Aim of the study: The aim of this study was to analyse the diagnostic accuracy of 18F-fluoro-ethyl-tyrosine (18F-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 18F-FET. In six patients, the number of lesions using CT and 18F-FET was the same, and two had more lesions with the 18F-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 18F-FET but not with CT.

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

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

Original paper

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

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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-[18F]fluoro-D-glucose [18F-FDG] PET/CT) can be more effective than a skeletal survey in upstaging patients with suspected smouldering myeloma [4, 5]. On the other hand, 18F-FDG PET/CT can be equivocal and difficult to interpret in some patients with a new diagnosis. For this reason, the main indication for 18F-FDG PET/CT is currently evaluating and monitoring response to therapy [6]. Fluoro-ethyl-tyrosine (18F-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 18F-FET [9]. Similarly to 11C-methionine, 18F-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 18F-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 18F-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.
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 β2 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 18F-FET PET/CT

Patients fasted for at least four hours before the administration of 18F-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

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### Table 1. Clinical characteristic of the analysed patients

| Number of patient | Sex | Age | Previous treatment | Disease status | Bone disease assessment |
|-------------------|-----|-----|--------------------|----------------|------------------------|
|                   |     |     |                    |                |                        |
| 1                 | M   | 62  | Yes                | VGPR           |                        |
| 2                 | F   | 44  | Yes                | Active, relapsed |                        |
| 3                 | M   | 55  | Yes                | Active, relapsed |                        |
| 4                 | M   | 75  | Yes                | Active, relapsed |                        |
| 5                 | F   | 58  | Yes                | VGPR           |                        |
| 6                 | F   | 73  | Yes                | Active, relapsed |                        |
| 7                 | M   | 68  | Yes                | Active, relapsed |                        |
| 8                 | F   | 60  | Yes                | Active, relapsed |                        |
| 9                 | M   | 62  | Yes                | Active, relapsed |                        |
| 10                | M   | 64  | Yes                | Active, relapsed |                        |
| 11                | M   | 55  | Yes                | Active, relapsed |                        |
| 12                | F   | 55  | Yes                | VGPR           |                        |
| 13                | M   | 63  | Yes                | VGPR           |                        |
| 14                | F   | 57  | Yes                | VGPR           |                        |
| 15                | M   | 79  | Yes                | VGPR           |                        |
| 16                | M   | 41  | No                 | Active, not treated | 3.4 (3.4-5.3) |
| 17                | F   | 73  | Yes                | Active, relapsed |                        |
| 18                | F   | 52  | Yes                | Active, relapsed | 3.3 (3.2-3.3) |
| 19                | F   | 64  | No                 | Active, not treated | 5.7 (4.9-6.5) |
| 20                | F   | 50  | Yes                | Active, relapsed | 1.9 (1.8-1.9) |
| 21                | M   | 56  | No                 | Active, not treated | 4.9 (2.6-8.2) |
| 22                | M   | 61  | No                 | Active, not treated | 3.2 (2.6-8.2) |
| 23                | F   | 71  | Yes                | VGPR           |                        |
| 24                | M   | 54  | Yes                | Active, relapsed | 7.4 (2.2-3.0) |
| 25                | M   | 64  | No                 | Active, not treated | 3.9 (2.6-5.2) |
| 26                | F   | 79  | No                 | Active, not treated | 3.4 (2.9-4.4) |
| 27                | M   | 75  | Yes                | VGPR           |                        |
| 28                | M   | 43  | Yes                | Active, relapsed | 1.3 (3.1-3.7) |
| 29                | F   | 78  | No                 | Active, not treated | 1.4 (1.3-3.7) |
| 30                | F   | 63  | No                 | Active, not treated | 1.4 (1.3-3.7) |
| 31                | F   | 59  | Yes                | Active, relapsed | 1.2 (1.3-3.7) |
| 32                | F   | 52  | Yes                | CR             |                        |

FET – fluoro-ethyl-tyrosine, CT – computed tomography, VGPR – very good partial remission, CR – complete remission
then from the upper quarter of the thigh down to the feet. Patients received $350 \pm 10$ MBq of $^{18}$F-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 x 200 matrix, 3-mm intervals, three iterations, 21 and 24 subsets). The standardised uptake value (SUVmax) for each lesion was calculated on PET images using the whole-body low-dose CT as a reference. To compare the metabolic activity of $^{18}$F-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 SUVmax values were calculated. During the PET examination, the result was considered positive when focal myeloma infiltration, defined as circumscribed areas of high $^{18}$F-FET metabolism with increased FET activity and with no visible lesions on CT. The PPV was defined as the set of lesions predicted by $^{18}$F-FET as being positive in CT out of the total positive lesions in CT (PPV = TP/TP + FP), and expressed as a percentage. The positive 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 $^{18}$F-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 $^{18}$F-FET. In six patients, the number of lesions on CT and $^{18}$F-FET was the same, and two had more lesions on $^{18}$F-FET than on CT (Table 1). In this subgroup the sensitivity of $^{18}$F-FET was 100% (95% CI: 96.65–100%), 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%).

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-$^{18}$F-fluoro-D-glucose [$^{18}$F-FDG]) used as a tracer. Subsequent examination with $^{18}$F-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: 94.3–99.16%), 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 | SUVmax 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 1.1 | 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 1.6; 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 1.0 | 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 |
**Discussion**

Numerous studies have shown the usefulness of $^{18}$F-FDG PET/CT in the diagnosis of bone disease in patients with myeloma [12]. In a prospective study designed to compare $^{18}$F-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 $^{18}$F-FDG PET/CT with WBXR and MRI, a higher sensitivity of FDG PET in the detection of myeloma bone lesions was shown in six studies [15]. Other reviews confirmed no difference between $^{18}$F-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 $^{18}$F-FDG PET, including: inflammation or infection, bone remodelling, recent chemotherapy or radiotherapy, or growth factor support; and for false negativity: hyper-

**Table 2. Cont.**

| 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 $^{18}$F-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) $^{18}$F-FET PET/CT fusion image with high FET uptake in iliac crest.
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 sterna. 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$_{\text{max}}$ 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...
18F-fluoro-ethyl-tyrosine (18F-FET) PET/CT as a potential new diagnostic tool in multiple myeloma: a preliminary study

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’tithymidine (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 1C-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 SUVmax 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

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**Fig. 4.** Patient no. 32. **A)** Solitary myeloma lesion suspected in the right palatine tonsil, positive in FDG PET/CT, showing high uptake SUVmax 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.
of functional imaging modalities [18F-FET in detecting myeloma-related lesions using CT as a standard of reference. A mismatch between PET/CT with [18F-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 PET 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 [18F-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 [18F-FET uptake reflects activity of the plasma cell proliferation.

Association between intracellular Ig light chains with MET uptake was already reported by Lucketh et al. [9]. The presence of myeloma-related bone disease, reflected by positive lesions on CT, is a secondary event. It can explain why [18F-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 [18F-FET tracer will be able to overcome the weaknesses of PET/CT based on [18F-FDG. A lack of activity in the patient with complete remission can suggest better specificity of [18F-FET than standard [18F-FDG PET/CT. It is possible that [18F-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.

References
1. Dimopoulos M, Terpos E, Comenzo RL, Tosi P, Beksac M, Sezer O, et al. International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma. Leukemia 2009; 23: 1545-1556.
2. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014; 15: 538-548.
3. Caers J, Wirthofs N, Hillengass J, Simoni P, Zamagni E, Hustinx R, et al. The role of positron emission tomography-computed tomography and magnetic resonance imaging in diagnosis and follow up of multiple myeloma. Haematologica 2014; 99: 629-637.
4. Mihaliović J, Goldsmith SJ. Multiple myeloma: [18F-FDG PET/CT and diagnostic imaging. Semin Nucl Med 2015; 45: 16-31.
5. Brodella MA, Steinbach L, Caputo G, Segal G, Hawkins R. Value of FDG PET in the assessment of patients with multiple myeloma. AJR Am J Roentgenol 2005; 184: 1199-1204.
6. Cavo M, Terpos E, Nanni C, Moreau P, Lentzsch S, Zweigmann S, et al. Role of 18F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group. Lancet Oncol 2017; 18: e206-e217.
7. Floeth FW, Sabel M, Stoffels G, Pauleit D, Hamacher K, Steiger HL, et al. Prognostic value of [18F-fluoroethyl-L-tyrosine PET and MRI in small nonspecific incidental brain lesions. J Nucl Med 2008; 49: 730-737.
8. Wang HE, Wu SY, Chang CW, Liu RS, Hwang LC, Lee TW, et al. Evaluation of F-18-labeled amino acid derivatives and [18F]FDG as PET probes in a brain tumor-bearing animal model. Nucl Med Biol 2005; 32: 367-375.
9. Lucketh K, Lapa C, Spahmann A, Jorg G, Samnick S, Rosenwald A, et al. Targeting paraprotein biosynthesis for non-invasive characterization of myeloma biology. PLoS One 2013; 8: e84840.
10. Lucketh K, Lapa C, Albert C, Herrmann K, Jorg G, Samnick S, et al. 11C-Methionine-PET: a novel and sensitive tool for monitoring of early response to treatment in multiple myeloma. Oncotarget 2015; 6: 8418-8429.
11. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia 2006; 20: 1467-1473.
12. Cavo M, Terpos E, Nanni C, Moreau P, Lentzsch S, Zweigmann S, et al. Role of 18F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group. Lancet Oncol 2017; 18: e206-e217.
13. Zamagni E, Nanni C, Patriarca E, Englaro E, Castellucci P, Geatti O, et al. A prospective comparison of [18F-fluorodeoxyglucose positron emission tomography-computed tomography, magnetic resonance imaging and whole-body planar radiographs in the assessment of bone disease in newly diagnosed multiple myeloma. Haematologica 2007; 92: 50-55.
14. Nanni C, Versari A, Chauvie S, Bertone E, Bianchi A, Rensi M, et al. Interpretation criteria for FDG PET/CT in multiple myeloma (IMPeTUs): final results. IMPeTUs (Italian myeloma criteria for PET Use). Eur J Nucl Med Mol Imaging 2018; 45: 712-719.
15. van Lammeren-Venema D, Regelink JC, Riphagen IJ, Zweegman S, Hoekstra OS, Zijlstra JM. [18F]-fluoro-deoxyglucose positron emission tomography in assessment of myeloma-related bone disease: a systematic review. Cancer 2012; 118: 1971-1981.
16. Weng WW, Dong ML, Zhang J, Yang J, Xu Q, Zhu YJ, et al. A systematic review of MRI, scintigraphy, FDG-PET/CT and FDG-PET/CT for diagnosis of multiple myeloma related bone disease-which is best? Asian Pac J Cancer Prev 2014; 15: 9879-9884.
17. Shortt CP, Gleeson TG, Breen KA, McHugh J, O’Connell MJ, O’Gorman PJ, et al. Whole-Body MRI versus PET in assessment of multiple myeloma disease activity. A JR Am J Roentgenol 2009; 192: 980-986.
18. Derlin T, Peldschus K, Munster S, Bannas P, Herrmann J, Stubić T, et al. Comparative diagnostic performance of [18F-FDG PET/CT versus whole-body MRI for determination of remission status in multiple myeloma after stem cell transplantation. Eur Radiol 2013; 23: 570-578.
19. Cavo M, Rajkumar SV, Palumbo A, Moreau P, Orlowski R, Blade J, et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. Blood 2011; 117: 6063-6073.
20. Dankler A, Liebsch P, Glätting G, Friesen C, Blumstein NM, Kocot O, et al. Multiple Myeloma: Molecular Imaging with 11C-Methionine PET/CT – Initial Experience. Radiology 2007; 242: 498-508.
21. Nakamoto Y, Kurihara K, Nishizawa M, Yamashita K, Nakatani K, Kondo T, et al. Clinical value of 11C-methionine PET/CT in patients with plasma cell malignancy: comparison with [18F]-FDG PET/CT. Eur J Nucl Med Mol Imaging 2013; 40: 708-715.
22. Lapa C, Knoop S, Schredler M, Rudelius M, Knoett M, Jorg G, et al. 11C-Methionine-PET in Multiple Myeloma: Correlation with Clinical Parameters and Bone Marrow Involvement. Theranostics 2016; 6: 254-261.
23. Agool A, Schot BW, Jager PL, Vellenga E. 18F-FLT PET in hematologic disorders: a novel technique to analyze the bone marrow compartment. J Nucl Med 2006; 47: 1592-1598.

24. Ak I, Onner H, Akay OM. Is there any complimentary role of F-18 NaF PET/CT in detecting of osseous involvement of multiple myeloma? A comparative study for F-18 FDG PET/CT and F-18 FDG NaF PET/CT. Ann Hematol 2015; 94: 1567-1575.

25. Ho CL, Chen S, Leung YL, Cheng T, Wong KN, Cheung SK, et al. 11C-acetate PET/CT for metabolic characterization of multiple myeloma: a comparative study with 18F-FDG PET/CT. J Nucl Med 2014; 55: 749-752.

26. Cassou-Mounat T, Balogova S, Nataf V, Calzada M, Huchet V, Kerrou K, et al. 18F-fluorocholine versus 18F-fluorodeoxyglucose for PET/CT imaging in patients with suspected relapsing or progressive multiple myeloma: a pilot study. Eur J Nucl Med Mol Imaging 2016; 43: 1995-2004.

27. Zamagni E, Cavo M. The role of imaging techniques in the management of multiple myeloma. Br J Haematol 2012; 159: 499-513.

28. Paiva B, van Dongen JJ, Orfao A. New criteria for response assessment: role of minimal residual disease in multiple myeloma. Blood 2015; 125: 3059-3068.

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Submitted: 26.01.2019
Accepted: 02.02.2019