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18F-FDG PET/CT focal, but not osteolytic, lesions predict the progression of smoldering myeloma to active disease

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**18F-FDG PET/CT FOCAL, BUT NOT OSTEOLYTIC, LESIONS PREDICT THE PROGRESSION OF SMOLDERING MYELOMA TO ACTIVE DISEASE**

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## ABSTRACT

Identification of patient sub-groups with smoldering multiple myeloma (SMM) at high risk of progression to active disease (MM) is an important goal. 18F-FDG PET/CT allows for assessing early skeletal involvement. Identification of osteolytic lesions by this technique has recently been incorporated into the updated IMWG criteria for MM diagnosis. However, no data are available regarding the impact of focal lesions (FLs) without underlying osteolysis on time-to-progression (TTP) to MM. We hence prospectively studied a cohort of 120 SMM patients with PET/CT.

PET/CT was positive in 16% of patients (1FL: 8, 2FLs: 3, >3FLs: 6, diffuse bone marrow involvement: 2). With a median follow-up of 2.2 years, 38% of patients progressed to MM, in a median time of 4 years, including 21% with skeletal involvement. The risk of progression of those with positive PET/CT was 3.00 (95% CI 1.58 - 5.69, P= 0.001), with a median TTP of 1.1 versus 4.5 years for PET/CT negative patients. The probability of progression within 2 years was 58% for positive versus 33% for negative patients.

In conclusion, PET/CT positivity significantly increased the risk of progression of SMM to MM. PET/CT could become a new tool to define high-risk SMM.

**INTRODUCTION**

Smoldering multiple myeloma (SMM) is an asymptomatic clonal plasma cell disorder defined by the presence of a serum monoclonal component (MC) of  $\geq 3$  g/dL and/or of more than 10% clonal bone marrow plasma cells (BMPC), with no evidence of end-organ damage (CRAB features, including hypercalcemia, renal failure, anemia or lytic bone lesions and/or additional myeloma-defining events, MDE, including biomarkers of malignancy) (ref. 1). The progression rate into active multiple myeloma (MM) is 10% per year for the first five years, the cumulative probability of progression is 73% at 15 years (ref. 1). However, SMM is biologically and clinically highly heterogeneous, with some patients behaving like those with monoclonal gammopathy of undetermined significance (MGUS), with a very low rate of progression, and thus carrying a biological pre-malignancy, and a subset with biological malignancy, with a high risk of developing clinical symptoms, within the first years after diagnosis (ref. 2). Therefore, the identification of predictors of progression into MM is of great importance.

Several markers (serum MC, percentage of BMPC, serum free light chain (sFLC), ratio, immunophenotyping of aberrant plasma cells, tumor genetic abnormalities and focal lesions, FLs, at magnetic resonance imaging, MRI) have already been established to identify sub-groups of SMM patients with the highest risk of progression into MM (ref. 2).

Among imaging methods, positron emission tomography (PET) integrated with computed tomography (PET/CT) using glucose labelled with the positron-emitting radionuclide  $^{18}\text{F}$  (Fluorodeoxyglucose,  $^{18}\text{F}$ -FDG) is a reliable technique for assessing early skeletal involvement and for predicting outcomes at the onset of MM (ref. 3-5). The updated diagnostic criteria published by the International Myeloma Working Group (IMWG) nowadays consider patients with FLs and increased uptake with underlying osteolytic destruction in one of the newer imaging techniques as active MM (ref. 6). However, no data are available regarding the impact of PET/CT FLs in the absence of osteolytic lesions in SMM and their effect on time to progression (TTP) into symptomatic disease.

We herein report the results of a prospective analysis of the prognostic implications of FLs as detected by 18F-FDG PET/CT at the time of diagnosis in a series of patients with SMM who have been followed up without treatment.

Accepted manuscript

**PATIENTS AND METHODS****Patients**

From 2005 to 2014, a total of 120 patients (76 males and 44 females) with SMM entered this prospective observational study which was conducted at several European hematologic institutions and aimed at evaluating the prognostic relevance of PET/CT on the risk of progression to active MM. The definition of active MM was based on the revised IMWG diagnostic criteria, excluding biomarkers of progression (ref. 6). In particular, the presence of bone lesions to meet the criteria of a MDE was based either on whole body X Ray (WBXR) or on whole body low dose multi-detector computed tomography (WB-LDCT) or on the computed tomography part of PET/CT, showing one or more osteolytic lesions. On the contrary, patients presenting exclusively any one or more of the three newly established biomarkers of progression (i.e. clonal BMPC > 60%, sFLC ratio  $\geq$  100 and > 1 FLs at MRI) were followed as the rest of the population. The main characteristics at enrollment in the study are summarized in Table 1. The median age was 61 years old (IQR 54-67); 29% of the patients were older than 65 years. In 50% of them, a previous history of MGUS was documented. IgG isotype was present in 73% of the patients. Median values (IQR) of the MC, involved/uninvolved sFLC ratio and BMPC were as follows: 2.4 g/dL (1.5-3.0), 14.27 (3.90-33.08), 27% (15%-40%), respectively.

Ten and 11% of the patients had more than 60% BMPC and an involved/uninvolved sFLC ratio superior or equal to 100, respectively; however, they were observed like the rest of the population. A slight increase in serum creatinine, superior to the upper normal limit, was observed in 12% of the cases, but was not attributed to light chain damage but to intercurrent diseases. Overall, only 30% of the patients were screened for cytogenetic abnormalities by fluorescence in situ hybridization (FISH) analysis performed on CD138+ bone marrow plasma cells; del(13q), t(4;14), del(17p) and chromosome 1 alterations occurred in 34%, 10% , 7% and 20% of them, respectively.



All patients had given signed informed consent in accordance with the Declaration of Helsinki. The study was approved by the ethical committees at the participating institutions and is registered with Clinical Trials Gov., number NCT01134484 and NCT01208766.

### **Imaging studies**

All patients were studied at baseline with 18F-FDG PET/CT, performed locally in each hematologic institution; images were thereafter uploaded in a system for central review. Axial magnetic resonance (MRI) (spine and pelvis) or whole-body MRI (WB-MRI) were likewise executed at study entry in 91/120 patients and were interpreted locally in each institution. PET/CT or WB-LDCT or WBXR were performed when a progression to active MM was suspected, either on the basis of laboratory results or on the appearance of clinical symptoms, to verify the presence of organ damage.

PET/CT scans were acquired according to local protocol (applying EANM PET procedure guidelines for FDG studies) (ref. 7), but the following conditions were required for inclusion of scan data: (a) studies had to be carried out using full-ring PET/CT; (b) iterative reconstruction was applied to PET images; (c) CT and attenuation corrected baseline was available for central review and (d) the field of view of both PET and CT scans had to include the region from the tip of the skull to the lower third of the femoral heads and the upper limbs. After anonymization, PET/CT scans were uploaded by the participating PET centers into WIDEN® (Dixit srl, Torino, Italy). PET/CT scans were excluded from the study if: (a) they were poor-quality images with low statistics that were not considered suitable for diagnostic interpretation, (b) the image data set was incomplete and (c) large discrepancies concerning uptake time and administered dose were found analyzing DICOM headers of PET scans. After PET/CT scans had been uploaded into WIDEN, the system sent them automatically to 3 reviewers (CN, AV and PG), who downloaded them into their own workstation and proceeded to the central review. The reviewers then met to jointly report in a consensus session the cases that showed discrepant results during the previous independent review (following Krippendorff's method).

PET/CT was considered positive for SMM patients in the presence of one of the following:

1. focal areas of visually detectable increased tracer uptake within bones (e.g., more intense than background bone marrow (BM) uptake) excluding articular processes, without any underlying lesion identified by CT and present on at least two consecutive slices (to avoid a misinterpretation as BM mild non homogeneous FDG uptake). The number, size, and location of hypermetabolic focal lesions (PET-FLs) were recorded. The degree of FDG uptake was represented by standardized uptake value (SUV) maximum (max) in the hottest lesion;

2. diffusely increased tracer uptake with a  $SUV_{max}$  equal to, or greater than, the uptake in the liver. In this case,  $SUV_{max}$  was measured in the hottest area within the BM.

Patients presenting with underlying osteolytic lesions and/or para-medullary lesions, arising from bone, and/or extra-medullary disease, arising in soft tissues, were excluded from the study as they were considered to have active MM, according to the new diagnostic criteria (ref. 6).

MRI was performed using a 1.0 Tesla with a spinal coil. Sagittal images included a T1-weighted spin echo sequence and a fat-suppressed T2-weighted fast spin echo sequence. The T1-weighted images were repeated after intravenous injection of gadolinium chelate. Bone marrow infiltration was evaluated and, on the basis of previously reported criteria, the following different patterns of bone marrow involvement were identified: normal, focal and diffuse (ref. 8). In case of a focal pattern, the exact number and site of lesions were reported. Similarly to PET/CT, patients showing para-medullary or soft masses were excluded from the study.

WB-MRI was performed on 1.5 Tesla whole-body systems (Magnetom Avanto with phased-array body matrix surface coils, Siemens Medical Solutions, Erlangen, Germany) with the following parameters: T1-weighted turbo spin echo sequence (TR=627ms, TE=11ms) of the head (voxel size 1.25x1.25x5mm<sup>3</sup>, scan time 2 minutes 4 seconds), thorax and abdomen (voxel size 1.25x1.25x5mm<sup>3</sup>, scan time 2 minutes 4 seconds), pelvis (1.25x1.25x5mm<sup>3</sup>, scan time 2 minutes 4 seconds) and leg (voxel size 1.25x1.25x5mm<sup>3</sup>, scan time 2 minutes 4 seconds), all in coronal orientation; T2-weighted short-tau inversion recovery (STIR) sequence (TR=3340ms, TE=109ms,

TI=160ms) of the head (voxel size 1.25x1.25x5mm<sup>3</sup>, scan time 1 minute 20 seconds), thorax and abdomen (voxel size 1.25x1.25x5mm<sup>3</sup>, scan time 1 minute 20 seconds) and pelvis (voxel size 1.25x1.25x5mm<sup>3</sup>, scan time 1 minute 20 seconds), all in coronal orientation; T1-weighted turbo spin echo sequence (TR=400ms, TE=11ms) of the spine in sagittal orientation (voxel size 1.836x1.836x3.5mm<sup>3</sup>, scan time 1 minute 16 seconds); T2\*-weighted FLASH 2D sequence (TR=402ms, TE=12ms) of the spine in sagittal orientation (voxel size 0.84x0.84x5mm<sup>3</sup>, scan time 1 minute 38 seconds). Patients were positioned with their arms along their body, and the series covered the region between the skull vertex and the mid calf. Depending on the body height of the patient the distal calves and the feet were not included (ref. 9).

### **Laboratory investigations and criteria to define progression to active MM**

Physical examination, blood cell count, renal and liver function, calcium level, serum protein electrophoresis with immunofixation, 24-hour urine analysis with electrophoresis and urinary immunofixation were evaluated at study entry and every 3-4 months thereafter. Bone marrow aspirate and FISH analysis of del(13q), t(4;14) del(17p) were evaluated at baseline. Additional prognostic parameters registered at baseline were the following: serum levels of beta-2-microglobulin ( $\beta$ 2M), C reactive protein (CRP), albumin and lactate dehydrogenase (LDH). Progression to active MM was defined by the appearance of any one or more of the revised MDE that were listed above (ref. 6; 10). Skeletal MDE were defined by the appearance of one or more sites of osteolytic bone destruction, pathological fractures and/or paramedullary or extramedullary masses at PET/CT or WBXR or WB-LDCT, according to the updated IMWG criteria (ref. 6).

### **Statistical analysis**

Clinical characteristics were expressed as medians with IQR or as frequencies, as appropriate. Between-groups comparisons were made using the Kolmogorov-Smirnov test, Kruskal-Wallis test,  $\chi^2$  test or Fisher's exact test, as appropriate.

The kappa-statistic measure of agreement was evaluated to compare PET to MRI positivity.

Kaplan-Meier analysis was used to estimate time to progression to active MM (TTP). The first assessment of active disease was defined as the date of event for analysis of TTP. Between-group comparisons were made using the log-rank test. Multivariate Cox regression analyses were performed to evaluate the prognostic impact of risk factors, particularly, the significance of the number of FLs, of the presence of a diffuse FDG uptake and of the  $SUV_{max}$  value.

A multinomial logistic regression analysis was performed to identify the most powerful prognostic factor(s) predicting for progression to active MM with or without skeletal MDE.

The Krippendorff's alpha method was used for PET/CT overall consensus agreement measurement (ref. 11).

Investigators at the "Seràgnoli" Institute of Hematology and Nuclear Medicine Institute at the University of Bologna coordinated the study and contributed to the study design, data collection and analysis. All the authors had access to primary clinical trial data.

## RESULTS

### Imaging characteristics

PET/CT was completely negative in 101/120 (84%) of the patients at diagnosis and positive in 19/120 (16%) of them. More particularly, PET/CT was defined as positive according to the following imaging findings: 1 FL in 8 patients, 2 FLs in 3 patients, 3 or more FLs in 6 patients and diffuse BM involvement in 2 patients (table 2). The median  $SUV_{max}$  value in positive patients was 4.7 (IQR 3.9-5.6). No correlation between  $SUV_{max}$  and age was found. BMPC infiltration was significantly higher for patients with positive PET/CT than for negative ones (43 vs 25%,  $P=0.024$ ).

In 91/120 patients a baseline axial (79) or WBMRI (12) was performed and was completely negative in 73% of them and positive in 27%, with the following patterns of involvement: involvement: 1 FL in 5 patients (5%), more than 1 FLs in 12 patients (13%), diffuse in 10 patients (11%), salt and pepper in 13 patients (14%).

Agreement between PET/CT and MRI scans in the 91 patients for whom both the imaging techniques were available was 77% ( $\kappa=0.32$ , which means only fair agreement); more particularly both PET/CT and MRI were negative in 67% of the patients and positive in 10% of them. In 5% of the patients PET/CT was positive while MRI was negative (mainly out of the field of view) and conversely in 18% of cases MRI was positive in the axial skeleton, while PET/CT was negative. Analysis of the relationships between the PET/CT parameters and standard prognostic factors, such as ISS stage, cytogenetic abnormalities, sFLC ratio revealed no significant correlations.

### **Impact of PET/CT on clinical outcomes**

With a median follow-up of 2.2 years from the time of study entrance to December 2014 (IQR 1-5 years), 74(62%) of the patients remained in the smoldering phase, while 46 (38%) progressed to active MM, in a median time of 4 years. Progression to active MM was documented by skeletal MDE, with/without the presence of other CRAB features, in 21% of the patients, and by any one or more of the CRAB features, without skeletal MDE, in 17% of cases. The median OS for the entire population was 11 years.

The univariate analysis revealed that the presence of a positive PET/CT (i.e. at least 1 FL and/or diffuse involvement), the size of MC (as a continuous variable), BMPC higher than 60% and a diffuse bone marrow infiltration at MRI were adverse prognostic factors for progression to active disease (table 3). The risk of progression to active MM of the patients with a positive PET/CT was 3.00 (95% CI 1.58-5.69) and was 4.44 (95%CI 1.97-10.02) when progression with skeletal MDE was considered (fig. 1). The median TTP and TTP with skeletal MDE for patients with positive PET/CT were 1.1 and 2.2 years, respectively, in comparison with corresponding values of 4.5 and 6.9 years for PET/CT negative patients. The probability of progression within 2 and 3 years for patients with positive PET/CT was 58% and 66%, respectively, as compared to 33% and 42% for negative patients. The risk of progression to active MM increased with the increasing number of FLs or the presence of a diffuse pattern of FDG avidity (1-2 FLs: HR 2.4 95%CI 1.1-5.6;  $\geq 3$  FLs:

HR 3.3 95%CI 1.3-8.6, diffuse pattern: HR 7.1 95%CI 1.6-30.3) and the increasing SUV<sub>max</sub> value (HR 1.3 95%CI 1.1-1.5). However, the limited sample size of patients with positive PET/CT findings precluded to establish the optimal cut-off for the number of FLs or the SUV<sub>max</sub> value and thus to more carefully discriminate the higher risk of progression into symptomatic disease.

Results did not significantly differ when patients with early MM, according to the updated IMWG criteria, were excluded from the analysis (data not shown).

In a Cox regression analysis of baseline prognostic factors, the presence of PET/CT positivity along with BMPC higher than 60% were independent predictors of shorter TTP to active MM. (table 4).

A multinomial logistic regression analysis showed that PET positivity was significantly related to the risk of progression to active MM with skeletal MDE, while BMPC exceeding 60% was significantly related to the risk of progression without skeletal MDE (table 5).

## DISCUSSION

This study demonstrates, for the first time to the best of our knowledge, the prognostic significance of FLs in the absence of underlying osteolytic lesions, as detected by 18F-FDG PET/CT, in patients with SMM, for progression into active disease.

SMM is an intermediate clinical stage between MGUS and MM, in which the risk of progression to active disease in the first 5 years after diagnosis is much higher, approximately around 10% per year (ref. 1). However, only a subset of SMM are at high risk of developing end organ damage within the first years of diagnosis. Different prognostic models have been proposed to predict the risk of progression, based either on conventional serologic parameters (size and isotype of the MC and progressive increase thereof, FLCs ratio, immunoparesis) (ref. 1; 12-15) or on the percentage and immunophenotype of BMPC (ref. 16). Furthermore, the presence of circulating PCs (ref. 17), presence of cytogenetic and molecular abnormalities in PCs (ref. 18-20) or presence and progression of FLs at MRI (ref. 21-22) have been shown to be of prognostic significance. Unfortunately, no single pathological or molecular feature can be used to distinguish

SMM patients who are certainly developing a malignant disease. In light of the advances in laboratory and imaging techniques, providing higher sensitivity and ability to detect early damage, and of the data showing improved outcomes with early intervention in high-risk SMM (ref. 23), diagnostic criteria were recently updated by the IMWG (ref. 6). In particular, two major changes were established, the first one, based on robust studies, defining those patients carrying at least one out of three biomarkers of progression (i.e. clonal BMPC > 60%, sFLC ratio  $\geq 100$  and > 1 FL at MRI), with approximately 80% risk of developing end organ damage within 2 years from diagnosis, such as active MM, requiring immediate treatment. The second major improvement was the definition of bone lesions, within MDE, not only on the appearance of sites of bone destruction on skeletal radiography, but also on the presence of osteolytic lesions on CT or PET/CT, thanks to the well-recognized higher sensitivity of newer imaging techniques over WBXR, more lesions being detected and at an earlier phase (ref. 5).

<sup>18</sup>F-FDG PET/CT is a nuclear imaging procedure that combines functional imaging (the PET part) and morphological assessment by CT, allowing high-sensitivity and specificity detection of hypermetabolic lesions, intramedullary and extramedullary, bone marrow involvement and osteolytic lesions as well as exact anatomic localization thereof. Bone lesions are identified with a resolution limit of 0.5 cm. In the diagnostic work-up of patients with suspected SMM, the use of PET/CT thus allows us to capture the presence of any early asymptomatic bone damage (FLs with underlying osteolytic lesions). In the present study, the percentage of patients with suspected SMM showing FLs plus lytic lesions could not be evaluated, as they were excluded a priori, but in a retrospective study from the Mayo Clinic group the corresponding value was about 20% (ref. 26). These patients should not be considered as having SMM, despite negativity by WBXR, but active MM, deserving prompt treatment<sup>6</sup>. Early detection of occult lesions may provide important benefits for patients, by preventing skeletal complications and pain, as well as promoting quality of life (ref. 24).

In addition to the identification of early skeletal destruction, in this prospective study of 120 SMM patients we found that PET/CT can show the presence of sites of focal hypermetabolic lesions (FLs) or diffuse bone marrow hypermetabolism, in the absence of osteolytic lesions, in approximately 16% of cases. Moreover, we firstly provide demonstration that this imaging technique is a reliable predictor of prognosis not only in active MM (ref. 3-4), but also in SMM. In the present study, the presence of a positive PET/CT (i.e. at least 1 FL and/or diffuse involvement), in the absence of skeletal damage, was a strong independent predictor of progression of SMM into active disease. In particular, the probability of progression within 2 and 3 years for patients with positive PET/CT was 58% and 66%, respectively, as compared to 33% and 42% for negative patients. The risk of progression into active MM increased with the increasing number of FLs and with the increasing  $SUV_{max}$  value. However, the low number of patients, when grouped for FLs, diffuse pattern or  $SUV_{max}$  value, prevented us from finding an optimal cut-off to discriminate higher risk of progression into active disease, in the 80% range at 2 years. This latter group of patients, once being identified, could be considered as having an MDE, similarly to those carrying more than 1 FL in MRI. In addition, a multinomial logistic regression analysis showed that PET positivity was significantly related to progression to active MM with skeletal MDE, with or without other CRAB features.

Seventy-six percent of the patients were studied at baseline by MRI as well, either axial (79 patients) or WB-MRI (12 patients); 13% of them presented more than 1 FL, 5% 1 FL and 11% a diffuse marrow infiltration pattern. At the time of initiation of the study, no formal recommendations for the use of MRI in SMM were available and the start of treatment in MM patients, based on the presence of CRAB criteria, was established by WBXR, from an imaging point of view. After the clear demonstration that the presence of more than 1 FL either in WB-MRI (ref. 21) or axial MRI (ref. 25) in SMM patients was an independent predictor of progression into active disease, giving a 70% of risk to progress within 2 years, MRI is recommended as part of the initial assessment in these patients (ref. 26). Nowadays, patients carrying more than 1 FL are



considered to have active MM which requires therapy while, in the absence of similar strong data, those with 1 FL or a diffuse marrow infiltration pattern are considered as high-risk SMM (ref. 2; 21). In our analysis, diffuse bone marrow infiltration on MRI was an adverse prognostic factor for progression into symptomatic disease in univariate analysis, while we did not find any significance for FLs. The small number of patients with positive MRI findings, as well as lack of any centralized revision of MRI scans, may justify this discrepancy with previously published results (ref. 21).

Agreement between PET/CT and MRI in the 91 patients for whom both imaging techniques were available was only fair; in particular, as already previously demonstrated in symptomatic MM (ref. 27), MRI seemed to be more sensitive in the axial skeleton, detecting abnormalities in 18% more patients, while PET/CT was more sensitive in 5% of cases, out of the MRI field of view. It could be speculated that WB-MRI might be the elective imaging technique in this patient population to capture the risk of progression; however, it is not widely available and moreover PET/CT may capture patients with suspected SMM who are already displaying early bone damage (FLs with underlying osteolytic lesions). The combination of PET/CT with axial MRI might be a good alternative to WB-MRI in the diagnostic work-up of SMM. A recent study from the German group demonstrated a predictive value of longitudinal follow-up with WB-MRI in patients with SMM, regardless of findings at the initial MRI (ref 31). In the absence of available data, it can be hypothesized that PET/CT might play a similar role in the follow-up of SMM patients. Performing PET/CT plus axial MRI or WB-MRI every 12-24 months or on the appearance of clinical symptoms might be a reasonable approach for the monitoring of SMM, balancing costs and the possibility to capture early appearance of organ damage.

Ten and eleven percent of the patients in our study presented with more than 60% BMPC and an involved/uninvolved sFLC ratio superior or equal to 100, respectively. These patients were observed like the rest of the population and not considered as active MM requiring treatment, since for most of the time the study was conducted, the new diagnostic criteria had not yet been established (ref. 6). However, because of the small proportion of patients carrying these

characteristics, the effect of their presence on estimates is likely to be minimal; moreover, on excluding them from the analysis, we did not find any difference in the results. In line with other studies (ref. 28), the presence of more than 60% BMPC was an independent predictor of shorter TTP, in particular without skeletal progression. On the contrary, we did not find any significant correlation between the involved/uninvolved sFLC ratio and TTP; this might be due to the fact that baseline sFLC values were only available in 65% of patients.

One concern with the serial use of PET/CT in clinical trials could be the heterogeneity of the visual criteria and the lack of inter-observer reproducibility in interpreting results. Several attempts to standardize criteria for PET/CT imaging definitions and use of semi-quantitative SUV evaluations are now on-going to consolidate the use of this technique as a prognostic tool (ref. 29). In this study, PET/CT scans were acquired according to local protocol, applying EANM PET procedure guidelines for FDG studies (ref. 7), and images were then uploaded by the participating PET centers for central revision, on the basis of pre-established criteria.

In conclusion, approximately 16% of the patients with SMM have a positive PET/CT, mainly with few FLs, and a low FDG uptake; these patients show a significantly higher risk of progression into active MM. PET/CT could become a new risk factor, enabling one to define high-risk SMM patients which might be candidates for future clinical trials aimed at investigating the value of early therapy (ref. 2; 30-31). Further studies are warranted to find an optimal cut-off point of FLs and/or  $SUV_{max}$  and thus more carefully detect the highest risk of progression at 2 years. Furthermore, the combination of PET/CT with other prognostic factors warrants further analysis. On the basis of our results, integrating PET/CT scanning and axial MRI into the work-up of patients with suspected SMM may improve the management of the disease.

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Figure legend:

**Figure 1:**

**A) time to progression of SMM to active MM, with or without skeletal MDE;**

**B) time to progression of SMM to active MM with skeletal MDE, according to baseline PET/CT**

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Table 1: Baseline patient characteristics

N° patients: 120	Median (IQR)	%
Sex		
Male		63
Female		37
Age (years)	61 (54-67)	
Previous MGUS		50
IgG isotype		73
Hb (g/dL)	13.2 (12.2-13.9)	
Creat (mg/dL)	0.9 (0.8-1.1)	
Ca (mg/dL)	8.9 (3.5-9.4)	
LDH (UI/L)	261 (176-337)	
CRP (mg/L)	0.4 (0.1-1.0)	
Plt (x 10 <sup>3</sup> /L)	231 (195-279)	
MC (g/dL)	2.4 (1.5-3.0)	
FLC ratio inv/uninv	14.3 (3.9-33.1)	
BMPC (%)	27 (15-40)	
del (13q)*		34
del (17p)*		7
t (4;14)*		10

\*screened on 30% of the patients

MGUS monoclonal gammopathy of undetermined significance, Hb haemoglobin, creat creatinine, Ca calcium, LDH lactate dehydrogenase, CRP C reactive protein, Plt platelets, MC M component, FLC free light chain, inv involved, uninv uninvolved, BMPC bone marrow plasma cells, del deletion, t translocation

Table 2: Baseline PET/CT characteristics

N° (%) Patients with negative PET/CT	101 (84%)
N° (%) Patients with positive PET/CT	19 (16%)
1 FL	8 (7%)
2 FLs	2 (2%)
≥ 3 FLs	3 (2%)
diffuse	6 (5%)
median SUVmax (IQR)	4.7 (3.9-5.6)

FLs focal lesions, SUVmax maximum standardized uptake value

Table 3: Univariate analysis of baseline variables adversely affecting time to progression of SMM into active MM (TTP)

TTP			
Variables	HR	95% C.I.	
BMPC > 60%	3.7	1.5	9.1
MC	1.00	1.0	1.0
PET/CT pos	3.0	1.6	5.7
MRI pos	2.3	1.1	4.6
MRI diffuse	2.8	1.2	6.5

BMPC bone marrow plasma cells, MC M component, pos positive, HR hazard ratio, CI confidence interval

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Table 4: Multivariate Cox regression analysis of baseline variables adversely affecting time to progression of SMM into active MM (TTP)

TTP			
Variables	HR	95% C.I.	
BMPC > 60%	4.8	1.9	12.2
PET/CT pos	3.6	1.7	7.6

BMPC bone marrow plasma cells, pos positive, HR hazard ratio, CI confidence interval

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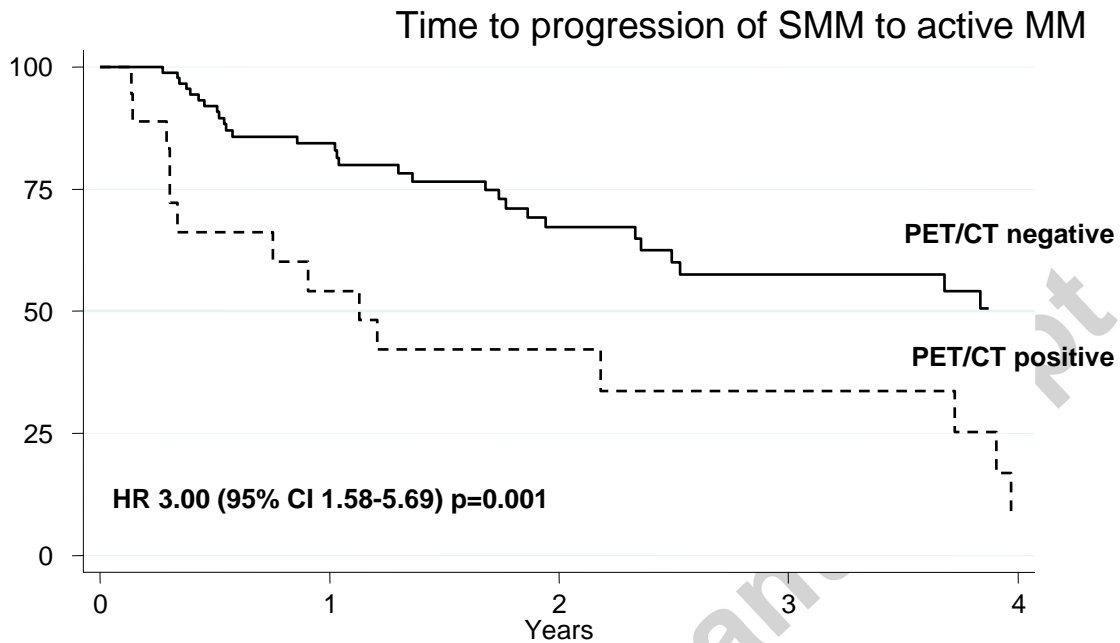
Table 5: Multinomial logistic regression analysis of baseline variables adversely affecting the risk of progression of SMM into active MM, either with or without skeletal MDE

	<b>Relative Risk Ratio (95% CI)</b>
<b>NO PD</b>	baseline
<b>PD with skeletal MDE (with or without other CRAB features)</b>	
BMPC > 60%	0.7 (0.1-7.1)
PET/CT pos	5.6 (1.5-20.3)
<b>PD without skeletal MDE</b>	
BMPC > 60%	7.1 (1.6-32.4)
PET/CT pos	4.1 (0.9-19.1)

BMPC bone marrow plasma cells, pos positive, CI confidence interval, MDE, myeloma defining events, PD progressive disease

Figure 1:

A)



B)

