Dual-tracer PET/CT scan after injection of combined [$^{18}$F]NaF and [$^{18}$F]FDG outperforms MRI in the detection of myeloma lesions

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Abstract
The detection rates of whole-body combined [$^{18}$F]NaF/$^{18}$F]FDG positron emission tomography combined with computed tomography (PET/CT), CT alone, whole-body magnetic resonance imaging (WB-MRI), and X-ray were prospectively studied in patients with treatment-requiring plasma cell disorders. The detection rates of imaging techniques were compared, and focal lesions were classified according to their anatomic location. Twenty-six out of 30 initially included patients were assessable. The number of focal lesions detected in newly diagnosed patients (n = 13) and in relapsed patients (n = 13) were 296 and 234, respectively. The detection rate of PET/CT was significantly higher than those of WB-MRI (P < 0.05) and CT (P < 0.0001) both in patients with newly diagnosed and in those with relapsed multiple myeloma (MM). The X-ray detection rate was significantly lower than those of all other techniques, while CT detected more lesions compared with WB-MRI at diagnosis (P = 0.025). With regard to the infiltration patterns, relapsed patients presented more diffuse patterns, and more focal lesions located in the limbs compared with newly diagnosed patients. In conclusion, the detection rate of [$^{18}$F]NaF/$^{18}$F] FDG PET/CT was significantly higher than those of CT, MRI, and X-ray, while the detection rate of X-rays was significantly lower than those of all other imaging techniques except for focal lesions located in the skull.

KEYWORDS
FDG-PET, myeloma, imaging, PET/CT fluoride

1 | INTRODUCTION

The revised International Myeloma Working Group (IMWG) criteria for the diagnosis of multiple myeloma (MM) incorporated computed tomography (CT), [$^{18}$F]fluorodeoxyglucose ([$^{18}$F]FDG) positron emission tomography combined with CT (PET/CT), and magnetic resonance imaging (MRI) in the diagnostic work-up of MM and its associated bone disease.3,4 By using X-ray (XR) or CT, the detection of MM lesions is indirect and relies on the recognition of tumor-induced bone destruction. Nevertheless, because of its higher detection rate, whole-body CT (WBCT) is increasingly replacing whole-body XR (WBXR) in the diagnostic work-up of MM.2,4-6 MRI and [$^{18}$F]FDG PET/CT directly detect tumor invasion and MM focal lesions (FLs) with similar performance.6,8 Furthermore, baseline MRI and [$^{18}$F]FDG
FDG PET/CT provide prognostic information in patients with newly diagnosed MM: The presence of a diffuse pattern with MRI, extramedullary disease, the number of FLs, and/or $^{[18F]}$FDG-avid lesions are associated with shorter survival. Based on its ability to indicate metabolic activity, $^{[18F]}$FDG is the preferred and widely used tracer for PET/CT; however, the sensitivity of $^{[18F]}$FDG PET/CT is about 80% to detect focal myeloma lesions.

$^{[18F]}$NaF targeting bone has been also investigated for the detection of MM bone lesions. The bone uptake of $^{[18F]}$NaF reflects bone formation and also depends on regional blood flow. The injection of $^{[18F]}$NaF in MM patients results in a tracer uptake at the margins of osteolytic lesions. Although the initial results in MM were promising, studies comparing $^{[18F]}$NaF PET/CT with $^{[18F]}$FDG PET/CT all showed inferior results for the detection and follow-up of MM lesions. At diagnosis, only 39% to 45% of the MM lesions were distinguished by $^{[18F]}$NaF PET/CT that also identified numerous degenerative bone lesions.

The rationale behind our combined strategy was that, in solid cancers including prostate and breast cancers, the combined injection of both $^{[18F]}$NaF and $^{[18F]}$FDG allowed PET/CT to be more effective than MRI and bone scintigraphy in assessing bone disease extent. This difference was mainly seen in patients with prostate cancer, where combinatorial PET/CT had a higher sensitivity compared with MRI and bone scintigraphy. In the current study, an FL is defined as a lesion observed on one of the imaging techniques (cf Table 1). A PET-positive lesion was considered as an area of focally increased tracer uptake within bones (compared with normal bone marrow background uptake). A diffuse pattern on PET/CT was defined based on the diffuse bone osteolysis seen in CT images only. A mixed focal/diffuse pattern

### Table 1: Definitions of bone involvement

<table>
<thead>
<tr>
<th>Imaging Technique</th>
<th>Bone Involvement Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET/CT</td>
<td>Focal lesion: Focal area of visually detectable increased tracer uptake, with or without underlying bone destruction in CT images or as a hypoactive area on PET images with underlying bone osteolysis on CT image, whatever the size of FLs. Diffuse pattern: Countless osteolytic lesions disseminated throughout the skeleton in CT image. The diffuse pattern was considered as an area of focally increased tracer uptake within bones (compared with normal bone marrow background uptake).</td>
</tr>
<tr>
<td>MRI</td>
<td>Focal lesion: A circumscribed area with decreased signal intensity on T1-weighted images (compared with para-spinal muscles) and/or with hypersignal in grayscale maximum intensity projection of DW images. Salt-and-pepper pattern: Diffuse, inhomogeneous patchy appearance of the bone marrow on T1-weighted images. Diffuse pattern: Diffuse homogeneous hypointensity in the bone marrow on T1-weighted images (compared with para-spinal muscles).</td>
</tr>
<tr>
<td>CT</td>
<td>Focal lesion: An osteolytic bone lesion suspected to correspond to an MM bone lesion, whatever the size of FLs. Diffuse pattern: Countless osteolytic lesions disseminated throughout the skeleton.</td>
</tr>
<tr>
<td>WBXR</td>
<td>Focal lesion: An osteolytic bone lesion suspected to correspond to an MM bone lesion, whatever the size of FLs. Diffuse pattern: Countless osteolytic lesions disseminated throughout the skeleton.</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; FL, focal lesion; MM, multiple myeloma; MRI, magnetic resonance imaging; PET/CT, positron emission tomography combined with CT; WBXR, whole-body X-ray.

Bone lesions corresponding to degenerative changes were excluded.

### 2.1 Patients

This prospective monocentric study was conducted from September 2011 until 2014. Patients with a treatment-requiring plasma cell disorder (solitary plasmacytoma, MM) were prospectively included. Relapsing patients were included if the last treatment was stopped more than 3 months before the inclusion. The protocol (EudraCT 2013-004807-38) was approved by the Ethics Committee of the University Hospital of Liege and enrolled patients signed a specific informed consent form.

### 2.2 Data acquisition and analysis

The imaging procedures are described in the Supporting Information. PET and CT images were reviewed by two experienced nuclear medicine physicians and one radiologist to detect FLs and/or diffuse bone marrow involvement. The greatest diameter of every osteolytic FL detected on CT images was measured, and the relationship between the detection rate of PET FLs and the size of osteolytic lesions was investigated. The MR, CT, and XR images were analyzed by four radiologists blinded to each other and to PET/CT results. The diameter of every FL was recorded.

### 2.3 Definitions

In the current study, an FL is defined as a lesion observed on one of the imaging techniques (cf Table 1). A PET-positive lesion was defined as an area of focally increased tracer uptake within bones (compared with normal bone marrow background uptake). A diffuse pattern on PET/CT was defined based on the diffuse bone osteolysis seen in CT images only. A mixed focal/diffuse pattern
was also classified as diffuse. Regarding MRI, a diffuse pattern was
diagnosed when no areas of normal marrow were seen. Marrow
involvement was characterized as focal when only focal areas of
abnormal marrow were seen. The pattern of bone involvement was
described by each technique for every patient according to
definitions given in Table 1. Degenerative bone lesions that showed
tracer uptake were not considered as PET-positive MM lesions.
Detection of extramedullary lesions was also considered. The FLs
were classified according to their location: pelvis, skull, limbs,
spine, ribs, and one location including the sternum, scapula, and
clavicles.

2.4 | Comparison of detection rates

The detection rate of FLs by every imaging technique was assessed
(including PET images considered alone), without considering the
size of FLs, and compared with each other. Because of the possibility
of detecting additional healed lesions in relapsed compared with
newly diagnosed settings, the analyses were performed in each
population separately. When comparing two imaging techniques,
we initially considered a technique capable of identifying a FL
(identified by another imaging technique) when the FL was recog-
nized or when a diffuse pattern was seen on CT or MRI. This com-
parison was critical for comparing MRI results where the diffuse
pattern was more prevalent. In a separate analysis, the comparison
of imaging techniques detection rates was conducted without taking
the diffuse pattern into account. Throughout the manuscript, a MM
lesion refers to a FL and/or the presence of a corresponding diffuse
pattern; a FL refers to a FL without any sign of a corresponding
diffuse pattern.

2.5 | Ionizing radiation exposure

Effective dose was calculated according to the 2015 International
Commission on Radiological Protection recommendations23 and was
estimated for every patient by cumulating the effective dose related
to the injected activity of [18F]NaF (mean ± SD: 132 ± 11 MBq) and
[18F]FDG (mean ± SD: 253 ± 15 MBq) and the effective dose related
to CT part.

2.6 | Statistical analyses

The McNemar test was used to compare the detection rates of imag-
ing techniques, and the Kruskal-Wallis test was used to estimate the
relationship between the detection rate of PET FLs and the size of
FLs measured with CT. The chi-square test was used to compare the
pattern of bone involvement between patients with newly diagnosed
MM or relapsed MM.

3 | RESULTS

3.1 | Patients

Four of the 30 initially included patients were excluded because of
delays between the imaging techniques (two patients) or incomplete
imaging (two patients). Finally, 13 patients with newly diagnosed and
suspected treatment-requiring MM and 13 patients with relapsed
MM were included. Patient characteristics are presented in Table 2.
The median delay between scans was 7 days (range: 0-36 d).

At diagnosis, overall, 296 FLs were detected. Per patient, one to
three FLs (n = 3), four to 10 FLs (n = 4), or more than 10 FLs (n = 6)
were detected (Table S1). The pattern of bone marrow involvement
was focal (n = 7/13; 54%) or combined diffuse and focal (n = 6/13;
46%). At relapse, overall, 234 FLs were detected. Per patient, one to
three FLs (n = 1), four to 10 FLs (n = 2), or more than 10 FLs (n = 9)
were detected; one patient with relapsed MM did not present any
FL (Table S2). No extramedullary disease was detected by any of the
imaging techniques.

3.2 | Detection rates on a per-lesion basis

In patients with newly diagnosed MM, 84% of FLs were detected with
[18F]NaF/[18F]FDG PET/CT (Figure 1A) while 50%, 59% and 14.5%
were detected by MRI, CT alone, and WBXR, respectively. At relapse,
the detection rates of [18F]NaF/[18F]FDG PET/CT, MRI, CT alone, and
WBXR were 64%, 45%, 43%, and 13%, respectively (Figure S1).

Overall, only 65% of FLs detected by PET/CT showed [18F]NaF/
[18F]FDG uptake, and osteolytic lesions showing [18F]NaF/[18F]FDG
uptake were generally larger (mean: 10 mm, range: 4-75 mm) com-
pared with those without uptake (mean: 6 mm, range: 4-40 mm;
P = 0.0003).

<table>
<thead>
<tr>
<th>TABLE 2 Patients’ characteristics</th>
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<tr>
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<tr>
<td>Newly diagnosed MM (n = 13)</td>
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<tr>
<td>Relapsed MM (n = 13)</td>
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<tr>
<td>Age (median, range)</td>
</tr>
<tr>
<td>64 y, 46-81 y</td>
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<tr>
<td>58 y, 31-82 y</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
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<td>IgA</td>
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<tr>
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<td>Stage II</td>
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<td>5</td>
</tr>
<tr>
<td>Stage III</td>
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<td>3</td>
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</tbody>
</table>

Abbreviation: MM, multiple myeloma.
Diffuse and salt-and-pepper patterns were described by MRI, in patients with newly diagnosed MM (n = 3 and n = 2, respectively) and in patients with relapsed MM (n = 6 and n = 3, respectively). The majority of FLs detected with MRI showed abnormal diffusion (94.5% at diagnosis and 90% at relapse).

When radiologists had access to the PET and CT acquisitions, they detect more osteolytic FLs compared with the analysis of CT results alone. This was observed at diagnosis ($P < 0.0001$) and at relapse ($P = 0.0009$), reflecting the synergy resulting from the combination of PET and CT.

### 3.3 Detection rates according to the location of FLs

Both at diagnosis and at relapse, the detection rate of WBXR was significantly lower compared with those of the other techniques (Figure 2), except for FLs in the skull where the results of WBXR were similar to PET/CT and in the limbs where the detection rate of XR was similar to CT and PET, but lower than those of PET/CT and MRI. At all other locations, the detection rate of PET/CT performed at diagnosis was significantly ($P \leq 0.0046$) higher than those of PET and CT alone and also outscored MRI ($P \leq 0.016$) except for FLs located in the pelvis and limbs for which their detection rates were similar (Figure 3A).

At relapse, the global detection rate of PET/CT was 97% and thus similar to CT and significantly higher than that of MRI (n = 200; 85%; $P < 0.0001$). PET/CT identified more lesions in the spine, limbs, and shoulder region, while MRI identified more lesions in the pelvis and in the ribs (Figure 3B). As expected, the detection rate of WBXR was significantly lower than those of all other techniques in both populations ($P < 0.0001$) as illustrated in Figure 4 where WBXR did not detect a large pelvic lesion.

### 3.4 Comparison of detection rates

At diagnosis, the detection rate of MM lesions, taking the diffuse pattern on CT or MRI (n = 296 FLs; 100%) into account, was significantly different ($P \leq 0.0047$) between techniques (Figure 3A): XR (n = 92; 31%) < PET (n = 160; 54%) < CT (n = 214; 72%) < MRI (n = 257, 87%) < PET/CT (n = 277; 94%). At relapse (Figure 3B), the detection rate of PET/CT (n = 226; 97%) was similar to CT (n = 228; 97%; $P = 0.16$) and significantly higher than that of MRI (n = 200; 85%; $P < 0.0001$). The detection rate of MRI was significantly higher than that of PET (n = 102; 44%; $P < 0.0001$). We also compared techniques without taking the diffuse pattern into account. In that case, the detection rate of PET/CT was significantly higher than those of MRI ($P \leq 0.0006$), CT ($P < 0.0001$), and PET ($P < 0.0001$), in patients with both newly diagnosed and relapsed MM (Figure 3).

### 3.5 Comparison of newly diagnosed MM and relapsed MM

The number of FLs per patient did not differ in the two populations. The proportion of osteolytic FLs detected with PET/CT and showing
tracer uptake was similar ($P = 0.2776$) in newly diagnosed ($n = 122/216; 57\%$) and in relapsed patients ($n = 64/129; 50\%$).

Few PET FLs were hypoactive, and the proportion of hypoactive PET FLs was significantly higher ($P = 0.0005$) in patients with relapsed ($n = 23/234; 10\%$) compared with newly diagnosed patients ($n = 7/296; 2\%$). An additional difference between the two populations was the higher prevalence of a diffuse pattern of bone marrow involvement (identified by CT or MRI) in relapsed compared with newly diagnosed patients ($n = 11/13; 85\%$ versus $6/13; 46\%; P = 0.0148$). Finally, the proportion of lesions according to their location was significantly different ($P = 0.0051$) with a significantly higher proportion of spine lesions in newly diagnosed patients ($n = 101/296; 34\%$ versus $n = 53/234; 22\%; P = 0.0039$) and a significantly higher proportion of limb lesions in relapsed patients ($n = 46/234; 20\%$ versus $n = 28/296; 9\%; P = 0.0008$).

Since $[^{18}\text{F}]\text{NaF}$ uptake is frequently seen in osteoblastic reactions at the border of bone lesions, especially in healed bone lesions after therapy, we studied the proportion of PET hypoactive osteolytic lesions and the presence of sclerotic margins in patients with relapsing disease. We found that the proportion of PET hypoactive lesions in the osteolytic lesions without peripheral sclerosis was $5.3\%$ ($5/94$) while it was $48.6\%$ ($17/35$) in osteolytic lesions with peripheral sclerosis in CT images. These results indicate that the proportion of hypoactive lesions is significantly more important in case of sclerosis ($P < 0.0001$, chi-square test; Table 3).

### 3.6 Clinical implication

On a per-patient basis, the detection rates of PET/CT and MRI were similar both at diagnosis (92\%) and at relapse (85\%). However, PET/CT did not show any abnormality in one newly diagnosed patient for whom MRI showed a single lesion in a thoracic vertebra (Figure S3). PET/CT was negative in two relapsing patients for whom MRI showed a diffuse infiltration in one and a single large sacral lesion with diffuse pattern in the other patient. The agreements and disagreements between MRI and PET/CT at the patient’s level are presented in Tables S3 and S4.

In newly diagnosed patients, carrying out PET/CT upgraded the diagnosis from solitary plasmacytoma to MM in one patient and confirmed the indication for treatment by identifying large lytic lesions in two additional patients, presenting only doubtful skull lesions if only WBXR and MRI would have been considered (as illustrated in Figure 4). For one patient with relapsed MM, PET/CT and MRI identified a large hypermetabolic lesion in the pelvis that required radiotherapy.

### 3.7 Exposure to ionizing radiation

The mean ± SD cumulative effective dose of the combined $[^{18}\text{F}]\text{FDG}$ and $[^{18}\text{F}]\text{NaF}$ PET/CT procedure was $14.3 \pm 1.2 \text{ mSv}$. The effective
dose related to CT, $^{18}\text{F}$NaF, and $^{18}\text{F}$FDG was $7.1 \pm 0.9$, $2.2 \pm 0.2$, and $4.8 \pm 0.3$ mSv, respectively. The effective dose of $^{18}\text{F}$FDG PET/CT without injection of $^{18}\text{F}$NaF would have been $11.9 \pm 0.9$ mSv.

### DISCUSSION

This work showed that the combined $^{18}\text{F}$NaF/$^{18}\text{F}$FDG PET/CT provided the highest detection rate of FLs, compared with MRI, CT alone, PET alone, or XR. The comparison of our results to previous studies assessing $^{18}\text{F}$FDG PET/CT for the detection of MM lesions is difficult, in particular due to the lack of standardized criteria for the definition of PET positivity.\textsuperscript{8,14,24,25} Moreover, when considering the comparison with MRI, the variations of MR acquisition parameters need to be taken in account. Regardless of these methodological aspects, studies showed FLs detection rate of $^{18}\text{F}$FDG PET/CT varying from 65% to 82% in patients with newly diagnosed MM on a per-patient basis, and studies showed similar performances when comparing $^{18}\text{F}$FDG PET/CT with MRI.\textsuperscript{8,14,24,25} The results obtained with our combined injection are not superior to the results obtained with $^{18}\text{F}$FDG PET/CT alone and do not support the routine use of combining both tracers.
A limitation of the combined injection of tracers is that the information on bone formation given by \(^{18}\text{F}\)NaF uptake and prognostic significance of \(^{18}\text{F}\)FDG uptake cannot be discriminated in PET/CT images (Figure S2). Additionally and presumably, it is most likely that combined \(^{18}\text{F}\)NaF/\(^{18}\text{F}\)FDG PET/CT will not be suitable for treatment assessment, in particular due to the delayed changes of \(^{18}\text{F}\)NaF uptake by MM lesions after treatment initiation. Our study was not designed to compare the detection rates of combined tracer injection versus \(^{18}\text{F}\)FDG alone. The latter would have required an additional separate \(^{18}\text{F}\)FDG PET/CT. In our study, combinatorial PET scan detected 65% of the lesions seen in newly diagnosed patients, and its detection rate was lower compared with standard low-dose CT. This percentage is comparable with the detection rate of \(^{18}\text{F}\)FDG PET, which ranges between 60% and 80%. Since the detection of lytic bone lesions is one of the main criteria for starting an anti-MM treatment, WBCT is currently considered as the standard technique for investigating MM-induced bone disease of myeloma bone disease.

According to the IMWG, an MRI of the spine and pelvis can be used in cases where WBMRI is not available. However, in our population, the prevalence of FLs located out of the field of view of an MRI limited to the spine and pelvis was high: 39% and 50% of the lesions would have been missed at diagnosis or at relapse, respectively. Therefore, MRI restricted to the spine and pelvis may not be sufficient in patients with MM and particularly so in relapsed patients (as illustrated in Figure 5).

The arms were positioned alongside the body during PET/CT image acquisition, inducing artifacts in CT images of the spine. Since the present work, in order to reduce CT artifacts in the spine in clinical setting, MM patient arms are raised above the head for acquisition, if possible. Peripheral FLs located beyond humeral bones and femurs were not detected in newly diagnosed patients, while they were detected in four patients at relapse (radius: \(n = 1\) patient; fibula: \(n = 3\) patients), suggesting that WB acquisition from vertex to toes could be considered in relapsing MM.

**TABLE 3** PET findings in osteolytic lesions with or without peripheral sclerosis, based on CT images, in patients with relapsed MM

<table>
<thead>
<tr>
<th>PET Findings</th>
<th>Without Sclerosis</th>
<th>Sclerotic Lesions</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions with tracer uptake</td>
<td>57</td>
<td>7</td>
<td>64</td>
</tr>
<tr>
<td>Sclerotic lesions</td>
<td>5</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>No lesion in PET images</td>
<td>32</td>
<td>11</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>94 (73%)</td>
<td>35 (27%)</td>
<td>129 (100%)</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; MM, multiple myeloma; PET, positron emission tomography.
The highest proportion of hypoactive PET FLs in relapsed MM may be related to potentially healed lesions. Nevertheless, out of the 23 hypoactive PET osteolytic FLs, 14 (61%) showed abnormalities in MR images (n = 6/23 FLs and n = 8/23 diffuse patterns) and only 9 of 23 (39%) did not show any abnormality in MR images. Additionally, hypoactive PET osteolytic FLs were also detected in newly diagnosed patients (n = 7), and all showed abnormalities in MR images (n = 6 diffuse patterns and n = 1 FL). These observations suggest that hypoactive FLs in \([^{18}\text{F}]{\text{NaF}}/[^{18}\text{F}]{\text{FDG}}\) PET images may not necessarily correspond to healed lesions.

Around 10% of FLs detected with PET/CT were pathological fractures (ribs or vertebra), and all corresponded to abnormalities on MR images (diffuse and/or focal patterns); nevertheless, specificity of both PET/CT and MRI for the differentiation of fracture with or without underlying MM lesion is limited.19,30

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**REFERENCES**


SUPPORTING INFORMATION
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