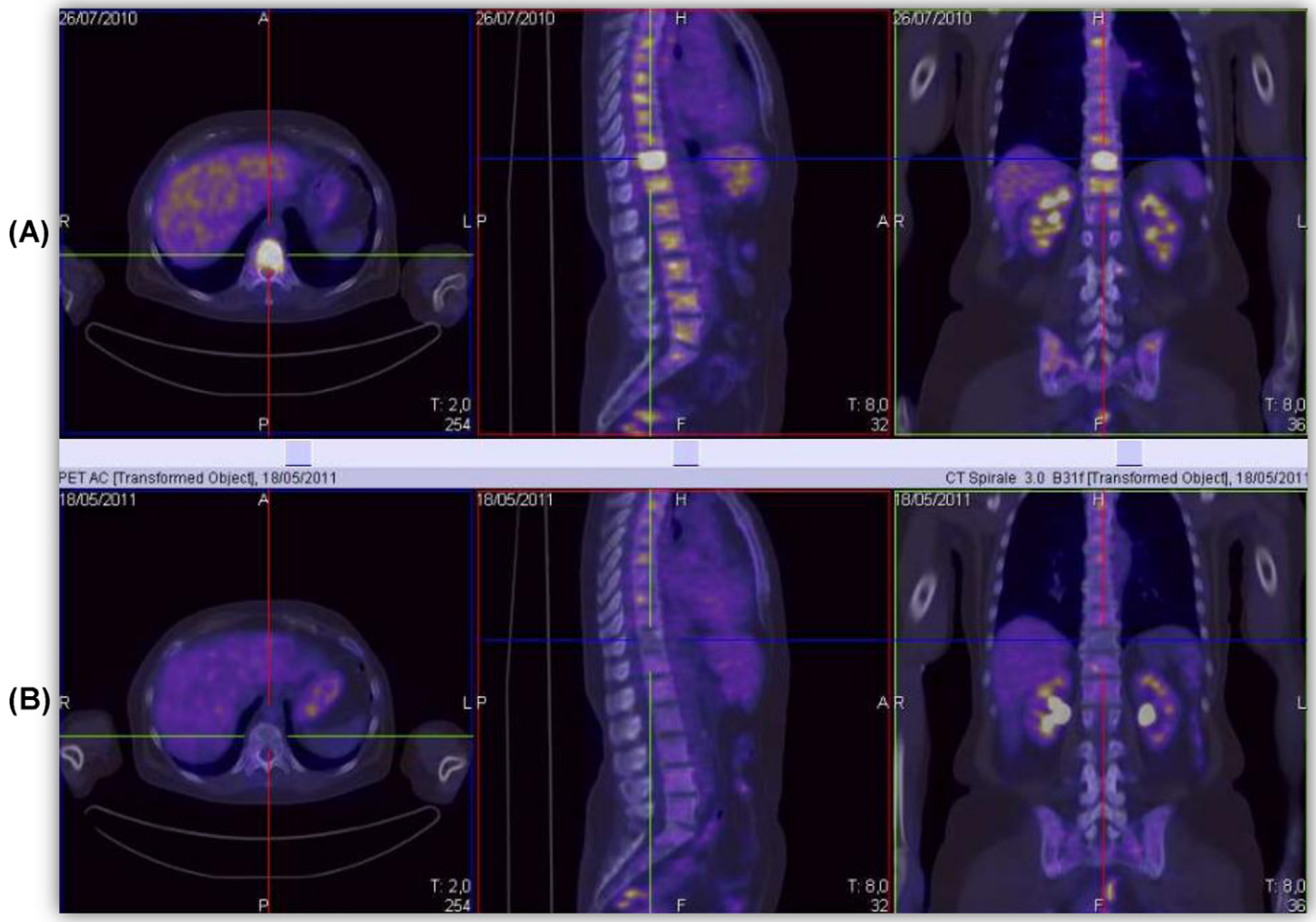

Fig. 2. An example of a patient with diffuse bone marrow involvement at PET/CT before (A) and after treatment (B).

with lung cancer, a BM focus in the rib was observed without visceral involvement. The patient with multiple myeloma showed multiple foci of BM involvement those were confirmed by control PET/CT study during subsequent follow-up. In this last patient, BM lesions disappeared after treatment. Finally, in the post-therapy assessment none of the 11 patients showed BM involvement.

Out of 71 patients without bone lesions at PET/CT, 25 (35%) had a visceral involvement (liver and lung), 26 (37%) had lymph node disease, and 20 (28%) had both visceral and lymph node disease.

3.2. Bone lesions: PET/CT vs. CT

At CT scan, 94 (47%) patients were positive and 104 (53%) were negative for bone metastases. CT and PET/CT were concordant in 178 patients, 86 negative for bone lesions and 92 positive for skeletal metastases in both. On the contrary, the findings were discordant in 20 patients, in particular two patients had only positive CT for osteoblastic lesions and 18 had only focal and diffuse skeletal FDG-uptake.

Twenty-one (12%) patients with PET and CT concordant findings had also BM lesions at FDG-PET/CT scan, confirmed by biopsy, MRI or sequential PET/CT scans, whereas nine out of 20 (45%) patients with discordant CT and PET/CT findings had only BM lesions. The additional PET/CT information in uni- or multifocal bone involvement upgraded the stage of lymphoma in seven (23%) patients, of myeloma in three patients (10%), of breast cancer in 17 patients (57%), of lung cancer in three patients (10%). The different distribution of bone lesions at PET/CT and CT are resumed in Table 2.

The SUVmax value of BM lesions was similar between patients with concordant and discordant findings against CT images (8.4 ± 5.0 and 8.3 ± 5.1; $P = 0.960$), whereas it resulted slightly higher in patients with negative than positive CT scan (8.3 ± 5.1 vs. 7.8 ± 4.3, respectively; $P = 0.79$).

4. Discussion

Skeletal system is often the target of metastatic disease and constitutes the third most common location of metastatic manifestations after the liver and the lung [7]. On morphologic imaging studies, bone metastases can be osteolytic, sclerotic (osteoblastic) or mixed. Bone metastases spread hematogeneously, starting as intramedullary lesions found in more than 90% of cases in the red marrow [8]. Until now, few studies evaluated the BM metastases at FDG-PET/CT in solid tumours. In the present study, we have considered a cohort of patients with breast cancer, lung cancer, lymphoma and multiple myeloma. Recent studies showed that FDG-PET is highly specific for detection of BM involvement in lymphoma, with a rate of true negative of 91 to 100% and a positive predictive value of 100% as confirmed by biopsy [11,12]. We have found the same findings in seven patients with lymphoma who showed focal ($n = 5$) and diffusive pattern ($n = 2$) of FDG-uptake.

Table 2
Distribution of bone lesions in the 30 PET/CT and CT positive examinations.

Disease	Bone lesion site at PET/CT	BM site	SUVmax BM	Bone lesion site at CT
Lymphoma	Sternum	Sternum	18.7	–
Breast	Humerus (R), ribs, spine, sternum	Sternum	3.9	–
Lung	V^ribe (L)	V^ribe (L)	3.1	–
Breast	Clavicole (L), spine (dorsal), iliac crest (L), sacrum	Clavicole (L)	4.4	Sternum, spine (dorsal), iliac crest (L)
Lung	Ileum (R), pelvis (R)	Pelvis (R)	6.9	Ileum (R)
Myeloma	Sacrum, sacrum iliac synchondrosis	Pelvis	19.0	VI^rib (R), clavicola (L), spine (dorsal-lumbar), iliac crest
Myeloma	Diffuse bone marrow and cortical lesions	All segments	11.0	–
Lymphoma	All segments	All segments	13.9	Sternum
Lymphoma	All segments	All segments	3.9	–
Breast	–	Pelvis	10.5	–
Breast	Humerus (L)	Humerus (L)	17.0	Spine, ribs (R&L), sternum
Lymphoma	Spine (dorsal-lumbar)	Spine (dorsal-lumbar)	11.1	-
Lung	Spine (lumbar), sacrum	Spine (lumbar)	9.8	Iliac crest (R&L)
Breast	Spine (lumbar), iliac (R), syncondrosis (L), acetabulum (L)	Spine (lumbar)	4.8	–
Breast	Spine (lumbar)	Spine (lumbar)	4.4	Iliac crest (R), spine (dorsal)
Breast	Spine (dorsal-lumbar), V^ribe (R), ileum (R), acetabulum (R)	Spine (lumbar)	4.4	–
Breast	Ischium (R), ribes (R), spine (dorsal)	Ischium (R)	8.9	Ribes (R), femorus (R), iliac crest (R), spine (dorsal)
Breast	Spine, pelvis, femorus	Pelvis	3.4	–
Lymphoma	Ischium	Ischium	3.6	–
Breast	Spine (dorsal)	Spine (dorsal)	4.9	–
Lymphoma	Spine (dorsal), VIII^ ribe (R), iliac crest (R)	Spine (dorsal)	9.0	Spine (dorsal), VIII^ ribe (R), iliac crest (R)
Breast	Pelvis, spine (dorsal), iliac crest (R), scapula (L)	Spine (dorsal)	6.5	Spine (dorsal)
Breast	Pelvis, spine (dorsal), iliac crest (R), scapola (L)	Spine (dorsal)	6.5	Spine (dorsal), iliac crest (R), scapola (L)
Breast	Spine (dorsal-lumbar), clavicole (R)	Spine (dorsal)	6.8	–
Myeloma	Spine (dorsal), clavicole, scapula, sternum	Spine (dorsal)	19.9	Spine (dorsal-lumbar), ileum (R), ischium (R), femorus (L)
Breast	–	Rib (L)	4.8	–
Breast	Ribes (R), pelvis, spine, homerus (R)	Pelvis	7.5	–
Breast	VIII^ribe (R)	VIII^ribe (R)	7.5	–
Breast	Spine (cervical-dorsal)	Spine (cervical)	4.6	–
Lymphoma	Homerus (R), ileum (R)	Homerus (R)	9.1	Ileum (R)

PET/CT: positron emission tomography/computer tomography; BM: bone marrow; R: right; L: left.

As already reported in literature [9,10], the early identification of BM metastases has a direct consequence on the choice of the therapeutic approach. In fact, we showed a patient with a history of breast cancer (Fig. 2) and bone marrow involvement at restaging PET/CT, received a good prognosis thanks to the early beginning of the systemic therapy. In particular, FDG-PET/CT images can be particularly useful when the BM involvement is still isolated. On the other side, CT is not able to evaluate this kind of lesions, although it is usually employed in the follow-up of these neoplasms. In the present study, we identified BM metastases in the 15% of the population, 24% of which in the initial stage and 52% in restaging, that otherwise would have been missed. In particular, 7% of our population showed only BM involvement at PET/CT, as oligometastatic or diffuse pattern. CT provided detailed anatomic information (useful for PET interpretation), but our data suggested that CT is not able to identify early BM lesions even when the optimal CT window width and level are used.

Therefore, even if CT is often used to evaluate bone metastases, also FDG-PET images are able to display diffuse BM involvement as intense activity throughout the skeletal system [13]. However, this pattern may be indistinguishable and confused with increased FDG-uptake owing to BM stimulation by colony-stimulating factor, granulocyte-macrophage-colony-stimulating factor, erythropoietin, and B thalassemia [14,15]. In the present report, we found five patients with lymphoma at initial staging with diffuse BM involvement due to myeloid hyperplasia, but we did not consider them as positive for BM disease.

Nowadays, MRI represents the gold standard for revealing BM alteration [16] although it was not indicated as a I level diagnostic approach in our study population. MRI protocols often do not include skull, sternum and ribs which are areas with high amounts of red marrow and represent frequent sites of infiltration [17]. MRI has also already been employed for the detection of bone tumours in children and young adults. It has proven to be the imaging

modality with the highest sensitivity to detect malignant BM infiltration without exposing the patient to ionizing radiation [17]. The limitation of MR imaging (as it is in practice) has been highlighted. However, a whole body T1, T2, STIR and DWI of the vertebral column is the preferred protocol if bone marrow involvement is to be studied. Therefore, whole-body MRI is an ideal candidate for skeletal manifestations of lymphoma, being already used in assessing BM infiltration and extramedullary involvement by lymphoma [7]. Although the modality of choice used in primary staging of this malignancy is FDG-PET, whole-body MRI may represent an alternative, especially to bone or ^{67}Ga-scintigraphy [18].

For the majority of our patients, the assessment of bone involvement was performed by imaging, such as subsequent PET/CT or MRI examinations. This choice can represent a limitation of this study, but we opted for these procedures because most of our patients had diffused skeletal lesions, visceral and non visceral metastases, thus the biopsies were not carried out for ethical reasons. BM biopsy has a high sensitivity in the case of diffuse BM disease particularly when BM involvement is located in the dorsal iliac crest. PET can be falsely negative or inconclusive in depicting BM disease, because the diffuse pattern of BM disease can mimic a functional BM activation or can not be detected at all in the case of low BM infiltration. Furthermore, an FDG diffuse BM uptake, probably due to the inflammatory context of the disease, is frequently observed at the initial staging of lymphoma. This limitation is even more common during the restaging of patients treated with chemotherapy or with colony stimulation factors and this pattern could hide some pathological focus [19].

5. Conclusion

^{18}F-FDG-PET/CT resulted more accurate than CT in detection of BM metastases; its inclusion in the diagnostic process changed the disease staging in 15% of patients. PET/CT detected BM lesions mainly on the basis of their increased metabolic activity instead of any anatomical alteration. Moreover, it provided an accurate identification of tumour viability that was useful for treatment planning and monitoring.

Disclosure of interest

The authors declare that they have no conflict of interest concerning this article.

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