

Aim of the study: The aim of this study was to analyse the diagnostic accuracy of ^{18}F -fluoro-ethyl-tyrosine (^{18}F -FET) PET/CT tracer in multiple myeloma.

Material and methods: The analysed group included: patients with newly diagnosed active myeloma (eight patients); in very good partial remission or complete remission (VGPR or CR) after treatment (nine patients); and with active disease after relapse (15 patients).

Results: In patients with newly diagnosed myeloma, 64 lesions were found using CT and 83 lesions using ^{18}F -FET. In six patients, the number of lesions using CT and ^{18}F -FET was the same, and two had more lesions with the ^{18}F -FET than with the CT. Patients in VGPR or CR had no FET-positive lesions. Fourteen out of 15 patients with active relapsed myeloma had 47 FET-positive lesions, CT assessment of the same group showed 282 lesions. In one patient with relapse soft tissue mass was found with ^{18}F -FET but not with CT.

Conclusions: ^{18}F -FET can be a promising alternative to ^{18}F -FDG PET/CT for myeloma-related bone disease diagnosis.

Key words: multiple myeloma, ^{18}F -FET, ^{18}F -FDG PET/CT.

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^{18}F -fluoro-ethyl-tyrosine (^{18}F -FET) PET/CT as a potential new diagnostic tool in multiple myeloma: a preliminary study

Jarosław Czyż¹, Bogdan Małkowski², Artur Jurczyszyn³, Norbert Grząsko⁴, Rita Łopatto², Monika Olejniczak⁵, Adriana Czyż¹, Anna Jachalska⁶

¹Department of Haematology, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Bydgoszcz, Poland

²Department of Nuclear Medicine, Professor Franciszek Lukaszczyk Oncology Centre in Bydgoszcz, Bydgoszcz, Poland

³Department of Haematology, Jagiellonian University Medical College, Krakow, Poland

⁴Department of Haematology and Bone Marrow Transplantation, Medical University of Lublin, Lublin, Poland

⁵Department of Oncology, Professor Franciszek Lukaszczyk Oncology Centre in Bydgoszcz, Bydgoszcz, Poland

⁶Department of Haematology, Dr. Jan Bizioł University Hospital No. 2 in Bydgoszcz, Bydgoszcz, Poland

Introduction

The majority of multiple myeloma patients develop bone lesions at some stage of their disease. According to the guidelines of the International Myeloma Working Group (IMWG), skeletal surveys have been considered the gold standard imaging modality for many years [1]. Unfortunately, this technique is insufficiently sensitive to detect early lesions or monitor treatment responses. A revision of the IMWG guidelines introduced magnetic resonance imaging (MRI) into routine clinical practice, but positive positron emission tomography (PET) alone remains insufficient to diagnose active myeloma [2]. In contrast to skeletal surveys and computed tomography (CT), PET combined with CT (PET/CT) allows for direct, non-invasive visualisation of the tumour burden [3]. PET/CT using fluorine-labelled deoxyglucose (2-deoxy-2- ^{18}F fluoro-D-glucose [^{18}F -FDG] PET/CT) can be more effective than a skeletal survey in upstaging patients with suspected smouldering myeloma [4, 5]. On the other hand, ^{18}F -FDG PET/CT can be equivocal and difficult to interpret in some patients with a new diagnosis. For this reason, the main indication for ^{18}F -FDG PET/CT is currently evaluating and monitoring response to therapy [6]. Fluoro-ethyl-tyrosine (^{18}F -FET) is an amino acid tracer used in the diagnosis of brain tumours [7, 8]. Myeloma cell lines have the ability to transport and partially metabolise ^{18}F -FET [9]. Similarly to ^{11}C -methionine, ^{18}F -FET is not only taken up but also is incorporated into newly synthesised proteins [9, 10]. It can be of special interest while visualisation of plasma cell mass is a target. The aim of this study was to analyse the metabolism of ^{18}F -FET tracer *in vivo*, in both the active phases of multiple myeloma and in patients who have responded to chemotherapy, to assess the potential utility of the application of ^{18}F -FET in the clinical setting.

Material and methods

This study was conducted between 2014 and 2017. Thirty-two patients were included (Table 1). There were eight patients with newly diagnosed active myeloma, nine with previously treated disease in plateau phase (one in complete remission [CR] and eight in very good partial remission [VGPR] after first-line treatment), and 15 with active, relapsed disease.

Table 1. Clinical characteristic of the analysed patients

Number of patient	Sex	Age	Previous treatment	Disease status	Bone disease assessment		
					Number of lesions on FET	SUV _{max} value (range)	Number of lesions on CT
1	M	62	Yes	VGPR	0	–	5
2	F	44	Yes	Active, relapsed	4	3.4 (2.7–3.9)	42
3	M	55	Yes	Active, relapsed	1	4.3	52
4	M	75	Yes	Active, relapsed	8	3.1 (2.1–3.7)	48
5	F	58	Yes	VGPR	0	–	0
6	F	73	Yes	Active, relapsed	5	3.7 (3.5–3.9)	13
7	M	68	Yes	Active, relapsed	4	6.2 (4.5–7.6)	31
8	F	60	Yes	Active, relapsed	2	3.3 (2.6–4.2)	8
9	M	62	Yes	Active, relapsed	1	3.0	1
10	M	64	Yes	Active, relapsed	5	5.1 (2.5–8.7)	58
11	M	55	Yes	Active, relapsed	3	2.4 (2.2–2.6)	5
12	F	55	Yes	VGPR	0	–	2
13	M	63	Yes	VGPR	0	–	61
14	F	57	Yes	VGPR	0	–	1
15	M	79	Yes	VGPR	0	–	34
16	M	41	No	Active, not treated	3	4.4 (3.4–5.3)	3
17	F	73	Yes	Active, relapsed	0	–	1
18	F	52	Yes	Active, relapsed	2	3.3 (3.2–3.3)	3
19	F	64	No	Active, not treated	2	5.7 (4.9–6.5)	2
20	F	50	Yes	Active, relapsed	2	1.9 (1.8–1.9)	8
21	M	56	No	Active, not treated	22	4.9 (2.6–8.2)	22
22	M	61	No	Active, not treated	6	3.2 (2.6–8.2)	6
23	F	71	Yes	VGPR	0	–	0
24	M	54	Yes	Active, relapsed	7	2.4 (2.2–3.0)	11
25	M	64	No	Active, not treated	3	3.9 (2.6–5.2)	3
26	F	79	No	Active, not treated	18	3.4 (2.9–4.4)	9
27	M	75	Yes	VGPR	0	–	68
28	M	43	Yes	Active, relapsed	1	3.6	0
29	F	78	No	Active, not treated	28	3.5 (3.1–3.7)	18
30	F	63	No	Active, not treated	1	4.1	1
31	F	59	Yes	Active, relapsed	1	2.90	1
32	F	52	Yes	CR	0	–	1

FET – fluoro-ethyl-tyrosine, CT – computed tomography, VGPR – very good partial remission, CR – complete remission

Patients were diagnosed as follows: 14 with IgG myeloma, followed by 11 with light chain disease and seven with IgA type, 16 with κ light chain, and 16 with λ . Among treated patients the median number of previous chemotherapy lines was two (range one to five), and seven patients had autologous stem cell transplant (Table 1). Only patients with VGPR or CR were included in the inactive myeloma group assessment [11]. The clinical evaluation was based on the following: physical examination, bone marrow aspirate or trephine assessment, blood count, concentration of monoclonal protein and free light chains in serum and urine, serum levels of creatinine, calcium, albumin, and β -2 microglobulin. Each complete remission (disappearance of monoclonal protein on immunofixation or Bence-

Jones protein on 24-hour urine collection) was histologically confirmed by trephine biopsy according to uniform criteria. Patients were not routinely explored by MRI unless surgical local procedure on the spine was considered. MRI tests were usually done after initiation of the treatment, so they could not be compared with PET/CT results.

Whole body imaging with ^{18}F -FET PET/CT

Patients fasted for at least four hours before the administration of ^{18}F -FET tracer, in order to maintain similar test conditions. The examinations were performed using Biograph mCT128 or Biograph mCT 20 scanners. All participants underwent whole body imaging in two steps: first from the top of the skull to the upper third of the thigh and

then from the upper quarter of the thigh down to the feet. Patients received 350 ± 10 MBq of ¹⁸F-FET intravenously. The time between the injection and acquisition was 60 minutes. Acquisition of the trunk image was performed with the patient's arms arranged alongside the body. The CT scan was acquired with the following parameters: Care Dose 4D, 120 kV, and pitch 0.8 or 0.7 depending on the scanner. The CT scan was acquired during shallow breathing. The PET-scan was acquired with an acquisition time of 2.7 minutes per bed position. The total acquisition time was approximately 50 minutes depending on the height of the patient. The CT data were used for attenuation correction. Images were reconstructed using a commercial three-dimensional iterative reconstruction algorithm called TrueX+tof (UltraHD-PET; 200 × 200 matrix, 3-mm intervals, three iterations, 21 and 24 subsets). The standardised uptake value (SUV_{max}) for each lesion was calculated on PET images using the whole-body low-dose CT as a reference. To compare the metabolic activity of ¹⁸F-FET in areas affected by MM with unaffected regions, several "background" areas of the body were tested: the Th10 and L4 vertebrae and the spleen, the brain, and the left gluteus maximus muscle. To assess the physiological activity in these organs SUV_{max} values were calculated. During the PET examination, the result was considered positive when focal myeloma infiltration, defined as circumscribed areas of high ¹⁸F-FET PET metabolism with a corresponding bone or soft tissue change, was found. The SUV_{max} values of the background areas were calculated in volume of interest (VOI) 5 cm³ ±10%. These regions were chosen according to observation of the whole-body PET. These areas were most stable and assured enough space to create VOIs as stated above. Each case was evaluated independently by two experienced nuclear medicine specialists working independently (BM, RL), as well as by an experienced radiologist.

Sensitivity was calculated as the number of lesions correctly diagnosed by FET as being positive in CT out of the total positive lesions in CT ($S = TP/TP + FN$), and expressed as a percentage. The positive predictive value (PPV) was calculated as the number of lesions correctly diagnosed by FET as being positive in CT out of the total positive lesions in FET ($PPV = TP/TP + FP$), and expressed as a percentage ($PPV = TP/TP + FP$). The true positive (TP) event number was defined as the set of lesions correctly diagnosed by FET as being positive in CT. The number of false positive (FP) events was defined as the set of lesions predicted by FET as being positive in CT.

The study was performed in accordance with the principles of the Helsinki Declaration and was based on the approval given by the local Bioethical Committee. Each participant signed an informed consent form to participate in the study.

Results

Because histological proof could not be obtained for every lesion, low-dose CT served as a standard of reference in this study. Focal lesions were found on CT in 29 of 32 patients (91%). In total, 518 lesions were found (median 6, range 1–68; Table 1). Foci described as positive presented

significant enhanced ¹⁸F-FET uptake. In all patients with multiple lesions the metabolic activity (SUV_{max}) in the background areas, apart from the spleen, was lower than the lowest SUV_{max} value in pathologically involved areas. The only exceptions were two patients in whom one lesion had a value lower than one background area, but the activity inside the lesion was clearly higher than in surrounding tissue. In total, 129 ¹⁸F-FET-positive lesions were found in 22 of 32 patients (69%), with a median of 3 (range: 1–28). The mean SUV_{max} of focal osteolytic ¹⁸F-FET-positive lesions was 3.45 (range: 1.9–6.2) in comparison to the mean SUV_{max} of the background: brain 1.15 (range: 0.6–1.8; $p < 0.00004$), the mean SUV_{max} of the spleen was 2.15 (range: 1.7–3.4; $p < 0.00008$), the mean SUV_{max} of the spine at Th10 was 1.90 (range: 1.2–3.7; $p < 0.00005$), the mean SUV_{max} of the spine at L4 was 1.80 (range: 1.1–4.9; $p < 0.00005$), and mean SUV_{max} of the gluteus muscle was 1.75 (range: 1.4–2.3; $p < 0.00001$) (Table 2). In total, 129 lesions were visible on ¹⁸F-FET and 518 lesions on CT. The sensitivity of the ¹⁸F-FET/CT assessment was 55.58% (95% CI: 52.31–58.80%), specificity was 9.09% (95% CI: 1.12–29.16%), PPV was 96.28% (95% CI: 95.23–98.55%), and the negative predictive value was 0.48% (95% CI: 0.13–1.78%).

From the myeloma activity point of view, three groups could be discriminated: those with newly diagnosed active myeloma (eight patients); myeloma patients with confirmed VGPR or CR after treatment (nine patients), and those with active disease after relapse (15 patients). On CT scans, lesions were found in all patients with newly diagnosed disease (median 5, range: 1–22), in all but two patients from the second group (median 5, range: 1–68), and in 14 patients with relapsed myeloma (median 8, range: 1–52; Figs. 1–3; Table 1).

All but one patient with active disease (group 1 and group 3) had ¹⁸F-FET-positive lesions (median 3, range: 1–28). In patients from group 1 with newly diagnosed myeloma, 64 lesions were found on CT and 83 on ¹⁸F-FET. In six patients, the number of lesions on CT and ¹⁸F-FET was the same, and two had more lesions on ¹⁸F-FET than on CT (Table 1). In this subgroup the sensitivity of ¹⁸F-FET was 100% (95% CI: 96.65–100%), specificity was 9.09% (1.12–29.16%), and PPV was 80.58% (95% CI: 78–82.57%).

Patients with CR and VGPR had no FET-positive lesions. One of the patients in CR, according to the assessment of the treating physician, had an equivocal lesion on CT, which was positive on standard PET with fluorine-labelled deoxyglucose (2-deoxy-2-[¹⁸F]fluoro-D-glucose [¹⁸F-FDG]) used as a tracer. Subsequent examination with ¹⁸F-FET tracer did not reveal any activity (Fig. 4). Obviously, the biopsy of the affected area could not be performed.

From 15 patients with active relapsed myeloma (group 3), 47 FET-positive lesions were found in 14 of them (median 3, range: 1–8). CT assessment of the same group showed 282 lesions in 14 patients (median 9.5, range: 1–58). One of the patients had soft tissue mass (soft palate) with increased FET activity and with no visible lesions on CT.

The sensitivity of the test was 54.44% (95% CI: 50.04–58.79%), specificity was 66.67% (95% CI: 9.43–99.16%), and the PPV was 99.65% (95% CI: 98.27–99.93%).

Table 2. SUV value of the affected area and the background in the analysed group of patients

Patients			Background				
Number of patient	Number of bone lesions in FET	SUV _{max} value (range)	Brain	Spleen	Spine Th10	Spine L4	Musculus gluteus
1	0	–	Max 1.3; Mean 0.9	Max 2.3; Mean 1.5	Max 3.1; Mean 1.6	Max 2.8; Mean 1.5	Max 1.6; Mean 1.1
2	4	3.4 (2.7–3.9)	Max 1.2; Mean 0.8	Max 2.5; Mean 1.4	Max 2.5; Mean 1.5	Max 2.5; Mean 1.5	Max 1.6; Mean 1.1
3	1	4.3	Max 0.8; Mean 0.5	Max 2.1; Mean 1.2	Max 2.2; Mean 1.1	Max 1.7; Mean 1.0	Max 1.8; Mean 1.2
4	8	3.1 (2.1–3.7)	Max 0.8; Mean 0.6	Max 2.1; Mean 1.5	Max 2.0; Mean 1.4	Max 1.8; Mean 1.1	Max 1.9; Mean 1.3
5	0	–	Max 1.3; Mean 0.9	Max 2.0; Mean 1.3	Max 1.6; Mean 1.1	Max 2.0; Mean 1.2	Max 1.7; Mean 1.1
6	5	3.7 (3.5–3.9)	Max 1.2; Mean 0.8	Max 3.0; Mean 2.0	Max 3.3; Mean 1.5	Max 2.2; Mean 1.4	Max 2.3; Mean 1.5
7	4	6.2 (4.5–7.6)	Max 1.3; Mean 0.8	Max 3.4; Mean 2.2	Max 3.7; Mean 2.0	Max 4.9; Mean 2.7	Max 2.2; Mean 1.3
8	2	3.3 (2.6–4.2)	Max 1.5; Mean 1.1	Max 2.1; Mean 1.4	Max 1.9; Mean 1.3	Max 1.3; Mean 0.7	Max 2.0; Mean 1.3
9	1	3.0	Max 1.1; Mean 0.9	Max 2.3; Mean 1.7	Max 2.0; Mean 1.3	Max 1.5; Mean 1.0	Max 1.7; Mean 1.3
10	5	5.1 (2.5–8.7)	Max 1.0; Mean 0.9	Max 2.5; Mean 2.2	Max 2.2; Mean 1.9	Max 1.2; Mean 1.1	Max 2.1; Mean 1.8
11	3	2.4 (2.2–2.6)	Max 1.5; Mean 1.4	Max 2.6; Mean 2.3	Max 1.8; Mean 1.7	Max 2.1; Mean 1.9	Max 2.0; Mean 1.8
12	0	–	Max 0.8; Mean 0.5	Max 2.0; Mean 1.4	Max 2.1; Mean 1.4	Max 1.4; Mean 0.9	Max 1.4; Mean 1.0
13	0	–	Max 0.6; Mean 0.5	Max 1.9; Mean 1.4	Max 1.5; Mean 1.0	Max 1.3; Mean 0.8	Max 1.4; Mean 1.1
14	0	–	Max 1.0; Mean 0.8	Max 2.0; Mean 1.8	Max 1.5; Mean 0.9	Max 1.5; Mean 1.2	Max 2.2; Mean 1.8
15	0	–	Max 1.1; Mean 0.9	Max 2.5; Mean 1.8	Max 1.9; Mean 1.0	Max 2.0; Mean 1.4	Max 1.8; Mean 1.4
16	3	4.4 (3.4–5.3)	Max 0.8; Mean 0.6	Max 2.1; Mean 1.5	Max 2.1; Mean 1.3	Max 2.1; Mean 1.2	Max 1.4; Mean 1.1
17	0	–	Max 1.2; Mean 1.0	Max 2.2; Mean 1.8	Max 1.6; Mean 1.1	Max 1.8; Mean 1.4	Max 1.8; Mean 1.5
18	2	3.3 (3.2–3.3)	Max 1.3; Mean 1.0	Max 2.6; Mean 2.1	Max 1.6; Mean 1.0	Max 1.8; Mean 1.4	Max 1.9; Mean 1.5
19	2	5.7 (4.9–6.5)	Max 1.0; Mean 0.8	Max 1.8; Mean 1.4	Max 1.3; Mean 1.0	Max 1.1; Mean 0.8	Max 1.5; Mean 1.3
20	2	1.9 (1.8–1.9)	Max 1.4; Mean 1.2	Max 2.4; Mean 1.9	Max 1.6; Mean 1.2	Max 1.2; Mean 0.8	Max 1.6; Mean 1.3
21	22	4.9 (2.6–8.2)	Max 1.2; Mean 1.0	Max 1.7; Mean 1.5	Max 2.5; Mean 1.7	Max 2.3; Mean 1.8	Max 1.5; Mean 1.3
22	6	3.2 (2.6–8.2)	Max 1.0; Mean 0.7	Max 1.8; Mean 1.2	Max 1.7; Mean 1.1	Max 1.5; Mean 1.1	Max 1.5; Mean 1.2
23	0	–	Max 1.4; Mean 1.1	Max 2.4; Mean 1.9	Max 1.6; Mean 1.1	Max 2.3; Mean 1.5	Max 2.0; Mean 1.6
24	7	2.4 (2.2–3.0)	Max 1.0; Mean 0.8	Max 2.2; Mean 1.7	Max 1.7; Mean 1.2	Max 1.3; Mean 0.9	Max 1.7; Mean 1.5
25	3	3.9 (2.6–5.2)	Max 1.0; Mean 0.8	Max 2.0; Mean 1.4	Max 1.8; Mean 1.2	Max 2.0; Mean 1.2	Max 1.7; Mean 1.2
26	18	3.4 (2.9–4.4)	Max 1.3; Mean 1.0	Max 2.5; Mean 2.0	Max 3.3; Mean 2.4	Max 3.5; Mean 2.4	Max 2.3; Mean 2.0

Table 2. Cont.

Patients			Background				
Number of patient	Number of bone lesions in FET	SUV _{max} value (range)	Brain	Spleen	Spine Th10	Spine L4	Musculus gluteus
27	0	–	Max 0.9; Mean 0.6	Max 2.1; Mean 1.8	Max 2.2 Mean 1.2	Max 1.2; Mean 0.8	Max 1.8; Mean 1.4
28	1	3.6	Max 1.0; Mean 0.8	Max 2.0; Mean 1.6	Max 1.5; Mean 1.0	Max 1.6; Mean 1.2	Max 1.7; Mean 1.5
29	28	3.5 (3.1–3.7)	Max 1.1; Mean 0.8	Max 2.7; Mean 2.2	Max 3.7; Mean 2.5	Max 3.3; Mean 2.6	Max 1.6; Mean 1.3
30	1	4.1	Max 1.2; Mean 1.2	Max 2.5; Mean 2.4	Max 2.5; Mean 2.2	Max 2.3; Mean 2.0	Max 1.9; Mean 1.7
31	1	2.90	Max 1.1; Mean 0.9	Max 2.0; Mean 1.7	Max 1.2; Mean 0.6	Max 1.5; Mean 1.2	Max 1.8; Mean 1.5
32	0	–	Max 1.2; Mean 0.9	Max 2.4; Mean 1.7	Max 1.6; Mean 1.3	Max 1.8; Mean 1.3	Max 1.8; Mean 1.4

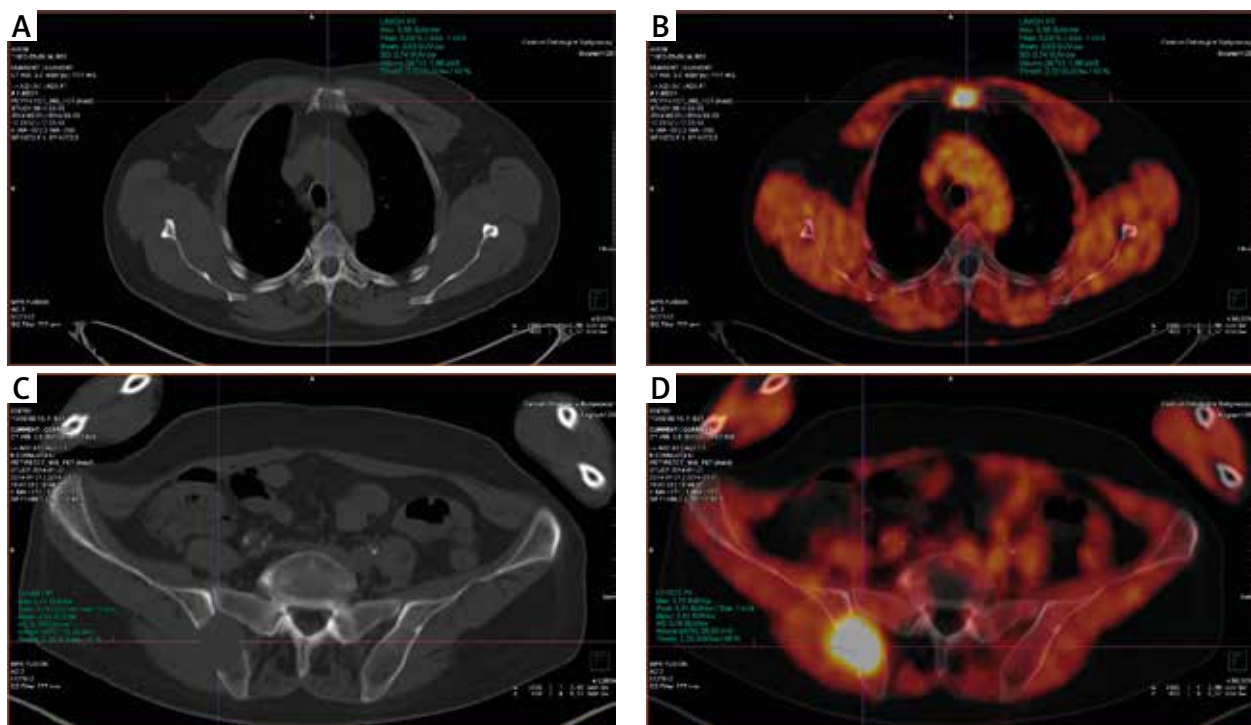


Fig. 1. Patient no. 12, newly diagnosed multiple myeloma before the treatment. **A)** Computed tomography – lytic lesion localised in the sternum. **B)** The same lesion on ¹⁸F-FET PET/CT fusion image with high FET uptake (converted to black and white). **C)** Computed tomography – lytic lesion localised in the right iliac crest. **D)** ¹⁸F-FET PET/CT fusion image with high FET uptake in iliac crest

Discussion

Numerous studies have shown the usefulness of ¹⁸F-FDG PET/CT in the diagnosis of bone disease in patients with myeloma [12]. In a prospective study designed to compare ¹⁸F-FDG PET-CT with whole-body X-ray (WBXR) and MRI, the latter was shown to be the most sensitive in the detection of diffuse bone marrow involvement, but PET/CT provided additional and valuable information for the assessment of myeloma bone disease in areas not covered by MRI and WBXR [13, 14]. In a systematic review of eight studies, including 798 patients, and comparing ¹⁸F-FDG PET/CT with WBXR and MRI, a higher sensitivity of FDG PET in the detec-

tion of myeloma bone lesions was shown in six studies [15]. Other reviews confirmed no difference between ¹⁸F-FDG PET/CT and MRI in the detection of myeloma-related bone disease in terms of sensitivity and specificity [3, 16]. The IMWG updated criteria for diagnosis of multiple myeloma says that increased uptake on PET/CT alone is not adequate for diagnosis of myeloma [2]. The reason for this is the possibility of false positive and false negative results [17, 18]. There are multiple reasons for false positivity of ¹⁸F-FDG PET, including: inflammation or infection, bone remodelling, recent chemotherapy or radiotherapy, or growth factor support; and for false negativity: hyper-

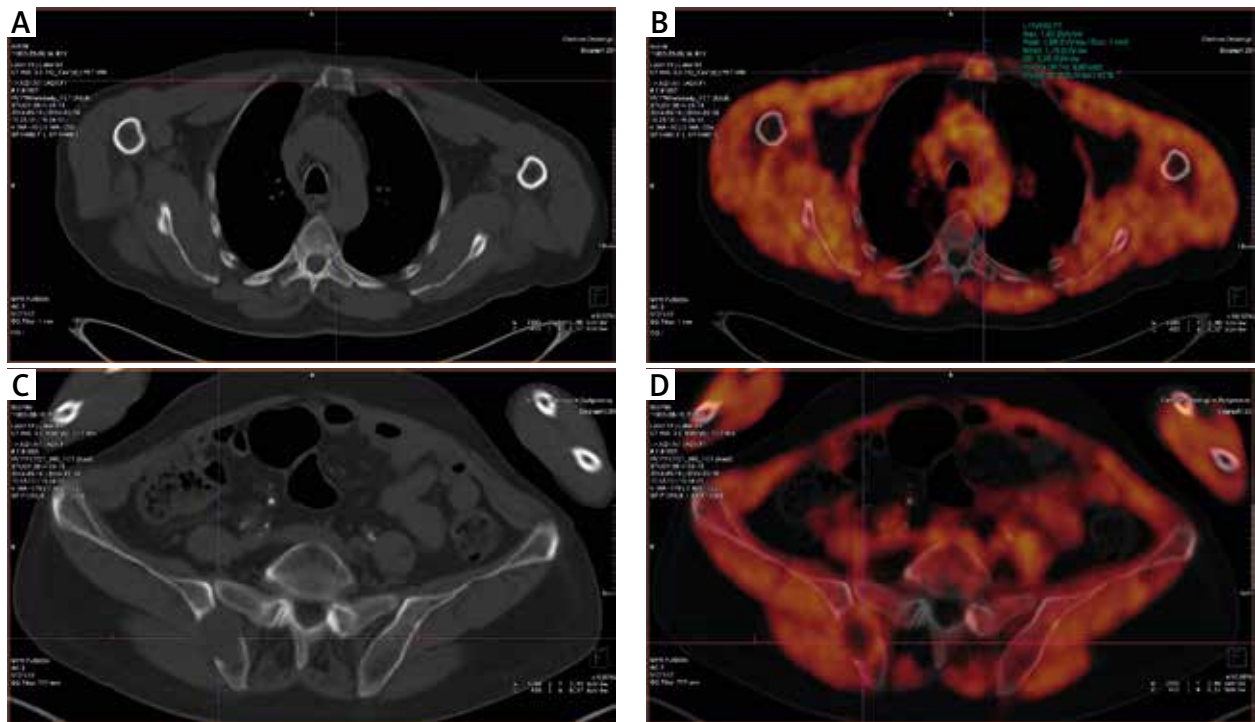


Fig. 2. The same patient after completion of therapy. **A)** Computed tomography (CT) – lytic lesions localised in the sternum – no difference to the status before therapy. **B)** ^{18}F -FET PET/CT, fusion image with low FET uptake in the lytic lesion visible on CT in sternum. **C)** Computed tomography – lytic lesion localised in the right iliac crest – no difference to the status before therapy. **D)** ^{18}F -FET PET/CT fusion image with low FET uptake in iliac crest

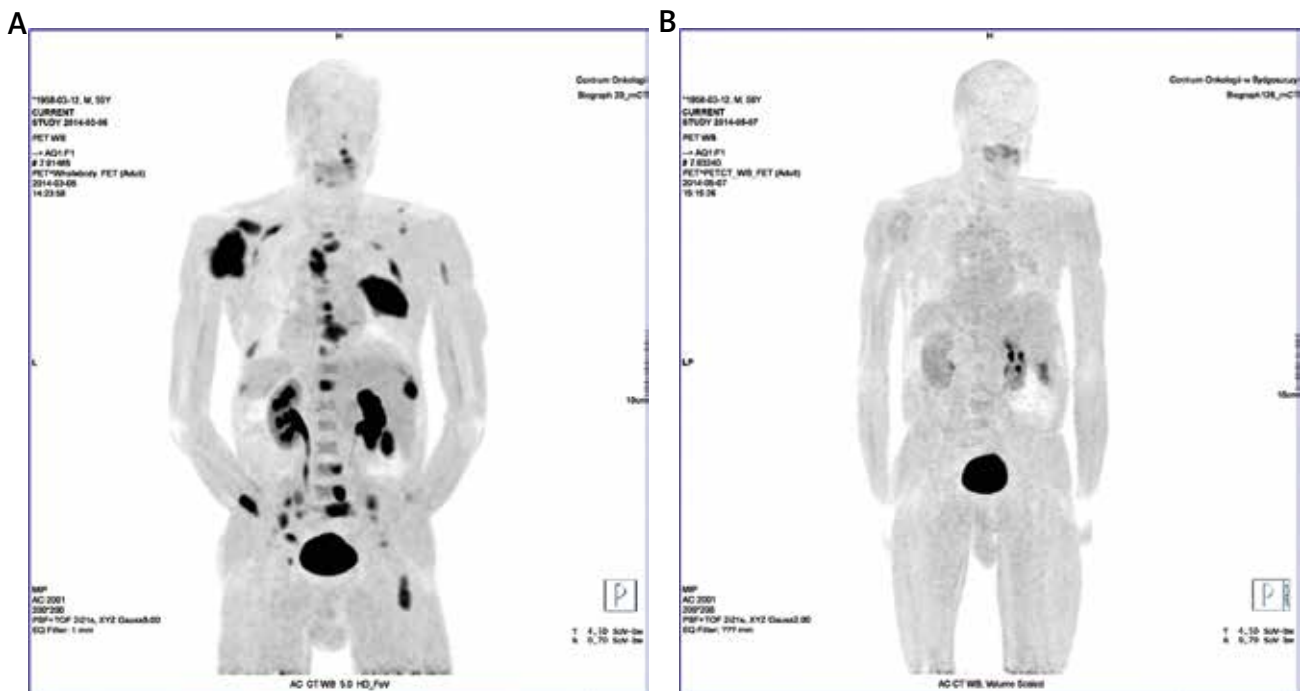


Fig. 3. Patient no. 21. Myeloma-related lesions before and after the treatment. MIP images of the FET uptake in the patient body. **A)** Multiple FET lesions localised in the skeleton of the pathological uptake of FET. **B)** MIP image after chemotherapy. Complete disappearance of pathological FET uptake may suggest metabolic response to the treatment

glycaemia, recent administration of high-dose steroids, or the presence of sub-centimetre lytic lesions close to the brain [6]. As yet, no consensus has been reached regarding an appropriate SUV_{max} cut-off value to distinguish positive and negative readings [19].

In order to individualise and improve patients' management there is an obvious need to develop a novel tracer. In an attempt to find such a tracer some research groups focused on a characteristic feature of plasma cells – excessive production of immunoglobulin particles and used

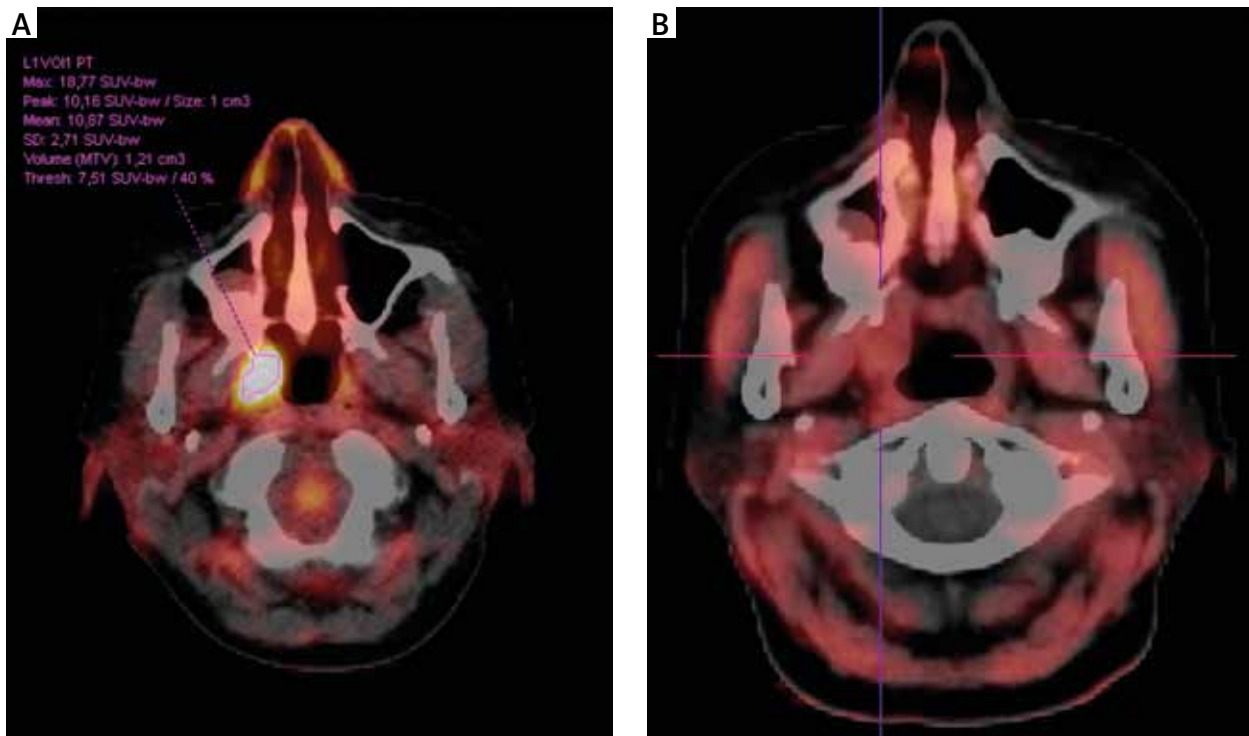


Fig. 4. Patient no. 32. **A)** Solitary myeloma lesion suspected in the right palatine tonsil, positive in FDG PET/CT, showing high uptake SUV_{max} 18.77. **B)** Negative FET PET/CT result showing no tracer uptake in the right tonsil. No subsequent clinical progression of myeloma was observed on further follow-up

amino acid labelled with radioisotopes, such as methionine labelled with carbon (¹¹C-MET) or a fluorine-labelled fluoro-ethyl-tyrosine (¹⁸F-FET) instead of FDG. One of them is ¹¹C-MET, which is used in the diagnosis of a wide range of cancers. In preliminary myeloma studies it was found that the uptake of ¹¹C-MET exceeds that of ¹⁸F-FDG by 1.5- to 5-fold [9, 20].

Luckerath *et al.* evaluated the radiotracers ¹¹C-MET and ¹⁸F-FDG, on myeloma cells, to monitor the response to anti-myeloma-therapy, and for outcome prediction [10]. ¹¹C-MET-uptake, but not ¹⁸F-FDG, significantly decreased after a bortezomib injection to myeloma cell lines. Early reduction of ¹¹C-MET correlated with improved survival in mice.

Usefulness of ¹¹C-MET in a clinical scenario was described by Nakamoto *et al.*, who compared ¹¹C-MET and ¹⁸F-FDG *in vivo* using this tracer to analyse 20 patients (six patients with active myeloma and 14 after the treatment) [21]. All the results were compared between the two scans. ¹¹C-MET uptake tended to be higher and more lesions of grade 3 or 4 were depicted by ¹¹C-MET than by ¹⁸F-FDG PET/CT. The patient-based sensitivity, specificity, and accuracy of ¹¹C-MET for restaging were 89%, 100%, and 93%, respectively, while those of FDG were 78%, 100%, and 86%, respectively [21].

Recent results were published by Lapa *et al.*, who presented 43 patients with myeloma, who underwent both MET- and FDG-PET/CT for staging or re-staging [22]. Eleven of them had a new disease, and 32 had been pre-treated with various numbers of chemotherapy regimens. Scans

were compared regarding patients and lesions. Both tracers correlated with a degree of plasma cell bone marrow involvement and clinical parameters reflecting disease activity with ¹¹C-MET demonstrating a stronger correlation. ¹¹C-MET was also superior in staging and re-staging intra- and extramedullary bone lesions.

Okasaki *et al.* compared ¹¹C-MET with ¹⁸F-FDG and ¹¹C-4-thymidine (¹¹C-4DST) in 64 patients. Traditional CT was able to find 55 focal lytic lesions in 24 patients. Both ¹¹C-MET and ¹¹C-4DST were equally effective in myeloma-related lesions, and both were more sensitive than ¹⁸F-FDG. Unfortunately, ¹¹C-MET can be used only in centres that are equipped with cyclotron and have the possibility of ¹¹C production.

Another tracer investigated in patients with multiple myeloma by Nanni *et al.* was ¹¹C-Choline. Ten of the patients underwent standard ¹¹C-Choline PET/CT and ¹⁸F-FDG PET/CT. ¹¹C-Choline PET/CT was capable of finding more lesions and showed a higher mean SUV_{max} than ¹⁸F-FDG. Other tracers investigated by various groups were: 3'-fluoro-3'-deoxy-L-thymidine (¹⁸F-FLT), ¹⁸F-Sodium Fluoride (¹⁸F-NaF), or ¹⁸F-fluorocholine (FCH) [23–26]. All of them required further investigations.

In contrast to the above, very little is known about ¹⁸F-FET in the setting of multiple myeloma bone disease. For ¹⁸F-FET PET/CT cyclotron on-site is not necessary; it can be implemented in every centre using PET/CT, but the data from cell lines suggests that the relative uptake of ¹¹C-MET exceeds that of ¹⁸F-FET 7 to 20-fold [9]. In our study, we tried to assess the sensitivity and positive predictive value

of functional imaging modalities ^{18}F -FET in detecting myeloma-related lesions using CT as a standard of reference.

A mismatch between PET/CT with ^{18}F -FDG as a tracer and anatomic imaging modalities, regarding demonstration of myeloma lesions, was described by Caers *et al.* [3]. It confirmed that standard low-dose CT is not capable of discriminating between vital and fibrotic myeloma-related lesions [27].

Focal lesions may remain positive on CT or hyperintense on MRI for several months after treatment, in responding or non-responding patients, because of treatment-induced necrosis or inflammation [28], which could be an explanation for the difference between the number of lesions observed in CT and in FET in patients previously treated and being in plateau or with recurrence of the disease in our patients. On the other hand, in untreated patients from our cohort the number of observed lesions on ^{18}F -FET PET/CT was higher than on standard CT, which might suggest a possible increased sensitivity of our tracer in the detection of active disease. Our hypothesis is that high ^{18}F -FET uptake reflects activity of the plasma cell production.

Association between intracellular Ig light chains with MET uptake was already reported by Luckeath *et al.* [9]. The presence of myeloma-related bone disease, reflected by positive lesions on CT, is a secondary event. It can explain why ^{18}F -FET-positive lesions were found in areas negative on CT in patients with primary or secondary active disease but not in patients in CR or VGPR.

We hope that ^{18}F -FET tracer will be able to overcome the weaknesses of PET/CT based on ^{18}F -FDG. A lack of activity in the patient with complete remission can suggest better specificity of ^{18}F -FET than standard ^{18}F -FDG PET/CT. It is possible that ^{18}F -FET PET/CT is capable of patients with active disease, which we saw in the group of patients with newly diagnosed myeloma. Because of the small cohort of patients in our study the presented results require further validation.

The authors declare no conflict of interest.

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Address for correspondence

Jarosław Czyż

Department of Haematology
Ludwik Rydygier *Collegium Medicum* in Bydgoszcz
Nicolaus Copernicus University in Torun
75 Ujejskiego St.
85-168 Bydgoszcz, Poland
e-mail: jczyz@onet.pl

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