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Metabolic Tumor Volume Assessed by ^{18}F-FDG PET/CT for the Prediction of Outcome in Patients with Multiple Myeloma

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^{18}F-FDG PET/CT allows the direct measurement of metabolic tumor burden in a variety of different malignancies. The aim of this study was to assess whether metabolic tumor volume (MTV) determined by ^{18}F-FDG PET/CT could be used in the prediction of progression-free and overall survival in multiple myeloma patients. **Methods:** Forty-seven patients (18 women, 29 men; mean age ± SD, 63 ± 11 y) with stage IIIA disease who had undergone whole-body ^{18}F-FDG PET/CT were retrospectively evaluated. Images underwent a 3-dimensional region-of-interest analysis including all focal lesions with a maximum standardized uptake value > 2.5. The MTV of each lesion was calculated using an automated contouring program based on the standardized uptake value and developed with a threshold of 40% of the maximum standardized uptake value. The total MTV of each patient was defined as the sum of metabolic volume of all focal lesions. Patients were treated and then subjected to a mean follow-up period of 24 mo. **Results:** In the 47 patients studied, MTV range was 1.3–316.3 mL, with a median of 23.7 mL. A direct, significant correlation was found between MTV and the percentage of diffuse infiltration of bone marrow by plasma cells ($r = 0.46$, $P = 0.006$), whereas hemoglobin levels were inversely correlated with MTV ($r = -0.56$, $P = 0.0001$). At follow-up, patients who developed progressive disease ($n = 18$) showed a significantly higher MTV (74.7 ± 19.3 vs. 29.8 ± 5.1 mL, $P = 0.009$) than patients without progressive disease ($n = 29$). Furthermore, patients who died of myeloma ($n = 9$) had a significantly higher MTV (123.2 ± 30.6 vs. 28.9 ± 4.2 mL, $P = 0.0001$) than survivors ($n = 38$). No differences in age, plasma cell infiltration, M protein, albumin, β2-microglobulin, performance status, International Staging System score, and presence or absence of a bone marrow transplant were found between groups. The MTV cutoff level was determined by receiver-operating-characteristic curve analysis, and the best discriminative value found for predicting progression-free and overall survival was 42.2 and 77.6 mL, respectively. By Kaplan–Meier analysis and log-rank testing, progression-free and overall survival at follow-up were significantly better in patients showing an MTV lower than the cutoff than in those having an MTV higher than the cutoff ($\chi^2 = 3.9$, $P = 0.04$, and $\chi^2 = 56.3$, $P < 0.0001$, respectively). **Conclusion:** The direct measurement of tumor burden obtained by calculating MTV on ^{18}F-FDG PET/CT images may be used in the prediction of progression-free and overall survival in myeloma patients.

Key Words: multiple myeloma; ^{18}F-FDG-PET/CT; metabolic tumor volume; prognosis

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Multiple myeloma (MM) is a malignant hematologic disorder characterized by the proliferation of a single clone of plasma cells infiltrating the bone marrow and invading adjacent bone structures frequently and multiple organs occasionally (*1*). This disease has a greatly variable clinical outcome. Patient survival, in fact, can range from a few months to more than 10 y (*2*). Therefore, the identification of reliable prognostic factors is important in order to estimate the individual patient's outcome. One of the most important prognostic factors is the extent of disease; however, because of different patterns of bone marrow involvement, the extent may be difficult to assess, leading to potential difficulties in staging and prognostic classification of patients (*3*).

Currently, the most widely used system for staging MM is that of Durie and Salmon—a system based on readily available clinical and hematologic parameters such as percentage of diffuse infiltration of bone marrow by plasma cells, hemoglobin levels, M protein level, calcium levels, and number of osteolytic bone lesions traditionally defined by skeletal radiography (*4*) and in the updated version, the Durie and Salmon PLUS, which includes the addition of more advanced imaging modalities such as ^{18}F-FDG PET/CT or MRI (*5,6*). The clinical and hematologic parameters included in the Durie and Salmon staging system may simply represent or correlate with the underlying tumor burden, which may be instead a more direct predictor of disease progression and patient survival.

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Previous studies performed in patients with a variety of different neoplastic diseases—such as head and neck cancer (*7,8*), lung cancer (*9,10*), pleural mesothelioma (*11*), pharyngeal cancer (*12*), thyroid cancer (*13*), non-Hodgkin lymphoma (*14,15*), osteosarcoma (*16,17*), and soft-tissue sarcoma (*18*)—showed that ^{18}F-FDG PET/CT, by determining the uptake and volume of metabolic active lesions in the whole body, allows direct measurement of metabolic tumor burden. In MM, therefore, metabolic tumor burden measured by ^{18}F-FDG PET/CT may reflect plasma cell mass throughout the bone marrow in the whole body, thus providing a novel potential prognostic factor. Therefore, we hypothesized that MTV may contribute to the prognostic stratification of patients who, despite allocation in the same stage, may show a wide spectrum of tumor burden.

The aim of our study was to determine the value of metabolic tumor volume (MTV) in the whole body of MM patients using ^{18}F-FDG PET/CT and to test whether it can be used in the prediction of progression-free and overall survival in MM patients. Furthermore, we compared and correlated MTV with the most important clinical and hematologic parameters of MM patients such as hemoglobin levels and percentage of diffuse infiltration of bone marrow by plasma cells.

TABLE 1
Patient Characteristics

Characteristics	Value
Age (y)	
Mean ± SD	63 ± 11
Range	32–81
Sex	
Female	18 (38%)
Male	29 (62%)
Type of myeloma	
IgG	38 (80%)
IgA	5 (11%)
Light chain	2 (4%)
Nonsecretory	2 (4%)
Bone lesions	
<3 lesions	33 (70%)
≥3 lesions	14 (30%)
Performance status	
≤70%	15 (32%)
80%	13 (28%)
90%	19 (40%)
ISS	
I	28 (60%)
II	6 (13%)
III	2 (4%)

MATERIALS AND METHODS

Patients

We reviewed retrospectively the medical records of 47 patients (18 women, 29 men; mean age ± SD, 63 ± 11 y) with newly diagnosed untreated MM who had undergone whole-body ^{18}F-FDG PET/CT at our institution. The study was approved by the ethics committee, and informed consent was obtained from all patients for the PET/CT procedure. At the time of the ^{18}F-FDG PET/CT study, all patients were classified as stage IIIA according to the Durie and Salmon staging system on the basis of standard criteria including hematologic and biochemical examinations and a skeletal radiographic survey. In fact, all patients met one or more of the following conditions indicating stage IIIA: hemoglobin value < 8.5 g/dL, serum calcium value > 12 mg/dL, advanced lytic bone lesions, M protein serum levels > 7 g/dL for IgG or > 5 g/dL for IgA, urine light chain M component > 12 g/24 h, and serum creatinine value < 2 mg/dL (*5*). [**Table 1**] Patient characteristics are reported in Table 1. All patients were treated according to therapeutic regimens containing novel agents such as thalidomide, lenalidomide, or bortezomib in combination with conventional agents and followed, in 19 patients, by autologous bone marrow transplantation. Patients were subjected to a mean follow-up period of 24 mo (range, 1–40 mo; median, 22 mo). At reevaluation, patients were considered to have progressive disease when showing an increase in the percentage of diffuse infiltration of bone marrow by plasma cells or in M protein or new bone lesions, partial remission when M protein decreased >50%, and complete remission when the percentage of diffuse infiltration of bone marrow by plasma cells was <5% and M protein was absent (*19*).

^{18}F-FDG PET/CT Study

^{18}F-FDG PET/CT scans were acquired after the patient fasted for 8 h and 60–90 min (mean ± SD, 68 ± 10 min) after intravenous administration of ^{18}F-FDG (350–370 MBq). The blood glucose level, measured just before tracer administration, was <120 mg/dL in all patients. ^{18}F-FDG PET/CT images were obtained using a combined PET/CT Discovery LS scanner (GE Healthcare). All scans were acquired in 2-dimensional mode. The emission scan was obtained in the caudocranial direction, from the upper thigh to the top of skull (4 min/each bed position) and from the feet to the base of the thigh (2 min/each bed position). Iterative image reconstruction was completed with an ordered-subset expectation maximization algorithm (2 iterations, 28 subsets). A CT device with a 4-slice multidetector helical scanner was used (detector row configuration, 4 × 5 mm; pitch, 1.5; gantry rotation speed, 0.8 s per revolution; table speed, 30 mm per gantry rotation;140 kV; and 80 mA). Attenuation-corrected emission data were obtained using filtered-backprojection CT-reconstructed images (gaussian filter of 8 mm in full width at half maximum) to match the PET resolution. Transaxial, sagittal, and coronal images and coregistered images were examined using Xeleris software (GE Healthcare).

Focal lesions were defined as focal areas of increased ^{18}F-FDG uptake visible on at least 2 contiguous PET slices, showing a maximum standardized uptake value (SUVmax) > 2.5 (*20–22*) and corresponding to CT abnormalities not attributable to benign bone pathologies. In particular, hypermetabolic sites corresponding to spondylopathy, osteoarthrosis, joint disease, or traumas were carefully excluded from the analysis whereas those corresponding to CT abnormalities such as lytic lesions, minor lytic changes, and osteopenic areas were included (*22*).

Measurement of MTV and Total Lesion Glycolysis (TLG)

To measure MTV values, PET/CT data were transferred in DICOM format to an OsiriX workstation (Pixmeo Sari). A 3-dimensional region of interest including each focal lesion previously localized was drawn, and SUVmax (using body weight normalization) was determined in the selected volume. In lesions showing an SUVmax > 2.5, MTV was calculated from PET data by grouping all spatially connected voxels within a threshold of 40% of

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the SUVmax, using an SUV-based automated contouring program developed in-house that provides the mean SUV (SUVmean) of the delineated volume. The 40% SUVmax threshold was set using a phantom, simulating lesions with a volume ranging between 1 and 12 mL, filled with ^{18}F activities corresponding to those clinically observed in bone lesions. A phantom study was acquired and reconstructed on the PET/CT Discovery LS scanner subsequently used for human studies, and the 40% SUVmax threshold best fitted the actual volume of simulated lesions.

In the human studies, the contour of each lesion was saved as an XML (extensible markup language) file and checked using the OsiriX DICOM viewer. The total MTV of each patient was defined as the sum of MTVs of all focal lesions selected.

The TLG was obtained by multiplying the MTV of each focal lesion for the corresponding SUVmean determined in the selected volume by isocontouring. The global TLG of each patient was defined as the sum of TLGs of all focal lesions selected.

Statistical Analysis

Statistical analysis was performed using SPSS software (IBM SPSS Inc.). All data were expressed as mean ± SE. Differences between groups were analyzed by the Student *t* test, whereas correlations among continuous variables were tested by simple regression. Univariate and multivariate analyses of clinical and imaging variables were performed using Cox proportional hazards regression. Only variables that predicted progression-free and overall survival by univariate analysis were included in the multivariate analysis. Receiver-operating-characteristic (ROC) curve analysis was performed to estimate the best discriminative value of independent prognostic variables between patients who had died and survivors and between patients with and without progression. Survival analysis was performed using the Kaplan–Meier method and log-rank tests. Survivors were censored at the time of the last clinical control. A probability value of <0.05 was considered statistically significant.

RESULTS

^{18}F-FDG PET/CT scans of 47 MM patients were analyzed, and imaging parameters including SUVmax, SUVmean, MTV, and TLG were measured in each patient. The SUVmax of the lesion with the highest metabolic rate ranged from 3.5 to 41.8, with an average of 11.2 and a median of 8.1 (Table 2). We also determined the mean of the SUVmax and of the SUVmean of all lesions analyzed in each patient; these values ranged from 3.5 to 37.0, with an average of 7.8 and a median of 6.0, for SUVmax and from 2.0 to 15.7, with an average of 4.0 and a median value of 3.2, for SUVmean. [Table 2]

TABLE 2
Range, Mean, and Median Values of Imaging Parameters Determined by ^{18}F-FDG PET/CT

Parameter	Range	Mean ± SE	Median
SUVmax (g/mL)	3.5–41.8	11.2 ± 1.2	8.1
Mean SUVmax (g/mL)	3.5–37.0	7.8 ± 0.9	6.0
Mean SUVmean (g/mL)	2.0–15.7	4.0 ± 0.4	3.2
TLG (g)	3.5–1645.7	286.7 ± 59.2	91.4
MTV (mL)	1.3–316.3	46.0 ± 8.5	23.7

Whole-body MTV values ranged from 1.3 to 316.3 mL, with an average of 46.0 mL and a median of 23.7 mL, and whole-body TLG values ranged from 3.5 to 1,645.7 g, with an average of 286.7 g and a median of 91.4 g (Table 2). MTV was determined by an automated contouring program (Fig. 1). MTV values positively and significantly correlated with percentage of diffuse infiltration of bone marrow by plasma cells ($r = 0.46$, $P = 0.006$) and inversely and significantly correlated with hemoglobin levels ($r = -0.56$, $P = 0.0001$). On the other hand, TLG showed a significant direct correlation with β2-microglobulin levels ($r = 0.38$, $P = 0.02$). [Fig. 1]

After a mean follow-up period of 24 mo, 9 patients died from MM, 9 had progressive disease, 14 showed partial remission, and 15 were in complete remission. For subsequent analysis, patients who had progressive disease or had died were grouped ($n = 18$) and compared with patients in complete or partial remission ($n = 29$). Similarly, patients showing progressive disease or partial or complete remission were grouped as survivors ($n = 38$) and compared with those who had died ($n = 9$).

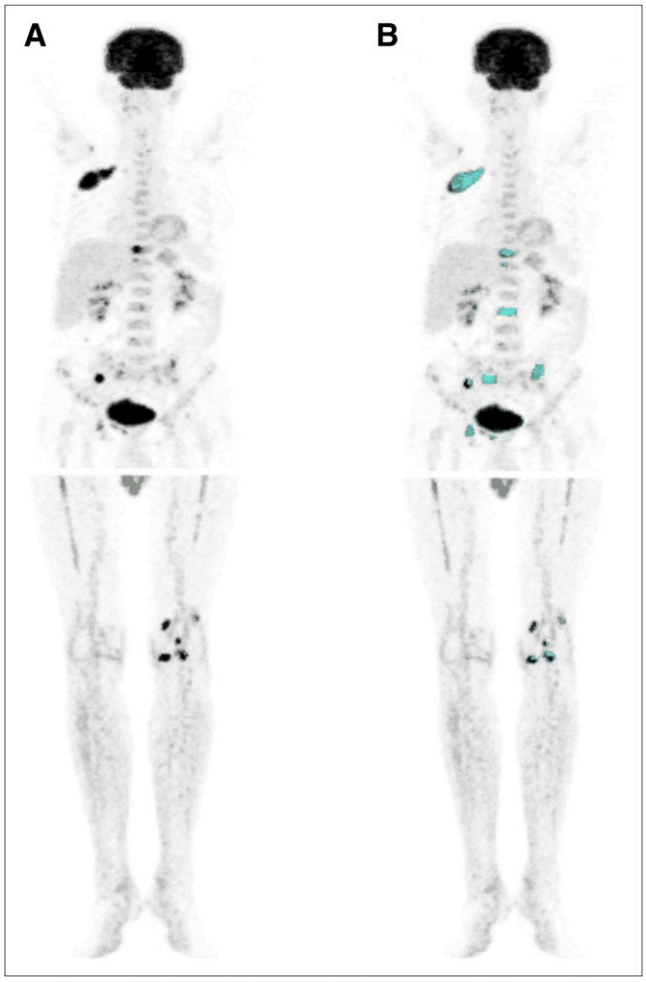

FIGURE 1. Maximum-intensity-projection views of ^{18}F-FDG PET/CT scans of MM patient without (A) and with (B) overlay of segmented MTVs. MTV = 77.2 mL.

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No statistically significant differences were found in clinical variables such as age, percentage of diffuse infiltration of bone marrow by plasma cells, M protein, albumin levels, β2-microglobulin, performance status, International Staging System (ISS) stage, and presence or absence of bone marrow transplantation between patients who had died and survivors, or between patients with progression and patients with remission. Hemoglobin levels were significantly lower in patients who died than in survivors (9.3 ± 0.61 vs. 13.0 ± 2.0 g/dL, $P < 0.0001$) but were not significantly different between patients in progression and patients in remission (11.4 ± 0.66 vs. 12.7 ± 0.43 g/dL, $P = 0.09$).

No statistically significant differences were found in imaging parameters such as SUVmax, mean SUVmax, and mean SUVmean between patients in progression and patients in remission. Conversely, patients in progression showed MTV and TLG values (74.7 ± 19.3 and 451.2 ± 125.2 mL, respectively) significantly higher than those in remission (29.8 ± 5.1 mL, $P = 0.0090$, and 198.1 ± 50.8 mL, $P = 0.0365$, respectively), as shown in Table 3. [Table 3]

Univariate analysis showed that both MTV ($\chi^2 = 6.26$, $P = 0.0124$) and TLG ($\chi^2 = 5.60$, $P = 0.0180$) predicted progression-free survival, whereas hemoglobin was not significant ($\chi^2 = 1.93$, $P = 0.1646$) (Table 4). At multivariate analysis, only MTV was retained in the model ($\chi^2 = 5.00$, $P = 0.0253$). ROC curve analysis showed that the best discriminative value of MTV between patients in progression and patients in remission was 42.2 mL (area under the curve [AUC], 0.68). Progression-free survival was significantly prolonged in patients with an MTV < 42.2 mL as compared with that in patients with an MTV ≥ 42.2 mL ($\chi^2 = 3.96$, $P = 0.0465$) (Fig. 2). [Table 4] [Fig. 2]

There were no statistically significant differences among the SUVmax, mean SUVmax, and mean SUVmean between patients who had died and survivors. The 9 patients who had died before follow-up showed an MTV value of 123.2 ± 30.6 mL, which was significantly higher ($P < 0.0001$) than the MTV value of 28.9 ± 4.2 mL shown by the remaining 38 patients. Furthermore, TLG was significantly higher in those who had died than in survivors (707.3 ± 198.9 vs. 197.4 ± 45.1, $P = 0.0004$), as shown in Table 5. [Table 5]

Univariate analysis showed that hemoglobin ($\chi^2 = 15.37$, $P = 0.0001$), MTV ($\chi^2 = 9.96$, $P = 0.0016$), and TLG ($\chi^2 = 8.44$, $P = 0.0037$) predicted overall survival (Table 4). At multivariate analysis, only hemoglobin and MTV were retained in the model ($\chi^2 = 24.23$, $P = 0.0003$), showing a statistically significant improvement of the prognostic value of combined variables, compared with each variable alone ($P < 0.05$).

A cutoff level was determined by ROC curve analysis for MTV, TLG, and hemoglobin, and the best discriminative

TABLE 3
Comparison Between Mean Values of Imaging Parameters Measured in Patients with Progression or Remission at Follow-up

Parameter	Progression ($n = 18$)	Remission ($n = 29$)	P
SUVmax (g/mL)	12.7 ± 2.1	10.4 ± 1.5	0.3518
Mean SUVmax (g/mL)	7.8 ± 0.9	8.0 ± 1.3	0.8954
Mean SUVmean (g/mL)	4.4 ± 0.5	3.8 ± 0.5	0.4839
TLG (g)	451.2 ± 125.2	198.1 ± 50.8	0.0365
MTV (mL)	74.7 ± 19.3	29.8 ± 5.1	0.0090

Data are mean ± SE.

TABLE 4
Predictors of Progression-Free Survival and Overall Survival by Univariate Analysis Based on Clinical and Imaging Parameters

Parameter	Progression-free survival		Overall survival	
	χ^2	P	χ^2	P
Age (y)	0.01	0.9530	0.74	0.3900
Hemoglobin	1.93	0.1646	15.37	0.0001
Plasma cell concentration	1.34	0.2465	2.62	0.1059
M protein	3.07	0.0797	0.29	0.5934
Albumin	1.01	0.3156	0.55	0.4595
β2-microglobulin	1.34	0.2472	2.99	0.0840
Performance status	0.08	0.7776	1.22	0.2689
International staging system	0.32	0.5662	0.35	0.5518
Bone marrow transplantation	1.39	0.2379	1.80	0.1793
SUVmax	1.60	0.2070	1.34	0.2475
Mean SUVmax	0.07	0.7932	0.27	0.6022
Mean SUVmean	0.50	0.4792	0.98	0.3219
TLG	5.60	0.0180	8.44	0.0037
MTV	6.26	0.0124	9.96	0.0016

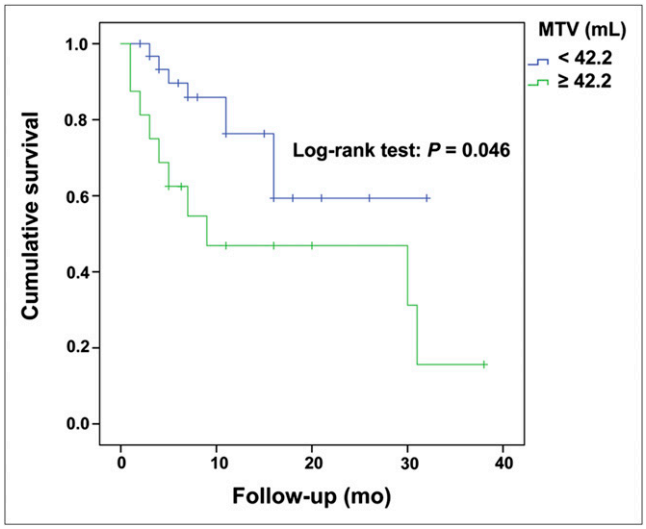

FIGURE 2. Progression-free survival by Kaplan–Meier analysis and log-rank test showing significant difference at 40 mo of follow-up between MM patients with MTV lower than cutoff of 42.2 mL and those with MTV higher than cutoff as assessed by ROC curve analysis ($P = 0.046$).

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TABLE 5
Comparison Between Mean Values of Imaging Parameters Measured in Patients Who Died and Survivors at Follow-up

Parameter	Patients who died (n = 9)	Survivors (n = 38)	P
SUVmax (g/mL)	14.1 ± 1.7	10.6 ± 1.4	0.2492
Mean SUVmax (g/mL)	8.7 ± 1.5	7.7 ± 1.1	0.6841
Mean SUVmean (g/mL)	4.9 ± 0.8	3.8 ± 0.4	0.2445
TLG (g)	707.3 ± 198.9	197.4 ± 45.1	0.0004
MTV (mL)	123.2 ± 30.6	28.9 ± 4.2	< 0.0001

Data are mean ± SE.

values between those who had died and survivors were 77.6 mL (AUC, 0.88), 201.4 g (AUC, 0,82), and 10.3 g/dL (AUC, 0.91), respectively. By Kaplan–Meier analysis and log-rank testing, overall survival was significantly better in patients with an MTV < 77.6 mL than in those with an [**Fig. 3**] MTV ≥ 77.6 mL ($\chi^2 = 56.37$ $P < 0.0001$) (Fig. 3). Patients with a TLG < 201.4 g had a longer survival than patients with a TLG ≥ 201.4 g ($\chi^2 = 14.0$, $P = 0.0002$). Similarly, hemoglobin levels lower than 10.3 g/dL, compared with levels higher than the cutoff, were associated with a shorter [**Fig. 4**] overall survival ($\chi^2 = 17.98$, $P < 0.0001$) (Fig. 4). Finally, in patients with hemoglobin levels lower than 10.3 g/dL, compared with levels higher than the cutoff, MTV values ≥ 77.6 mL still corresponded to a shorter overall survival [**Fig. 5**] ($\chi^2 = 6.06$, $P = 0.14$), as shown in Figure 5.

DISCUSSION

The present study shows that MTV measured by ^{18}F-FDG PET/CT can be used as a prognostic index for disease progression and death in patients with MM, independently from other established prognostic factors such as percentage of diffuse infiltration of bone marrow by plasma cells and hemoglobin levels. In fact a large prognostic variability is reported even among patients in the same Durie and Salmon stage (*2*). Therefore, MTV can contribute, in addition to conventional staging, to the further stratification of patients for prognosis, thus allowing adaptation of therapy to individual patients.

The Durie and Salmon clinical staging system was developed >30 y ago to provide a practical way to measure MM tumor burden, which is difficult to assess because of the significant heterogeneity characterizing this disease at multiple levels such as clinical presentation, biologic characteristics, treatment response, and clinical outcome (*4*). The Durie and Salmon staging system uses conventional radiography for evaluating osteolytic bone lesions. Detection of such lesions has a critical value in staging, treatment evaluation, and prognosis of MM because up to 90% of patients develop lytic lesions during the course of their disease. Conventional radiography, though, can significantly underestimate lytic lesions because >30% of trabecular bone might not be seen on radiographs (*20*).

Therefore, in the effort to develop a more objective and easily feasible staging system for MM, the ISS was proposed. The ISS is based on the measurement of serum albumin and β2-microglobulin levels by readily available laboratory tests. However, cutoff levels remained a matter of controversy because in advanced ISS, tumor burden and renal failure could cause β2-microglobulin levels to increase. Therefore, this system cannot provide a good estimate for

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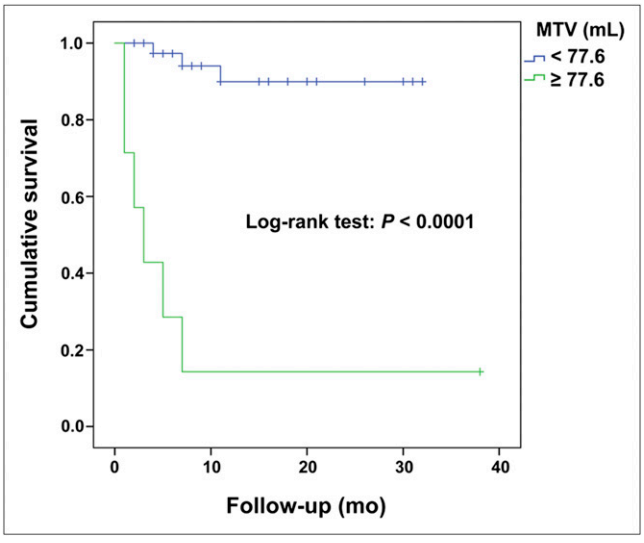

FIGURE 3. Overall survival by Kaplan–Meier analysis and log-rank test showing significant difference at 40 mo of follow-up between MM patients with MTV lower than cutoff of 77.6 mL and those with MTV higher than cutoff as assessed by ROC curve analysis ($P < 0.0001$).

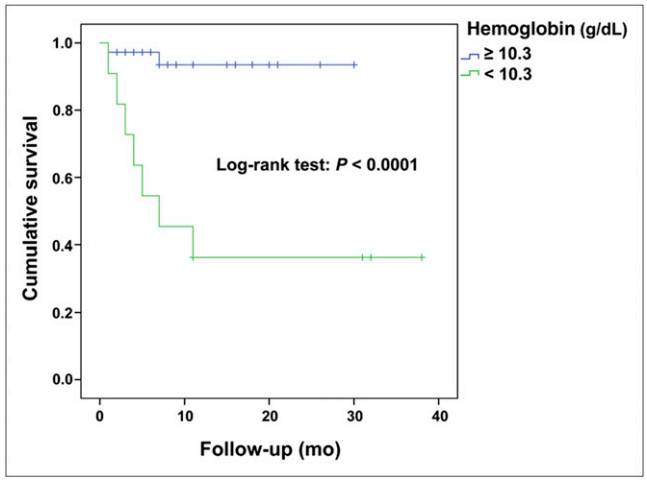

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FIGURE 4. Overall survival by Kaplan–Meier analysis and log-rank test showing significant difference at 40 mo of follow-up between MM patients with hemoglobin level lower than cutoff of 10.3 g/dL and those with hemoglobin higher than cutoff as assessed by ROC curve analysis ($P < 0.0001$).

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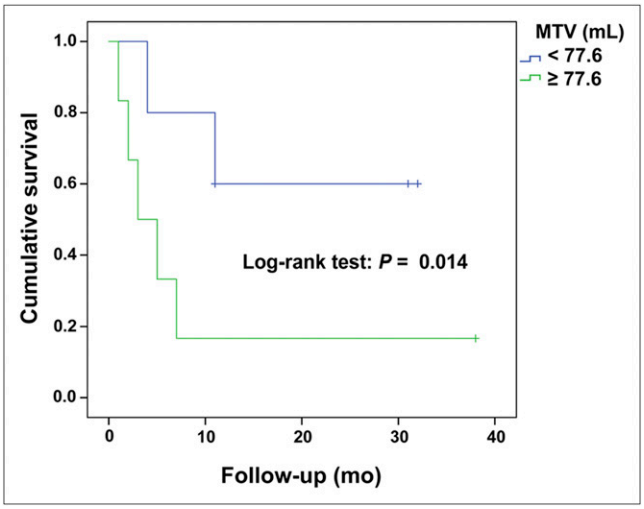

FIGURE 5. Overall survival by Kaplan–Meier analysis and log-rank test showing significant difference at 40 mo of follow-up between MM patients with hemoglobin level lower than 10.3 g/dL plus MTV lower than cutoff of 77.6 mL and patients with hemoglobin lower than 10.3 g/dL plus MTV higher than cutoff as assessed by ROC curve analysis ($P = 0.014$).

tumor burden or risk stratification. Moreover, with the introduction of new drugs for MM treatment, the prognostic role of ISS has not yet been established and it is possible that it may not retain its prognostic significance (*2,3*).

Recent studies showed that certain cytogenetic abnormalities such as translocation of t(4;14), t(14;16) or deletion of 17p by fluorescence in situ hybridization or deletion of chromosome 13 or hypodiploidy by conventional cytogenetics confer an adverse outcome in myeloma, but the role of these alterations in prognosis and therapeutic choices needs further evaluation in prospective clinical trials (*23*).

In the past few years, therefore, despite the combination of parameters related to demographics, features of the tumor clone or laboratory abnormalities were proposed for staging and prognosis of MM, yet none of the models turned out to be superior to the Durie and Salmon staging system (*2*). Thus, to improve the efficacy of this system in assessing the extent and severity of MM, newer imaging modalities such as ^{18}F-FDG PET/CT and MRI of the spine and pelvis were integrated in the Durie and Salmon PLUS staging system (*5,6*).

With respect to other imaging modalities, ^{18}F-FDG PET/CT provides both functional and morphologic assessment of MM patients. ^{18}F-FDG uptake, in fact, reflects the increased glycolysis usually occurring in tumor cells and thus the rapid growth and invasive characteristics of focal lesions (*19,24–26*). Moreover, the use of a hybrid PET/CT system allows a more precise anatomic localization of hypermetabolic MM lesions, allowing the detection of small or slightly active lesions hardly distinguishable by the surrounding normal tissue using PET images alone (*27*). A previous study performed by our group showed that ^{18}F-FDG PET/CT can significantly contribute to an accurate whole-body evaluation of MM patients by detecting more focal lesions than MRI of the spine and pelvis because of the presence of a consistent number of lesions outside this anatomic district (*22*). Similar findings were reported by other authors, indicating that ^{18}F-FDG PET/CT is a valuable tool in the management of MM patients (*20,25,26,28*).

Clinical outcome of MM has a great variability; therefore, to improve prognosis, ^{18}F-FDG PET/CT can be exploited in the effort to identify newer prognostic factors that could provide a more direct measure of tumor burden, thus complementing conventional staging. ^{18}F-FDG PET/CT has been examined in the context of prognostic evaluation of a variety of different malignancies. Disease activity is usually measured by determining the SUVmax, which represents the point of highest metabolic activity within the tumor and has been used for prognosis and therapy guidance in many neoplastic diseases (*29–34*). In our study, SUVmax alone did not predict disease progression or death. However, the new imaging parameter MTV, derived from SUVmax, showed prognostic significance, likely because MTV takes into account the metabolic active volume of all MM lesions, which can vary in size and uptake and be widespread throughout the body. A recent study reported that patients affected by MM at different stages with ^{18}F-FDG uptake–positive extramedullary lesions showed a shorter survival than patients without ^{18}F-FDG–positive lesions; the study also found that the SUVmax of the extramedullary lesion with the highest metabolic uptake was significantly associated with overall survival (*35*). In our study, we enrolled MM patients who were in the same stage. Therefore, to further stratify MM patients within the same stage we evaluated not only the one lesion with the highest SUVmax but also all focal lesions in each patient, in the attempt to obtain a complete evaluation of tumor burden using MTV that was predictive of both disease progression and death.

Among all clinical and imaging variables tested, univariate analysis showed that both MTV and TLG predicted progression-free survival but, at multivariate analysis, only MTV was an independent predictive factor of disease progression. Similarly, overall survival was predicted by hemoglobin, MTV, and TLG at univariate analysis, whereas at multivariate analysis only hemoglobin and MTV were retained in the model. In this respect, it should be pointed out that the combination of an established prognostic factor in MM such as hemoglobin with an imaging parameter such as MTV can improve prognostic stratification of patients in advanced stages.

CONCLUSION

In this study, we showed that MTV measured using ^{18}F-FDG PET/CT could be useful as a prognostic factor for progression-free and overall survival in MM patients. MTV, in fact, represents the metabolic active volume, thus reflecting the amount of total plasma cell mass in these patients. Moreover, MTV is an independent prognostic factor and can be used in addition to classic prognostic factors such as hemoglobin to better predict overall sur-

vival in MM patients. However, further studies are needed to validate our findings prospectively and in a larger patient cohort.

DISCLOSURE STATEMENT

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