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RESEARCH

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Multiple myeloma: characterization of patients through the analysis of semiquantitative parameters with 18F-FDG PET

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Abstract

Background Multiple myeloma (MM) is the second most common hematological malignancy after non-Hodgkin lymphoma. Recently, the use of 18F-FDG PET/CT has become more and more diffused thanks to its ability to combine functional and morphological information for diagnosis, prognosis assessment, and evaluation of treatment response. This study aims to describe the semiquantitative parameters obtained from 18F-FDG PET/CT in a population of patients with MM. A comparative analysis was performed with existing literature.

Methods This retrospective study included 50 patients with suspected MM who had undergone whole-body 18F-FDG PET/CT. The semiquantitative parameters obtained from 18F-FDG PET/CT positive scans were analyzed, specifically the number of focal lesions (FLs), the SUVmax of the "hottest" lesion, the ratio between SUVmax of the bone marrow and the spleen (marrow-to-spleen SUVmean ratio), marrow-to-spleen SULpeak ratio, and MTV.

Results Of the total cohort of 50 patients submitted to 18F-FDG PET/CT for suspected MM, 39 subjects resulted affected by MM. The 11 negative 18F-FDG PET/CT scans of the remaining subjects were not included. 59% of patients were males, and mean age (SD) was 65 ± 7.8 years. Based on the number of FLs, the entire cohort was divided into three groups: 14 patients in group A with more than 10 lesions; 5 patients in group B had a number of lesions between 5 and 10; and 24 patients in group C presented with less than 5 lesions.

Conclusions Semiquantitative parameters obtained through 18F-FDG PET can be useful in the assessment of staging criteria for MM, as the metabolic activity of lesions is higher in patients with extensive disease at the time of diagnosis. The predictive and prognostic relevance of these parameters as well as their role in guiding the therapeutic process toward ASCT worths further research.

Keywords Multiple myeloma, 18F-FDG PET/CT, SUVmax, MTV

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Background

Multiple myeloma (MM) is the second most common hematological malignancy after non-Hodgkin lymphoma [1]. It consists of uncontrolled growth of monoclonal plasma cells in the bone marrow and consequent overproduction of nonfunctional intact immunoglobulins or immunoglobulin chains that leads to several issues including anemia, bone lesions, infections,

hypercalcemia, renal failure, fatigue, and pain [2]. Diagnosis can be made with laboratory tests, bone marrow aspiration and biopsy, and imaging. Computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET) can detect both skeletal lesions and extraosseous disease localization. MM is often preceded by an initial monoclonal gammopathy of undetermined significance (MGUS). MGUS is a condition that can last several years before the development of asymptomatic or smoldering MM (SMM), an intermediate clinical stage between MGUS and MM [3, 4]. Patients with MM can show both non-specific and specific symptoms such as pain due to bone involvement, anemia, fatigue, renal failure, hypercalcemia, and weight loss [5]. Up to 10% of patients show extramedullary or extraosseous disease at the time of the diagnosis, reaching 20% with progressive disease [6]. MM skeletal lesions can be divided into four types, i.e., solitary lesion (plasmacytoma), diffuse skeletal involvement (myelomatous), diffuse skeletal osteopenia, and sclerosing myeloma [7]. The role of CT scan and MRI in MM is well-established. Recently, the use of 18F-fluorodeoxyglucose (18F-FDG) PET/CT has become more and more diffused in different settings due to its ability to combine functional and morphological information for diagnosis, prognostic assessment, and evaluation of treatment response [8, 9]. Specifically, PET/CT can successfully identify both active and inactive bone lesions as well as extramedullary focuses that sometimes could not be detected by other imaging techniques [10]. In addition, recent data are supporting the hypothesis that PET/CT functional imaging can predict possible outcomes and response to therapy in patients with MM [11]. However, a defined standardization of image interpretation is currently lacking. The "IMPETUS" criteria from the Bologna group tried to standardize the interpretation of PET images in MM with a visual scale improving inter-observer reproducibility, but an actual agreement has not yet been reached [12]. The total number of focal lesions identified with imaging and their metabolic activity assessed by PET/CT seem to be linked to event-free survival [13]. The identification of more than one focal bone lesion on MRI and of one or more lytic bone lesions on CT scan, low-dose CT, or 18F-FDG PET/CT meets the criteria for bone damage requiring therapy according to the International Myeloma Working Group (IMWG) [14]. 18F-FDG PET/CT semiquantitative parameters can help interpretation standardization through the definition of predictive factors of overall survival (OS) and progression-free survival (PFS). Three papers tried to identify baseline prognostic factors. For example, several focal bone lesions (FLs) > 3, the absence of extramedullary disease (EMD), and SUVmax < 4.2 seem to be associated with longer OS and PFS [15, 16]. This study aims to describe a population of patients with MM through the analysis of 18F-FDG PET/CT semiquantitative parameters. The obtained results were discussed in comparison with existing literature.

Methods

Patients

This retrospective study included 50 patients submitted to 18F-FDG PET/CT for suspected MM. Multiple semiquantitative parameters obtained from positive scans were collected and analyzed. All patients receiving a diagnosis of MM underwent chemotherapy, immunotherapy, or bone marrow transplantation. This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments, and a written informed consent was obtained from all participants.

18F-FDG PET/CT

All patients underwent 18F-FDG PET/CT scans after fasting for 6–8 h. The glucose level at the time of administration had to be < 120 mg/dl. The PET/CT device consisted of a Discovery ST (GE, Milwaukee, USA) with bismuth germanate crystal units arranged to form 24 rings combined with a 16-slice Light Speed Plus CT scanner. The average FWHM axial resolution of PET (full width at half maximum) is 5.2 mm, and system sensitivity is 9.3 cps/KBq for 3D acquisition mode. Scanning was performed from the neck to the toes in 3D modality, with an acquisition time of 3 min per bed/position. Images were reconstructed by using an ordered subset expectation maximization iterative algorithm (OSEM-SV, VUEPoint HD, GE, 2 iterations, 15 subsets). The CT was performed immediately before PET in the identical axial field of view using a standardized protocol consisting of automatic tube current modulation with auto mA, tube rotation time of 0.5 s/rotation, slice thickness of 3.75 mm. The CT data were resized from 512 × 512 to a 256 × 256 matrix to match the PET data. The data were transmitted to a nuclear medicine database, fused, and displayed using dedicated software (Advantage 4.7, GE).

PET-derived Parameters Calculation

MTV was defined on PET scan using dedicated software (PET VCAR, GE Healthcare). Every hepatic lesion was segmented with a threshold of 40% of the maximum SUV value within the bounding box of the lesion.

Semiquantitative Parameters

For each patient, imaging was analyzed and semiquantitative parameters were calculated, in particular the number of focal PET-positive lesions, SUVmax (maximum standardized uptake value) of the hottest lesions,

Table 1 Entire cohort semiquantitative PET parameter values

	Mean (SD)
Hottest lesion SUVmax	6.68 ± 3.87
Marrow-to-spleen SUVmean ratio	099 ± 0.36
Marrow-to-spleen SULpeak ratio	0.97 ± 0.38
MTV	66.62 ± 127.1

SD standard deviation

Table 2 Group A semiquantitative PET parameter values

Group A	Mean (SD)
Hottest lesion SUVmax	10.1 ± 2.85
Marrow-to-spleen SUVmean ratio	1.17 ± 0.41
Marrow-to-spleen SULpeak ratio	1.12 ± 0.41
MTV	99.6 ± 156.6

SD standard deviation

marrow-to-spleen SUVmean (mean standardized uptake value) ratio, marrow-to-spleen SULpeak (SUV corrected for lean body mass) ratio, and MTV (metabolic tumor value). Positive lesions were focal areas of increased 18F-FDG uptake above the surrounding background noise on two successive sections and corresponding to CT abnormalities such as a lytic lesions, minor lytic changes, and osteopenic areas; benign bone pathologies such as joint disease, spondylopathy, osteoarthrosis, and traumas were excluded. SUV is the ratio of the image-derived radioactivity concentration and the whole-body concentration of the injected radioactivity. Lesions showing SUVmax > 2 were considered positive. MTV was determined from PET data by grouping all spatially connected voxels within a threshold of 40% of the SUVmax. All patients were divided into three cohorts depending on the number of focal lesions, and for each of these, SUVmax was calculated by drawing 3D regions of interest into lesions.

Table 3 Group B semiquantitative PET parameter values

Group B	Mean (SD)
Hottest lesion SUVmax	7.43 ± 3
Marrow-to-spleen SUVmean ratio	0.92 ± 0.276
Marrow-to-spleen SULpeak ratio	0.98 ± 0.23
MTV	2 ± 0.44

SD standard deviation

Table 4 Group A semiquantitative PET parameter values

Group C	Mean (SD)
Hottest lesion SUVmax	6.01 ± 4
Marrow-to-spleen SUVmean ratio	0.9 ± 0.3
Marrow-to-spleen SULpeak ratio	0.89 ± 0.37
MTV	1.3 ± 19

SD standard deviation

Results

Of the total cohort of 50 patients submitted to 18F-FDG PET/CT for suspected MM, 39 subjects resulted affected by MM, as defined by the International Myeloma Working Group. The remaining 11 patients with negative 18F-FDG PET/CT scans were not included in this retrospective analysis. More than half patients, specifically 59%, were males with the female population represented by only 16 women. Mean age (SD) was 65 ± 7.8 years. Mean height (SD) and mean weight (SD) were 168.6 ± (10.4) cm and 81.5 ± (22.4) kg, respectively. Multiple PET parameters derived from 18F-FDG PET/CT were evaluated: SUVmax of the "hottest" lesion, the ratio between SUVmax of the bone marrow and the spleen (marrow-to-spleen SUVmean ratio), marrow-to-spleen SULpeak ratio, and MTV. Semiquantitative PET parameter values obtained from the entire cohort are shown in Table 1. Subdividing our cohort into groups according to the number of FLs, we obtained three groups: 14 patients in group A with more than 10 lesions (≥ 10); 5 patients in group B had a number of lesions between 5 and 10 (≥ 5); and 24 patients in group C presented with less than 5 lesions (< 5). PET parameters for these groups are shown in Tables 2, 3 and 4.

Discussion

This study aimed to characterize a population of patients with MM (Figs. 1 and 2), by comparing 18F-FDG PET semiquantitative parameters with those already described in the literature. The 39 patients with positive diagnostic 18FDG PET were divided into three groups according to the number of lesions detected: 14 patients had more than 10 lesions, 5 had more than 5 lesions, and 24 had less than 5 lesions. After undergoing 18FDG PET, 15 of these patients underwent autologous stem cell transplant (ASCT), while the whole cohort underwent chemotherapy, immunotherapy, or both. The number of FLs is considered an important prognostic factor in patients with MM. According to Paschali et al., the presence of ≥ 10 FLs negatively predicts overall response [17]. Zamagni et al. described how the number of PET-FLs was the most important independent variable associated with shorter survival,

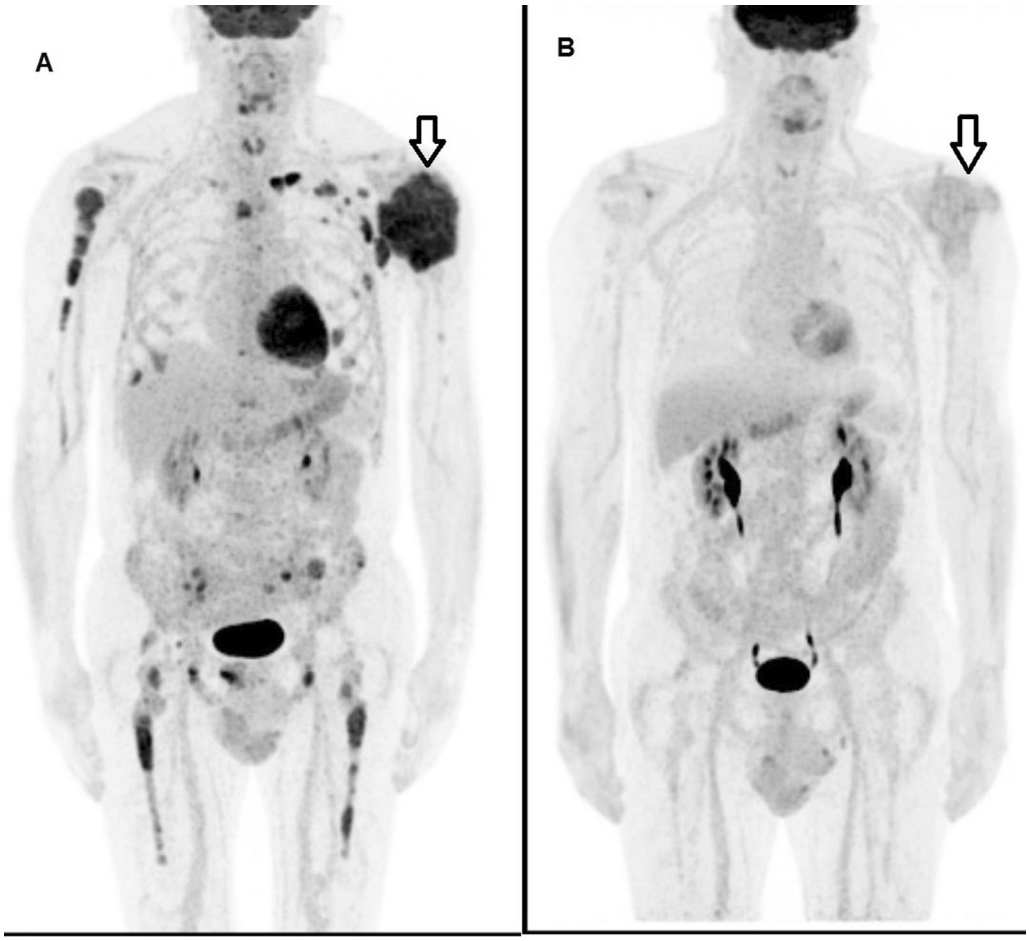

Fig. 1 A 60-year-old man with MM diagnosis. Whole-body PET (**A**) performed at baseline demonstrated multiple areas of increased tracer uptake in bones, particularly evident in the left shoulder (black bordered arrow). Six months after VTD (Velcade® + Thalidomide + dexamethasone) chemotherapy, whole-body PET (**B**) showed almost complete metabolic response, with minimal residual tracer uptake in the right shoulder (black bordered arrow)

both overall and event-free. Time to progression (TTP) and PFS values projected at 4 years were 50% each for patients who had either > 3 FLs or diffuse bone marrow (BM) uptake compared with those with less severe PET/CT involvement (69% and 68%) [16]. Bartel et al. also showed how several FLs > 3 are associated with the worst outcome [18]. The first semiquantitative parameter taken into account in this study was the SUVmax of the hottest lesion. Nowadays, no consensus has been reached regarding an appropriate SUVmax cutoff value to distinguish between PET-positive and PET-negative scans [10]. In a recent prospective study with 192 patients, osteolytic lesions were considered to be positive with a SUVmax cutoff of 2.5, based on body weight, for lesions bigger than 1 cm in size and a cutoff of at least 1.5 for lesions between 0.5 and 1 cm in size because of the partial volume effect [16]. Nanni et al. demonstrated a high variability of SUVmax within each patient and from patient to patient, ranging from 1.9 to 7.2, without finding any significant correlation between the SUVmax and the clinical stage of the disease. The high intrapatient variability in SUVmax was attributed to the partial volume effect in lesions smaller than 1 cm [19]. Sager et al., on the other hand, found a significant correlation between FDG SUVmax on PET/CT and bone marrow cellularity and plasma cell ratios on biopsy samples, suggesting that if FDG PET/CT is positive and SUVmax values are high at the time of initial diagnosis, these patients can be followed by FDG PET/CT scans without undergoing bone marrow biopsy [20]. In the first group of patients (≥ 10 lesions), the average SUVmax was 10.1(± 2.85); in the second group (≥ 5 lesions) the average SUVmax was 7.34(± 3), while in the third group (< 5 lesions) it was 6.01 (± 4). Although there is not a direct correlation between semiquantitative parameters and staging of

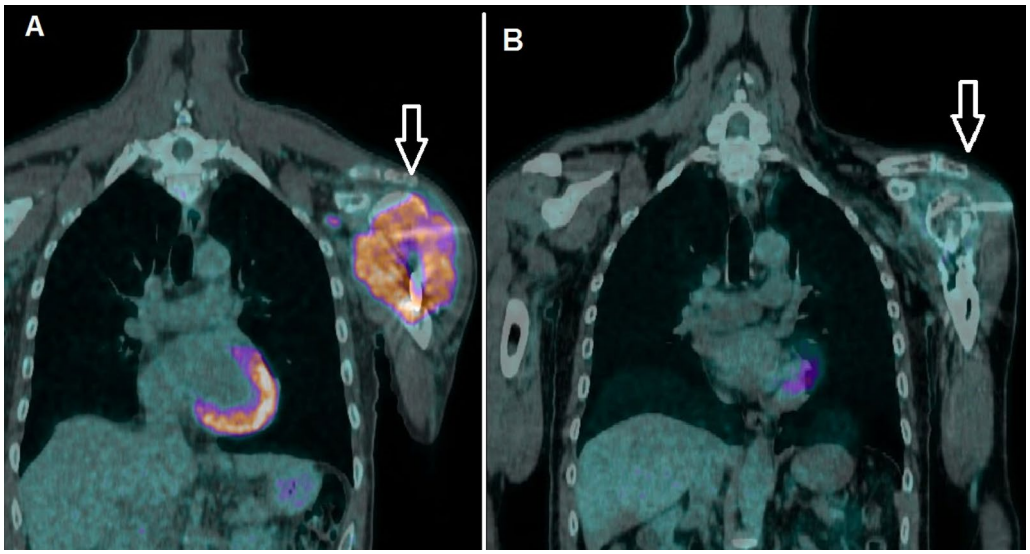

Fig. 2 Whole-body bone scintigraphy in anterior (**A**) and posterior (**B**) revelation of a patient with liver metastases and an atypical epigastric uptake in correspondence of liver metastasis. Same patient. Fused coronal PET/CT image (**A**) well localized the gross area of increased 18F-FDG uptake in the left shoulder (white bordered arrow), with involvement of scapula, humerus, and surrounding soft tissue. Coronal PET/CT (**B**), performed after chemotherapy and prosthesis implantation, demonstrated an almost complete metabolic response (white bordered arrow)

the disease, these data reflect how in patients with a high number of lesions, and therefore with extensive disease, there is an increasing value of SUVmax on the hottest lesion. Consequently, a similar trend was observed calculating the MTV of the hottest lesions in each group: Indeed, in the first group the average MTV is 99.6 cm3 (± 156.6), with a significant decrease in the second and third groups where the MTVs were, respectively, 2 cm3 (± 0.44) and 1.3 cm3 (± 19). In 2012, a study performed by Fonti et al. demonstrated how MTV can be used as an independent prognostic factor to predict OS in patients with MM, stating that OS was significantly better in patients with an MTV < 77.6 mL than in those with an MTV ≥ 77.6 mL [21]. Although this study is not designed to assess OS and PFS, data regarding MTV are consistent with previous studies, since in our population patients with a higher number of lesions, and therefore extensive disease, show high MTV as compared to patients with a smaller number of lesions, whose MTV is significantly lower. Recently, in two different studies, it was demonstrated how the use of the marrow-to-liver SUV ratio is considered an independent predictor of PFS and OS after therapy [22] and can be proposed as the standardized definition of PET complete metabolic response [23]. In this study, patients undergoing diagnostic 18F-FDG PET are characterized according to the marrow-to-spleen SUVmean ratio, showing the same decrease as seen with the previous parameters (BM/spleen SUV ratio: 1.17 ± 0.41 in the first group; 0.92 ± 0.276 in the second group; 0.9 ± 0.3 in the third group). These data show a linear correlation with the number of lesions seen in 18F-FDG PET since the highest average marrow-to-spleen ratio is seen in the group of patients with the highest number of lesions, while it progressively decreases in the following two groups. The last semiquantitative parameter we took into account is the marrow-to-spleen SULpeak ratio. The use of SUL (standardized uptake value normalized for lean body mass) is not yet extensively used in literature, but there is increasing evidence about the reliability of this parameter. Albano et al. studied, among other parameters, the predictive role of SUVlbm in the progression of solitary plasmacytoma to MM (time to progression to multiple myeloma, TTMM), stating that a SUVlbm > 5.2 was significantly correlated with TTMM [24]. In our study, in parallel with the marrow-to-spleen SUVmean ratio, we also considered the marrow-to-spleen SULpeak ratio. As expected, the outcomes considering these two parameters were similar: The marrow-to-spleen SULpeak ratio was 1.12 ± 0.41 in the first group; 0.98 ± 0.23 in the second group; 0.89 ± 0.37 in the third group. In this study, we characterized patients undergoing diagnostic 18F-FDG PET through the analysis of semiquantitative parameters. As ascertained from our results, the extension of the disease significantly correlates with the values of the parameters we took into account (hottest lesion SUVmax, MTV, marrow-to-spleen SUVmean ratio, marrow-to-spleen SULpeak ratio). In particular, SUVmax and MTV were significantly higher in the

group of patients with 10 or more lesions at 18F-FDG PET as compared with the groups of patients with, respectively, 5 or more lesions and less than 5 lesions, reflecting how the metabolic activity of these lesions is higher in patients with extensive disease at the time of diagnosis. The same results were observed considering the marrow-to-spleen SUVmean ratio and marrow-to-spleen SULpeak ratio, although the differences in these parameters among the three groups were not as broad as seen with SUVmax and MTV.

Conclusions

The use of semiquantitative parameters for the characterization of patients with MM undergoing 18F-FDG PET can be useful in the assessment of staging criteria, as the metabolic activity of lesions is higher in patients with extensive disease at the time of diagnosis. All analyzed semiquantitative parameters correlate with the extension of disease even if the differences observed considering marrow-to-spleen SUVmean ratio and marrow-to-spleen SULpeak ratio are not as broad as seen for SUVmax and MTV. Whether these parameters could have a predictive and prognostic relevance or guide the therapeutic process toward ASCT needs further research.

Abbreviations

MM	Multiple myeloma
CT	Computed tomography
PET	Positron-emitting tomography
MRI	Magnetic resonance imaging
MGUS	Monoclonal gammopathy of undetermined significance
SMM	Smoldering MM
18F-FDG	18F-fluorodeoxyglucose
OS	Overall survival
EMD	Extramedullary disease
FLs	Focal bone lesions
SUVmax	Maximum standardized uptake value
SULpeak	SUV corrected for lean body mass
MTV	Metabolic tumor value
SUVmean	Mean standardized uptake value
BM	Bone marrow
ASCT	Autologous stem cell transplant
TTP	Time to progression

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Author contributions

MSDF, VF, LF, and GDV contributed to conceptualization; VF was involved in data curation; MSDF contributed to formal analysis; CDA, MM, and FC were involved in investigation; LF contributed to methodology; CDA, MM, and FC were involved in resources; LF provided software; VF, GB, and GDV contributed to validation; CDA, MM, FC, and GB were involved in writing—original draft; and VF, LF, OS, and GDV contributed to writing—review and editing. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This was a retrospective study on data available for clinical practice in which clinical records of all patients in ongoing biologic therapy were reviewed. Data were anonymously collected in each center and were cumulatively gathered in an electronic database for analysis. Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained after each patient agreed to being followed up and to collect clinical records by institutions. No experimental procedures, novel devices, or experimental drugs were used, and no funds were received. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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