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Can ^{18}F-FDG PET/MR Imaging Contribute to the Assessment of Bone Lesions in Patients with Plasma Cell Dyscrasias?

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Abstract

Objective: Two patient groups were studied for evaluation of detection efficacy of 18F-fluorodeoxyglucose positron emission tomography/magnetic resonance imaging (18F-FDG PET/MRI). The first group was dedicated to assess the possible early bone lesions of those patients who had been diagnosed with monoclonal gammopathy of undetermined significance/smouldering multiple myeloma (MGUS/SMM). In the second group, the detection sensitivity of the PET/CT and PET/MRI for bone lesions was compared to each other in patients with symptomatic plasmacytic myeloma (PCM).

Methods: 14 patients with MGUS/SMM and 27 patients with PCM were enrolled in this study. Initially, all patients underwent an 18F-FDG PET/CT examination and it was followed by a PET/MRI imaging.

Results: No bone lesion was detected with PET/CT and PET/MRI in patients either with MGUS and SMM. Bone marrow alteration was also not detected with PET/MRI in this group. Disease progression has not been revealed in the course of the 18 months follow-up period.

In regard to lesion detection, there was no difference between the PET/CT and PET/MRI in the symptomatic PCM group. The metabolic tumor volume (MTV) was found to be strongly correlating with both the β2-microglobulin serum level and the ISS stage.

Conclusion: PET/MRI is a reliable diagnostic tool for detection of bone lesions in plasma cell discrasias, and it is not inferior to the PET/CT imaging. The MTV measurement can provide a promising diagnostic tool for the direct assessment of myeloma tumor loading in the future.

Keywords: Plasmacytic myeloma; Monoclonal gammopathy of unknown significance Pet/Ct; Pet/Mri; suvmax; Metabolic tumor volume

Background

The wide spectrum of plasma cell dyscrasias includes the PCM, as the second most frequent haematological malignancy, and its pre-malignant conditions the MGUS and SMM [1]. Uncontrolled clonal proliferation of plasma cells and infiltration to bone marrow cause such end-organ damages as anaemia, hypercalcaemia, renal failure and bone disease [1]. By definition, MGUS and SMM are asymptomatic diseases and they do not exhibit end-organ damages [1].

The bone disease is the most frequent appearance of the multiple myeloma which occurs approximately in two-thirds of patients at the time of diagnosis and occurs almost in all patients during the course of the disease [2,3]. The bone involvement in myeloma substantially impairs the life quality and it is considered to the major cause of morbidity and mortality. Presence of lytic bone lesion calls for an immediate start of systemic therapy. The skeletal X-ray survey has been used for screening for a long period of time because it is widely available, simple, operates at low cost and characterized by low radiation dose. Lytic lesions only becoming evident at skeletal X-ray when more than 30-50% of the bone mineral density has already been lost [3], thus the skeletal survey underestimates the presence of lytic bone disease in a significant proportion of the patients. In a systematic review, Regelink et al. [4] have drawn a comparison between such modern imaging techniques as the MRI, the whole body low dose CT (WBLDCT), the PET/CT and the conventionally used radiography. The newer imaging methods had higher sensitivity than the skeletal survey, resulting as many as 80% or more efficiency in lesion detection [4]. The skeletal radiograms, the PET/CT and WBLDCT images were accepted as diagnostic evidence for the end-organ damages in PCM and they got proposed to use in the recommendation of the International Myeloma Working Group (IMWG) in 2014 [1]. The combination of PET with MRI has provided information simultaneously. The PET/MRI has had higher potential in the assessment of bone and bone marrow lesions and it secured a higher lesion detectability and diagnostic confidence in comparison to the performance of the PET/CT [5].

In our prospective study, the first cluster of our aims was the efficacy evaluation of the ^{18}F-FDG PET/CT and PET/MRI in detection of early lesions of bones and skeletal structures of patients with MGUS and SMM. Our second bunch of goals was to assess and compare the PET/CT and PET/MRI data in symptomatic-myeloma-multiple bone lesions, based on qualitative (lesion detection) and quantitative (lesional SUVmax, metabolic tumor volume) manners.

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Patients and Methods

Patients

Patients with monoclonal gammopathy were included in the study. Eligibility criteria included: the age of 18 years or above, previous laboratory and pathological confirmation of monoclonal gammopathy based on the recommendations of the International Myeloma Working Group [1]. All the study participants were newly diagnosed patient. The study was conducted according to the rules of good clinical and laboratory practice and the principles of the Helsinki Declaration. Written informed consent was obtained from the patients after that the purpose, nature and potential risks of the study had been explained to them and an institutional approval had also been issued by the local ethics committee. Diabetics, as well as patients representing general contraindications for MRI (e.g., pacemaker or internal metal fixateur) were excluded from the study.

Data acquisition

4.2.1 PET/CT: After intravenous injection of an average 280 MBq ± 89 MBq ^{18}F-fludeoxyglucose tracer, whole-body ^{18}F-FDG PET/CT was performed on a Biograph Truepoint 64 scanner (Siemens, Healthcare GmbH, Erlangen, Germany) within 67 ± 15 minutes. The blood glucose level of patients was duly controlled by samplings and kept under 200 mg/dL. The CT component of ^{18}F-FDG PET/CT was acquired using the manufacturer-supplied dose reduction software CareDose 4D (Siemens Healthcare GmbH, Erlangen, Germany) with pre-sets of 120 kV and 60 reference effective mAs. The PET data acquisition was performed in 10-15 bed positions (3 min per bed position for torso and 1.5 min per bed position for lower extremities) in axial field of view (FOV): 16.2 cm, having matrix size 168 × 168 and a Gaussian filter of 4 mm Full Width at Half Maximum (FWHM). Iterative ordered subset expectation maximization algorithm (OSEM) reconstruction (3 iterations and 8 subsets) was applied. Attenuation correction was calculated based on the obtained CT datasets.

PET/MRI: The whole-body ^{18}F-FDG PET/MRI examinations were performed on an integrated 3 Tesla PET/ MRI scanner (Biograph mMR, Siemens Healthcare GmbH, Erlangen, Germany) without contrast agent administration, and obtained with an average delay of 70 ± 57 minutes after the end of the PET/CT. No additional tracer was injected for the subsequent PET/MRI examinations. PET images were obtained in 3D mode, and got reconstructed using the OSEM algorithm, 3 iterations and 21 subsets, having a Gaussian filter with 4mm FWHM and a 172 × 172 image matrix. The PET data acquisition was performed in 9-11 bed positions (5 min per bed position). For MR-based PET attenuation, correction a two-point (fat, water) coronal 3D-DIXON-VIBE sequence was performed to generate a four-compartment model (background air, lungs, fat and muscle). The MRI data were obtained simultaneously including axial T1-weighted DIXON, coronal T2-weighted turbo-inversion-recovery-magnitude (TIRM) and axial DWI sequences as well, and for the vertebral column addition sagittal TIRM sequence was obtained. Both PET systems (from PET/CT and PET/MRI) were cross-calibrated by an activity-meter.

Data Analysis

Diagnostic images were evaluated using a dedicated Syngo.via software package (Siemens, Erlangen, Germany). Patient and lesion-based analyses of PET/CT and PET/MR images were performed separately to avoid recognition bias. The first session had comprised interpretation of the PET/CT images, and after 2 months the PET/MRI images were evaluated. A nuclear medicine physician and a radiologist, with more than 10 years of experience, visually analysed the images of the patients in random order, searching for myeloma suspicious foci. Lesion characterization was based on both metabolic and morphologic criteria and consensus was reached between the readers. Lesions likely to have other benign aetiology were excluded.

Measurement of MTV

For Metabolic Tumor Volume assessment, a dedicated Syngo. via MM Oncology application (version: VB 10, Siemens, Erlangen, Germany) was used. MTV was defined as it had been proposed by Fonti et al. [6]. Spheric volume of interest (VOI) was placed around each focal PCM lesions and VOI related SUVmax was calculated. All spatially connected voxels were added to the volume exceeding 40% of SUVmax level. Patient related overall MTV consisted of the sum of all measured lesion MTVs.

Statistical Analysis

For all the statistical analysis, R-software environment for statistical computing (version 3.3.0, R Foundation for Statistical Computing, Vienna, Austria) based on in-house developed programs were used. The statistical evaluation was performed using descriptive statistics, and Spearman's rank correlation analysis. The cut-off value of significance was $p<0.01$.

Results

41 patients (24 male, 17 female; mean age 64.5 years) with monoclonal gammopathy were enrolled to the study. The main characteristics of the included patients are shown in Table 1. The PET/CT and PET/MRI images were of good diagnostic quality having no artefacts in any cases. The cytogenetic results of the MGUS and SMM patients were normal. According to the ISS staging system, 8 patients have suffered from stage I, 10 patients from stage II and 9 patients from stage III PCM. The mean B2 microglobulin level was 3.8 mg/L in the multiple myeloma group (ranged: 2.9-7.2 mg/L).

All patients got characterized by both PET/CT and PET/MRI imaging, being either positive or negative case. All 14 patients with MGUS/SMM had negative ^{18}F-FDG bone marrow uptake pattern in both modalities. They had neither osseal nor extraosseal plasmocytoma. Their disease characteristics (M-component, lack of end-organ disease) had remain stable during a mean of 19 months after imaging. Two patients with SMM had no skeletal lesion on skeletal survey X-ray examination, however, they had a PET-negative skeletal lesion on CT-scan and a positive marrow pattern on MRI. Despite the presence of

Monoclonal gammopathy	Mean age (years)	Sex (M/F)	ISS stage			Mean of B2 uglobuline (mg/L)	CRAB-criterias positive (number of patients)			
			I	II	III		Hyper-calcaemia	Renal	Anemia	Bone
MGUS	66.5	7/5				2.1	no	no	no	no
SMM	61.2	1/1	2			2.3	no	no	no	no
Multiple myeloma	63.8	16/11	8	10	9	3.8	4	9	7	10

Table 1: The main characteristics of the patients with MGUS, SMM and MM.

bone and marrow lesions, these PET-negative patients did not progress to symptomatic myeloma during the 1.5 years observation period.

Before the start of anti-myeloma treatment, the 27 patients with multiple myeloma were examined by both modalities. The main disease characteristics are shown in Table 2.

The skeletal survey found lytic lesions in 10 patients (7 lytic lesions on the skull, 2 femoral, 1 lumbar spinal, 1 right rib and 2 pelvic lytic lesions). The PET/CT and PET MRI found more lytic lesions than the conventional skeletal survey (Figure 1). Figure 2 shows the PET-positive lesions of a patient, who has had a negative skeletal survey.

Paraprotein type	IgA-kappa	6
	IgA-lambda	2
	IgG-kappa	9
	IgG-lambda	4
	Kappa	2
	Lambda	3
	Non-secreter	1
Mean serum calcium (mmol/L)		2.38
Mean serum creatinine (umol/L)		97.4
Mean hemoglobine concentration (g/L)		107.93
Mean bone marrow clonal plasma cell infiltration (%)		68
Cytogenetics	normal	18
	hyperdiploid	7
	t(11:14) cyclin D1 upreg.	1
	t(14:16) MAF	1
	t(4:14) FGFR3 upreg.	0

Table 2: The main disease characteristics of patients with MM.

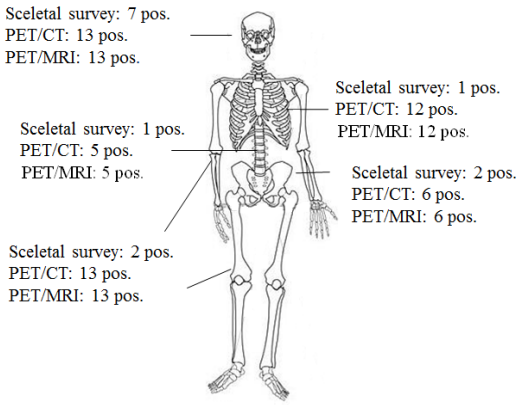

Figure 1: Distribution of focal lesions by sceletal regions detected by sceletel survey, PET/CT and PET/MRI. The positivity means that minimum one lesion was detected in a given patient in demonstrated region. The total amount of lytic lesions of each regions are not showed on figure. The new imaging techniques demonstrate more lesions, than conventional sceletal survey in all examined regions. There was no difference between the lesion detection of PET/CT and PET/MRI.

81 bone lesions related to myeloma were revealed by PET/CT in 27 patients. All the 81 lesions, which were detectable with PET/CT, were also found and described with PET/MRI in a later assessment. Regarding the ^{18}F-FDG bone marrow uptake pattern, 2 patients demonstrated a negative result, 17 patients a focal pattern, 4 patients a diffuse one and 4 patients a mixed pattern of tracer uptake in both modalities.

The mean of SUVmax values of skeletal lesions was 6.55 (ranged from 3.4-17.9). The SUVmax values did not correlate significantly with any clinical parameters.

The whole-body MTV values ranged from 11.9 to 3778 cm^3, with an average of 801.21 cm^3. We have found a statistically significant correlation between the MTV and β2 microglobulin levels (r=0.86) (Figure 3) and between the MTV and ISS stage (r = 0.87) using Spearman analysis.

Discussion

Importance of the ^{18}F-FDG PET and the PET/CT examinations in evaluation of PCM bone lesions remarkably increased in the last few years. PET/CT has high sensitivity to detect both medullary and extramedullary myeloma. Its role in the treatment response assessment and prognostic value have been documented in several papers [3,4,7,8]. In a recent report, on 149 patients with smouldering myeloma, the presence of focal lesions on whole-body MRI was the strongest adverse prognostic factor for subsequent progression to symptomatic myeloma [9].

PET/MRI is a novel combined functional imaging method, which could evaluate the microcirculation within the bone marrow and the diffusion of interstitial water molecules and glucose uptake, as they are surrogate markers for tumour activity [10,11]. Sachpekidis et al. [10] assessed the feasibility of use, the image quality and reproducibility of the ^{18}F-FDG PET/MRI method in 30 multiple myeloma patients.

MGUS is an asymptomatic plasma cell dyscrasia which has an average multiple myeloma progression risk of 1% per year [12]. Another asymptomatic plasma cell disorder is the SMM, which in comparison to MGUS is characterised with a higher risk of progression (10% per year) to PCM [13].

In these precursor diseases, due to the lack of end-organ damage such as lytic bone lesions, the "watch and wait" strategy is the cornerstone of the management. During this observation period, repeated laboratory investigations and skeletal surveys are needed.

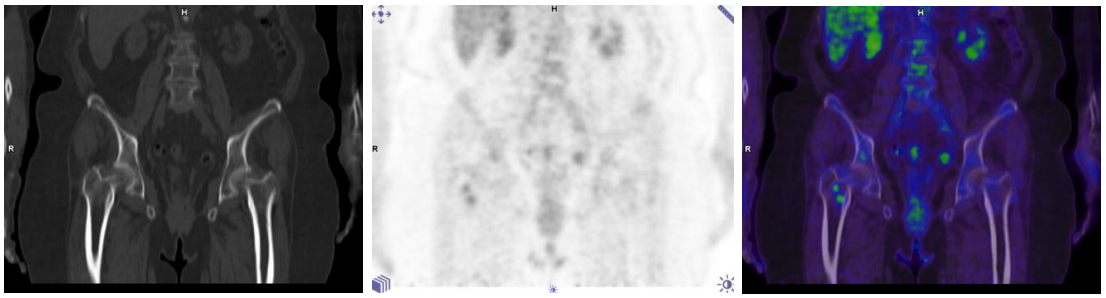

Figure 2a: Coronal CT, PET and PET/CT images. Focal radiopharmacon activity increase without structural change in right femur.

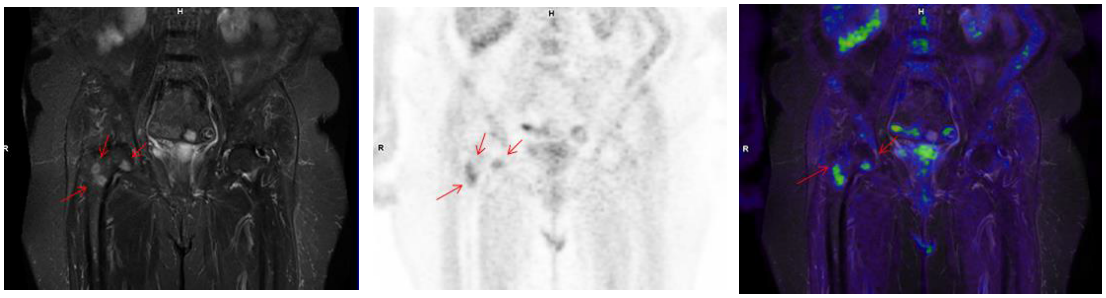

Figure 2b: Coronal T2 STIR MRI, PET and Fusioned PET/MRI images. T2 high intensity foci and focal radiopharmacon activity increase in right femur.The sceletal survey and other CRAB criterias were negative in a 76 years old woman with IgA-λ MM. (M-komp.: 11 g/l, bone marrow infiltration 40%)

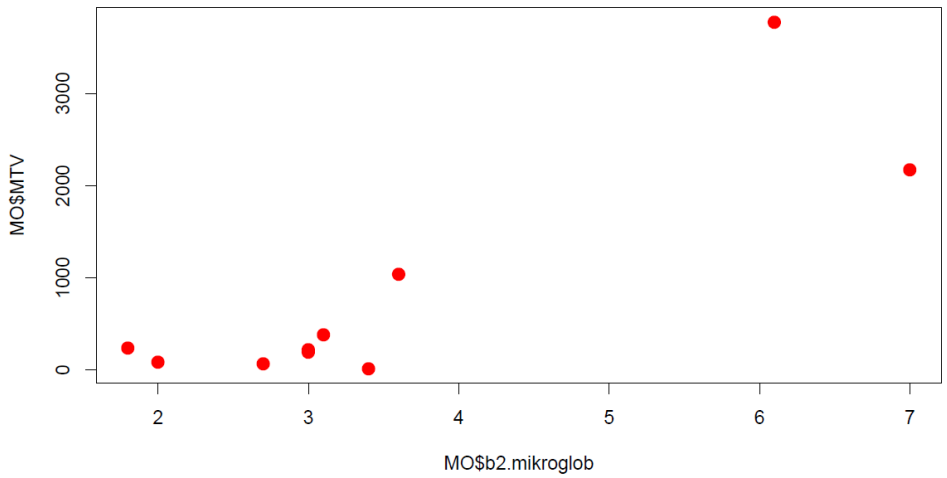

Figure 3: Correlation between metabolic tumor volumen and β2 microglobulin level. In the case of 2 patients who demonstrated a negative pattern, and in the case of 4 patients, who have a diffuse pattern in bone marrow, MVT was not calculated by our method.

The latter is the gold standard imaging modality for detection of osteolytic lesions, however it is not sensitive enough for detection of early osteolytic lesions requiring at least 30% cortical bone destruction [14] for a positive finding. This technique can detect neither intra- nor extramedullary disease. Therefore, it is difficult to determine that exact time point when the active treatment should be introduced. The new imaging techniques detect early bone lesions in plasma cell dyscrasias and therefore clinical investigations have already been started to assess their role in the assessments of these clinical conditions.

In our preliminary study the hybrid PET/MRI system provided good image quality in all cases without artefacts. None of the detection techniques, either the X-ray skeletal survey or the PET/CT and PET/MRI, detected skeletal lesions in our patients with MGUS. According to the repeated 3 months interval laboratory follow-up, these patients did not show progress at an average of 19 months period after imaging. The two SMM patients had negative findings for a lesion on skeletal survey, however, they had skeletal lesions on the CT-scan and positive bone marrow pattern by MRI. However, these lesions were PET-negative. During 1.5 years observation period PCM did not developed in these patients. These results showed that the premalignant PET-negative plasma cell dyscrasias did not progress to symptomatic myeloma for a long period of time. Therefore, longer follow-up is needed to find the exact time-point when the progression may occur.

We demonstrated that the 100% of all focal lesions were found by PET, independently whether it had belonged to either PET/CT or PET/MRI imaging systems. Our results confirm the findings of a similar study by Sachpekidis et al. [10] in which the PET parts of PET/CT and PET/MRI showed 94.2% lesion detection capability in multiple myeloma patients. Using the two devices, same uptake on PET images were detected, however, two different imaging time points had been applied. These data confirm that the lesion detection capability of PET/MRI in myeloma is not inferior to PET/CT imaging.

The low SUVmax values indicate that the metabolic activity in myeloma is mostly low. Only one patient had extremely high SUVmax value (17.9) who died soon after the treatment start. The SUVmax values did not correlate significantly with any clinical parameters.

The ^{18}F-FDG PET metabolic tumor volume assessment provides information about the 3D structure and the intratumoral biological variations of tumors [15,16]. MTV has been found a predictor of the patient outcome in human solid tumors and proved to be superior to SUVmax [17,18]. The MTV measured by ^{18}F-FDG PET may reflect the plasma cell mass throughout the whole body in PCM patients, thus it may provide a novel potential prognostic factor.

The Salmon-Durie staging system was first developed to measure PCM tumour burden [19]. The assessment is difficult because a significant heterogeneity characterizes this disease at multiple levels such as clinical presentation, biologic characteristics, treatment response, and clinical outcome. Some years later, a more objective and feasible staging system, the ISS was introduced. It was established on the measurement of serum albumin and ß2-microglobulin levels.

However, cut-off levels remained a matter of controversy because in the advanced ISS the tumour burden and renal failure could increase the ß2-microglobulin levels [20,21]. Therefore, this system cannot provide a good estimate for tumour burden or risk stratification in patients with renal failure.

We compared and correlated MTV with the most important clinical and hematologic parameters of PCM patients. The strong correlation between ß2-microglobulin and MTV, or between ISS stage and MTV could provide a potential new marker for tumour mass measurement at diagnosis and during the course of treatment. 9. **Conclusion**

The MRI combined with the ^{18}F-FDG PET provides a good opportunity for both, functional and morphologic assessments of bone lesions in PCM patients. The combination also allows a more precise anatomic localization of the PCM lesions and may provide new perspectives in the early diagnosis and prognosis establishments. Our study has some limitations since a low number of patients were studied, so these results should be considered as the preliminary findings of an ongoing study.

Author Contributions

PR has collected and interpreted the data and wrote the manuscript. ZT is a nuclear medicine physician who has collected the data and collaborated in the writing of the manuscript. PZ is a radiologist and he has been responsible for the image analysis and the writing, as well. ME has designed and partially performed the research activities and contributed in the manuscript writing, while IR, ÁK and MM have performed research activities.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Limitations

The small sample size is a limitation of our preliminary study. More sample is needed to the stronger evidences in the future, which may be conduct in a multicentre analysis setting.

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