Clinical Cancer Research

PET/CT Improves the Definition of Complete Response and Allows to Detect Otherwise Unidentifiable Skeletal Progression in Multiple Myeloma

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Abstract

Purpose: To evaluate the role of 18F-FDG PET/CT in 282 symptomatic multiple myeloma patients treated up-front between 2002 and 2012.

Experimental Design: All patients were studied by PET/CT at baseline, during posttreatment follow-up, and at the time of relapse. Their median duration of follow-up was 67 months.

Results: Forty-two percent of the patients at diagnosis had >3 focal lesions, and in 50% SUV_{max} was >4.2; extramedullary disease was present in 5%. On multivariate analysis, ISS stage 3, SUV_{max} >4.2, and failure to achieve best complete response (CR) were the leading factors independently associated with shorter progression-free survival (PFS) and overall survival (OS). These 3 variables were used to construct a prognostic scoring system based on the number of risk factors. After treatment, PET/CT negativity (PET-neg) was observed in 70% of patients, whereas conventionally defined CR was achieved in 53%. Attainment of PET-neg favorably influenced PFS and OS. PET-neg was an independent predictor of prolonged PFS and OS for patients with conventionally defined CR. Sixty-three percent of patients experienced relapse or progression; in 12%, skeletal progression was exclusively detected by systematic PET/CT performed during follow-up. A multivariate analysis revealed that persistence of SUV_{max} >4.2 following first-line treatment was independently associated with exclusive PET/CT progression.

Conclusions: PET/CT combined with ISS stage and achievement or not of CR on first-line therapy sorted patients into different prognostic groups. PET/CT led to a more careful evaluation of CR. Finally, in patients with persistent high glucose metabolism after first-line treatment, PET/CT can be recommended during follow-up, to screen for otherwise unidentifiable progression. *Clin Cancer Res; 21(19); 4384–90. ©2015 AACR.*

Introduction

PET integrated with CT (PET/CT) using the positron-emitting radionuclide ^{18}F labeled with Fluorodeoxyglucose (18F-FDG) proved to be a reliable technique for assessing skeletal involvement in multiple myeloma and a valuable tool at the onset of the disease for predicting outcomes in those patients who are eligible to subsequently receive autologous stem cell transplantation (ASCT; refs. 1, 2). However, the prognostic role of PET/CT for transplant-ineligible patients still remains less defined.

The clinical course of multiple myeloma is highly variable, and many studies have identified prognostic factors predicting this heterogeneity in survival. More recently, several groups have combined some of the available markers, significantly improving the prognostic value in terms of progression-free survival (PFS) and overall survival (OS; ref. 3). Imaging features have been combined and correlated, with a series of established prognostic variables, such as beta-2-microglobulin (β2M), C reactive protein (CRP), albumin and lactate dehydrogenase (LDH), and genetic abnormalities (2, 4).

Incorporation of novel agents into ASCT and in the treatment of newly diagnosed transplant-ineligible multiple myeloma patients has brought unprecedented rates of complete response (CR), a gain that has extended PFS and OS (5). Novel imaging techniques, such as MRI and FDG PET/CT, have been proposed as complementary investigational tools to improve the definition of CR, potentially detecting the presence of focal lesions harboring viable monoclonal plasma cells (1, 2). However, only preliminary data have been published on the outcomes of patients achieving conventionally defined CR but still having positive PET/CT scans.

Although novel imaging techniques have a clear role in both the staging and restaging of multiple myeloma at the time of relapse and in the evaluation of treatment response (6–8), their serial use during follow-up of the disease is currently not recommended because of the high cost and radiation exposure. However, to the best of our knowledge, no formal cost/benefit analysis has yet been performed.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

The number of focal lesions, the SUV_{max} value, and the presence of extramedullary disease, as detected by FDG PET/CT, are reliable predictors of outcome in newly diagnosed multiple myeloma patients who are candidates to receive or not autologous stem cell transplantation. In this analysis, baseline SUV_{max} >4.2 combined with ISS stage 3 and failure to achieve complete response (CR) upon first-line treatment identified a subgroup of patients (10%) with very poor prognosis who might be candidates for alternative treatment strategies. PET/CT provides a more accurate definition of CR, allowing to stratify patients in conventional CR after up-front therapy into different prognostic subgroups with different progression-free survival and overall survival, according to the persistence or absence of FDG metabolic activity. PET/CT scans serially performed during the follow-up phase after first-line treatment can detect skeletal progression in 12% of patients with persistent high glucose metabolism and no additional criteria of progressive disease.

We herein report the results of a retrospective analysis of PET/CT's prognostic track record as performed at baseline in 282 newly diagnosed multiple myeloma patients, as well as the value of this imaging tool after treatment in improving the definition of CR and in the follow-up phase of the disease.

Patients and Methods

Patients and treatment protocols

We retrospectively analyzed 282 newly diagnosed symptomatic multiple myeloma patients, who were treated at the University of Bologna, Italy, from January 2002 to December 2012. Two hundred and seven (73%) patients were eligible for high-dose therapy (HDT) and ASCT; 48 of 207 (23%) received induction therapy with conventional chemotherapy (VAD regimen; ref. 9), in 88 of 207 (43%), thalidomide-dexamethasone (TD) was incorporated into ASCT, as described elsewhere (10), and in 71 of 207 (34%), bortezomib plus thalidomide plus dexamethasone (VTD) was given prior to and after ASCT (11). Transplant-ineligible patients were treated with the combination of bortezomib–melphalan–prednisone (VMP) in 34 of 75 (46%) cases or with the combination of thalidomide–melphalan–prednisone (MPT) in 25 of 75 (33%) cases, as described elsewhere (12, 13), and with conventional chemotherapy alone in 16 of 75 (21%) cases. Globally, first-line treatment incorporated a novel agent in 77% of the patients, including a bortezomib-based regimen in 37% (Table 1). All patients had given their signed informed consent in accordance with the Declaration of Helsinki.

Procedures

Imaging studies. All patients were studied at baseline with 18F-FDG PET-CT. PET/CT was repeated during posttreatment follow-up, every 12 to 18 months, irrespective of laboratory data and clinical symptoms. In 189 patients, PET/CT was performed 3 months after the end of first-line treatment.

Whole-body FDG PET/CT was carried out using standard procedures, as previously described (1). Briefly, 3 to 5.7 MBq/kg of FDG were intravenously injected. All patients were required to fast for 6 hours. The uptake time was 60 minutes in all the patients. Images were acquired on a two-dimensional tomograph (GE; Discovery LS) for 4 minutes per bed position or on a three-dimensional tomograph (GE; Discovery STE) for 2 minutes per bed position. Cross calibration was performed using an image quality NEMA phantom. Low-dose CT (120 kV; 80 mA) was performed both for attenuation correction and as an anatomical map. PET images were reconstructed using an iterative 3-D ordered subset expectation maximization method with two iterations, 20 subsets, followed by smoothing (with a 6-mm 3-D Gaussian kernel) with CT-based attenuation, scatter, random coincidence event correction. The field of view included the skull, superior limbs, and mid femurs.

PET/CT scans were evaluated by a team of nuclear medicine physicians who had extensive experience in the multiple myeloma field. Criteria to define PET/CT positivity included at least one of the following:

1. Presence of focal areas of visually detectable increased tracer uptake within bones (e.g., more intense than background bone marrow uptake) excluding articular processes, with or without any underlying lesion identified by CT and present on at least two consecutive slices (to avoid a misinterpretation of bone marrow mild inhomogeneous FDG uptake);
2. Alternatively, a standardized uptake value (SUV) maximum (max) based on body weight according to standard formula of 2.5 within osteolytic CT areas exceeding 1 cm in size. To harmonize SUV_{max} measurements (especially in consideration of the long time course of the study), no time of flight reconstructed images were used;
3. Alternatively, a SUV_{max} based on body weight according to standard formula of 1.5 within osteolytic CT areas less or equal to 1 cm in size (this was done to roughly correct for partial volume effect).

Bone marrow was considered diffusely involved if the tracer uptake was diffusely increased with a SUV_{max} equal to, or greater than, the uptake in the spleen. In this case, SUV_{max} was measured in the hottest area within the bone marrow. The number, size, and location of hypermetabolic focal lesions (PET-FLs) were recorded. The degree of FDG uptake was represented by SUV_{max} in the hottest lesion. The presence of extramedullary disease (EMD), defined as FDG-avid tissue that, according to CT examination, was not contiguous to bone and arose in soft tissue, was described by location, size, number of lesion, and SUV_{max}. Paramedullary disease, arising from bone, was considered as a lesion but not as EMD (Supplementary Table S1).

Table 1. Patient characteristics at baseline and treatment received

Patients, *N*	282
Median age, y (range)	59 (22–83)
Median LDH (UI/L; range)	303 (99–2,020)
Patients with ISS stage 3 (%)	20
Patients with del (17p) and/or t(4;14) (%)	30
Patients receiving ASCT as first-line treatment (%)	73
Conventional chemotherapy-based	23
Thalidomide-based	43
Bortezomib-based	34
Patients not ASCT eligible (%)	27
Conventional chemotherapy	21
MPT	33
VMP	46
Patients receiving novel agents as first-line treatment (%)	77
Patients receiving bortezomib as first-line treatment (%)	37

Abbreviations: del, deletion; ISS, international staging system; t, translocation.

Laboratory investigations. 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 baseline, at the end of first-line treatment, and every 3 months thereafter. Bone marrow aspirate was evaluated prior to treatment and to confirm the achievement of CR. FISH analysis of del(13q), t(4;14) del(17p) was performed at baseline in 60% of the patients. Additional prognostic parameters registered at baseline were the following: serum levels of beta-2-microglobulin (β2M), C reactive protein (CRP), albumin, and LDH.

Definitions of response and relapse by laboratory and imaging. Response to treatment was assessed according to the International Myeloma Working Group criteria (14). Relapse from CR and progression after a very good partial response (VGPR) or less were defined as previously established (14). Two subsequent evaluations were required to validate the definition of relapse or progression.

PET/CT was considered negative if every area of increased tracer uptake found at baseline disappeared, whereas it was defined as improved if the number of sites of FDG uptake decreased and/or the SUV_{max} of the lesions decreased by at least 20%, in accordance with European Organisation for research and Treatment of Cancer (EORTC) criteria (15).

A SUV_{max} increase by more than 50% of residual PET-FLs or appearance of new FL(s) or EMD by PET/CT were criteria to define relapse or progression.

Statistical analysis

Kaplan–Meier analyses landmarked at 6 months from the start of primary therapy were used to estimate PFS (time from start of treatment to progression or relapse, or death from any cause) and OS. Survivors were censored at the time of last contact. Between-group comparisons were done using the log-rank test.

Multivariate Cox regression analyses were performed to identify baseline and posttreatment factors significantly affecting PFS and OS. The 3 leading factors (e.g., ISS stage 3, SUV_{max} >4.2, and failure to achieve best CR) were used to construct a prognostic scoring system based on the number of risk factors.

In the end, we performed a multinomial logistic regression analysis to identify the most powerful prognostic factor(s) predicting for exclusive skeletal progression, in the absence of any additional sign of relapse or progression.

Results

Patient and imaging characteristics

This retrospective analysis involved 282 newly diagnosed symptomatic multiple myeloma patients who were treated at our institution between 2002 and 2012, most of them with novel agent-based regimens. Their main characteristics at baseline are summarized in Table 1. The median patient age was 59 years (range, 22–83). ISS stage 3 was diagnosed in 20%, and the median LDH was 303 UI/L (range, 99–2020). Overall, 60% of patients were screened for cytogenetic abnormalities by FISH analysis performed on $CD138^+$ bone marrow plasma cells; 30% of them presented translocation t(4;14) and/or deletion (17p).

Seventy-three percent of the patients received a single or double ASCT, whereas the remaining 27% were treated with chemotherapy at conventional doses combined or not with novel agents.

Table 2. PET/CT characteristics at baseline and after first-line treatment

PET/CT characteristics	Baseline	After treatment
Patients with negative PET/CT (%)	30	70
Patients with positive PET/CT (%)	70	30
1–3 FLs	28	15
>3 FLs or diffuse	42	15
SUV $\leq$ 4.2	25	18
SUV >4.2	45	12
Patients with EMD (%)	5	3

Details of treatment received are reported in Table 1. With a median follow-up of 67 months (39–111), the best rates of CR and at least VGPR were 53% and 85%, respectively. Median durations of PFS and OS were 50 and 168 months, respectively.

Seventy percent of the patients had a positive PET/CT scan at diagnosis, with 41% of them showing 1 to 3 FLs and 59% either a diffuse bone marrow involvement or more than 3 FLs (Table 2). Eighty-five percent of PET-positive patients had an underlying lytic lesion by CT, whereas 15% had only one or more focal areas of increased tracer uptake with corresponding negative CT scans. In half of the patients (50%), the baseline FDG uptake was high (defined as SUV_{max} >4.2). The reference lesion turned out to be larger than 1 cm in >90% of scans, so that inaccuracy in SUV_{max} measurement due to partial volume effect did not significantly affect the final results. EMD was present in 5% of cases. The cutoffs for FLs and SUV had been previously identified (1).

Baseline PET/CT as prognosticator to construct a scoring system

On univariate analysis, ISS stage 3, failure to achieve best CR, and unfavorable PET/CT features, as defined by a number of FLs >3, SUV_{max} >4.2, and presence of EMD, adversely affected PFS and OS (for details, see Supplementary Table S2), and retained prognostic relevance independently of the treatment received (including or not ASCT, whether bortezomib or nonbortezomib based; data not shown). The multivariate analysis showed that both PFS and OS were significantly related to a SUV_{max} value >4.2 at baseline PET/CT, ISS stage 3, and failure to achieve best CR (Table 3, model 1).

These 3 variables enabled us to draw up a scoring system, based on the number of risk factors (score 0: none of the 3 adverse

Table 3. PFS and OS according to ISS stage 3, failure to achieve best CR after first-line therapy, and PET/CT SUV_{max} >4.2 (Model 1, multivariate analysis) or according to their combination into a prognostic score (Model 2)

	HR (95% CI)	*P*
PFS		
Model 1		
ISS stage 3	1.49 (1.03–2.57)	0.041
Failure to achieve best CR	2.52 (1.51–4.21)	<0.001
SUV_{max} >4.2	1.90 (1.12–3.21)	0.017
Model 2		
Score 1 vs. 0	3.11 (1.52–6.35)	0.002
Score 2 vs. 0	5.70 (2.66–12.22)	<0.001
Score 3 vs. 0	7.17 (2.94–17.48)	<0.001
OS		
Model 1		
ISS stage 3	2.11 (1.04–5.15)	0.039
Failure to achieve best CR	1.61 (0.66–3.91)	0.295
SUV_{max} >4.2	3.65 (1.30–10.27)	0.014
Model 2		
Score 1 vs. 0	3.14 (0.79–12.48)	0.104
Score 2 vs. 0	6.01 (1.37–26.32)	0.017
Score 3 vs. 0	13.19 (2.71–64.09)	0.001

factors, 30% of the patients; score 1: only 1 of 3, 36%; score 2: 2 factors, whichever, 25%; and score 3: all three risk factors, 9% of cases). The score predicted for PFS and OS, with a progressive increase in the HRs (Table 3, model 2). More specifically, median PFS was 94 months for patients with score 0, 44 months for score 1, 30 months for score 2, and 14 months for score 3 ($P < 0.0001$, P trend < 0.0001; Fig. 1). The 60-month projected OS was 96%, 80%, 75%, and 30% in the 4 risk categories, respectively ($P = 0.003$, P trend = 0.0003; Fig. 1).

Although a similar stratification into different prognostic groups was obtained when FLs > 3 and presence of EMD replaced SUV_{max} >4.2 (data not shown), we included this latter parameter into the system because in a multivariate analysis it was a stronger predictor of poor outcomes in comparison with FLs (FLs > 3: PFS HR = 1.38, $P = 0.279$, OS HR = 2.14, $P = 0.171$; SUV_{max} >4.2: PFS HR = 2.24, $P = 0.009$, OS HR = 3.12, $P = 0.066$) and due to the limited sample size of patients presenting with EMD (5% of the overall population).

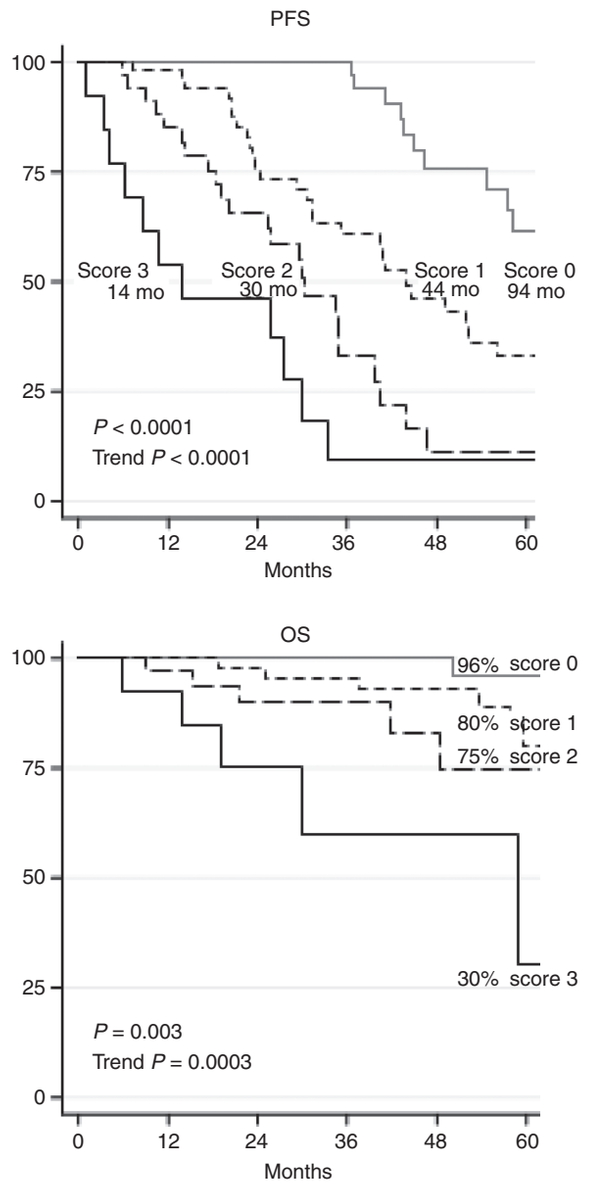

Figure 1.
PFS and OS according to the scoring system (ISS stage 3, failure to achieve best CR after first-line therapy, and PET/CT SUV_{max} >4.2).

PET/CT after treatment to fine-tune the definition of CR

By 3 months after the last cycle of first-line treatment, 85% of the patients obtained at least a VGPR, including 53% with conventionally defined CR. In 189 patients, PET/CT scans were repeated to evaluate skeletal response to therapy. The rates of CR and at least VGPR in this subgroup of patients were superimposable to those of the whole series (55% and 88%, respectively). PET/CT was negative in 70% of patients, whereas it remained positive in 30% who either improved (20%) or had PET/CT scans unchanged or worsened (10%; Table 2). Attainment of PET/CT negativity significantly influenced both PFS (median: 52 vs. 38 months for PET/CT-positive patients; $P = 0.0319$) and OS (5-year estimates: 90% vs. 71%, respectively; $P = 0.0014$). Notably, 29% of patients who achieved CR according to conventional criteria still had positive PET/CT scans, a finding that made for poorer prognosis. Indeed, the median PFS for PET/CT-positive patients was significantly shorter than for negative patients (44 vs. 84 months; $P = 0.0009$; Fig. 2). OS was significantly inferior, as well, for PET/CT-positive patients, with a 5-year estimate of 70% in comparison with 90% for PET/CT-negative patients ($P = 0.0032$; Fig. 2). On multivariate analysis, posttreatment PET/CT negativity was an independent factor predicting for prolonged PFS [HR, 0.43; confidence interval (CI), 0.24–0.77] and OS (HR, 0.33; CI, 0.13–0.86) for patients with conventionally defined CR.

PET/CT during the follow-up phase

Overall, 63% of patients experienced progressive disease. The definition of progression was based on previously established laboratory criteria (14) in 37% of them, on both serological and skeletal criteria (e.g., new bone lesions, or increased size of previously detected bone lesions, or appearance of EMD) in 48%, and on only skeletal criteria in 15%. Within this last subgroup, 88% of patients had clinical symptoms or findings, such as pain or pathologic fractures, that prompted performance of a PET/CT scan ultimately confirming progressive disease, whereas in 12%, otherwise clinically silent skeletal progression was occasionally detected by performing serial PET/CT scans during follow-up. We previously demonstrated that there is an inverse correlation between the residual SUV_{max} value after ASCT and time to progression, whereby all patients with SUV_{max} >4.2 subsequently relapsed (16). In this series of patients, 12% retained a SUV_{max} >4.2 at the end of first-line treatment. A multinomial logistic regression analysis of baseline variables included in the prognostic scoring system and of posttreatment PET features revealed that persistence of SUV_{max} >4.2 was the single factor independently associated with skeletal progression detectable by PET/CT in the absence of otherwise identifiable signs of progressive disease [$P = 0.039$, relative risk ratio (RRR), 11.05 (1.13–108.08; Table 4]. The low number of patients justifies the high variability in the CIs of the RRR.

Discussion

In this retrospective study of 282 patients who were evaluated at baseline and during posttreatment follow-up with serial FDG PET/CT scans, we confirmed that this imaging technique is a

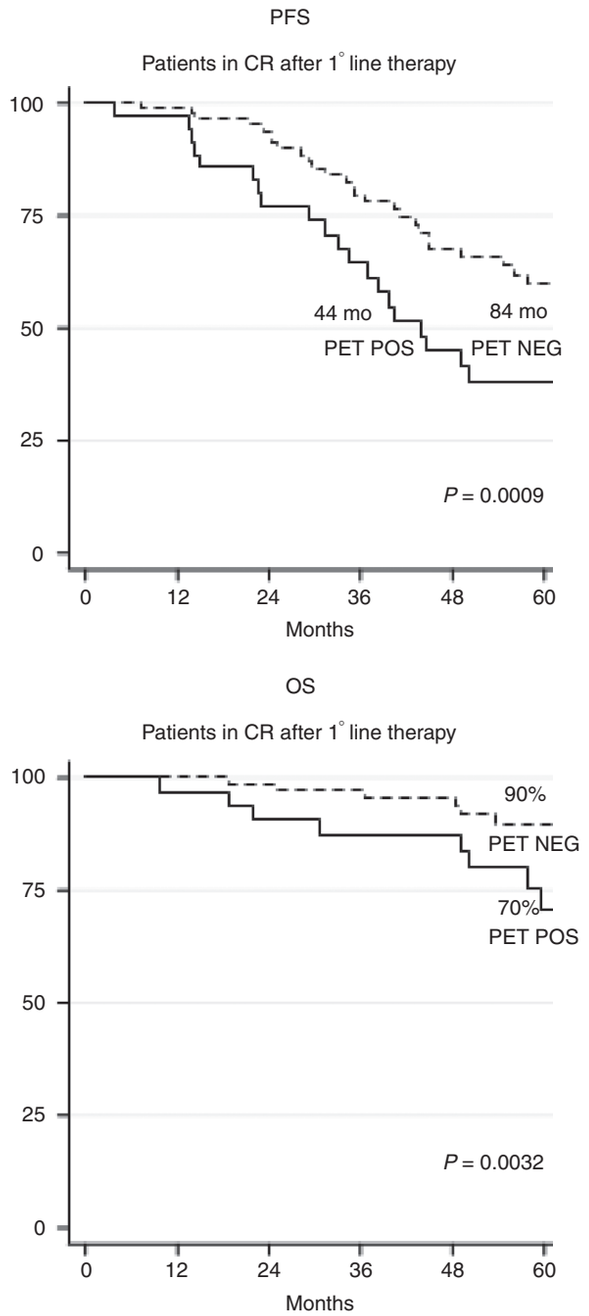

Figure 2.
PFS and OS according to PET/CT negativity or positivity in patients achieving conventionally defined CR after up-front therapy.

reliable predictor of prognosis, in both younger, transplant-eligible, and elderly multiple myeloma patients. As previously shown (1), the entity of PET/CT involvement at diagnosis, as reflected by the number of FLs, the intensity of tumor metabolism represented by the SUV value, and the presence of EMD were strong predictors of unfavorable clinical outcomes. In particular, a SUV_{max} value >4.2 retained independent prognostic relevance in multivariate regression analyses along with the presence of ISS stage 3 and failure to achieve CR during or after first-line treatment. Although other studies previously showed the prognostic value of FDG PET/CT at baseline in patients receiving novel agents plus ASCT (1, 2, 17), to the best of our knowledge, this is the first report providing demonstration that PET/CT involvement predicts outcomes also in elderly patients treated with novel agents and chemotherapy.

Several factors related to the myeloma cell burden and/or reflecting the biologic characteristics of the disease at the time of diagnosis have a well-defined prognostic role in multiple myeloma patients. In particular, β2M, albumin, CRP, LDH, cytogenetic abnormalities, and gene array–defined profiles are commonly used to classify patients in different stages and risk subgroups (3, 18). Imaging features have likewise been combined and correlated with a series of established prognostic variables, such as β2M, CRP, albumin, LDH, and genetic abnormalities (2, 4). Patients with more than 3 FLs on FDG PET/CT at diagnosis were reported to have significantly higher LDH and β2M values, more severe anemia, and to be more frequently in advanced stages of the disease (19). A diffuse pattern of bone marrow involvement on MRI was found to be associated with high-risk cytogenetics (4). In our study, we were unable to find a correlation between high-risk cytogenetics and high-risk PET/CT features, probably due to the fact that only 60% of the patients had a FISH study available at baseline.

It has been recently shown that the simultaneous presence of several unfavorable factors, whether laboratory tests or imaging scans, greatly worsens the prognosis of multiple myeloma patients (4, 20).

Pooling a baseline SUV_{max} >4.2 with the presence of ISS stage 3 and failure to achieve CR during or after first-line treatment, we identified a small subset of patients, averaging approximately 10%, who had a very dismal prognosis (median PFS: 14 months; OS: 30% at 5 years). These patients were mostly treated with novel agents, combined or not with ASCT, and might be the ideal candidates for exploring experimental treatment strategies.

With the availability of newer drugs and different therapeutic options in multiple myeloma, interest in the evaluation of the depth of response beyond the level of conventionally defined CR has progressively grown. More sensitive tools, such as multiparametric flow cytometry, polymerase chain reaction, and deep sequencing methods, are able to detect the presence of minimal residual disease (MRD) at the bone marrow level, a finding that worsens the prognosis of both ASCT-eligible and -ineligible patients (21, 22). However, these techniques fail to identify the persistence of FL(s) potentially harboring nonsecretory multiple myeloma cells or sites of active disease outside the medullary cavity of the bone. In addition, the pattern of bone marrow plasma cell infiltration constitutes a potential drawback of these techniques, to which PET/CT scanning and/or total body MRI are complementary investigational tools of MRD evaluation. We have previously shown that one fourth of the patients achieving conventionally defined CR after up-front thalidomide-dexamethasone and subsequent ASCT still had persistence of PET/CT FLs. These patients had a risk of progression which was two times higher in comparison with that observed for PET/CT-negative patients (1). In the present study, 53% of patients who had previously received novel agents combined or not with ASCT obtained a conventionally defined CR, but only approximately two thirds of them were PET/CT negative. In comparison with the 30% of patients who showed the persistence of FDG avidity, the achievement of PET/CT negativity ensured a significantly prolonged PFS, nearly halving the risk

Table 4. Multinomial logistic regression analysis of factors predicting for conventionally defined progressive disease and exclusive PET/CT skeletal progressive disease

	RRR (95% CI)	*P*
No PD (baseline)	Baseline	
Conventionally defined PD		
Score 1 vs. 0	11.53 (3.58–37.17)	<0.001
Score 2 vs. 0	13.02 (3.78–44.87)	<0.001
Score 3 vs. 0	11.58 (2.16–62.10)	0.004
PET SUV >4.2 after first-line treatment	3.18 (0.52–19.33)	0.208
Skeletal progression, without clinical symptoms and laboratory signs of PD		
Score 1 vs. 0	3.81 (0.53–27.18)	0.182
Score 2 vs. 0	1.41 (0.11–18.62)	0.796
Score 3 vs. 0	2.98 (0.17–51.32)	0.453
PET SUV >4.2 after first-line treatment	11.05 (1.13–108.08)	0.039

NOTE: Score based on ISS 3, failure of CR, and PET/CT SUV_{max}.
Abbreviation: PD, progressive disease.

of progression, and an extended OS. PET/CT negativity was confirmed to be an independent predictor of prognosis in a Cox regression analysis and should thus be recommended as a complementary end point to refine the definition of CR.

Differently from posttreatment evaluation of response, the serial use of novel imaging techniques during the follow-up phase is not recommended because of the high costs and the radiation exposure (6, 7). After the end of first-line treatment, 30% of our patients retained positive PET/CT scans, and in 40% of them (10% of the whole population), the glucose metabolism was still high. We previously demonstrated that there is an inverse correlation between a residual SUV_{max} value after ASCT and TTP, whereby all patients with SUV_{max} >4.2 subsequently relapsed (16). In this study, by using a multinomial logistic regression analysis, we found that the persistence of high FDG uptake after first-line treatment was associated with skeletal progression, in the absence of any additional clinical or laboratory sign of progressive disease, in a small subgroup of patients who represented 12% of the overall population of multiple myeloma patients. Based on these data, serial PET/CT evaluation (i.e., every 12 months) can be recommended in this subset of patients during the follow-up phase. Further studies are needed to evaluate the prognostic impact of treating PET/CT-documented residual disease in patients with conventional CR after first-line therapy.

Conclusion

In conclusion, we confirm the prognostic value of FLs, SUV_{max}, and EMD, as detected by FDG PET/CT, in newly diagnosed multiple myeloma patients who are candidates to receive an ASCT, consistently with two previously reported studies. Importantly, we found that the same variables were prognosticators of outcome also for elderly, non–ASCT-eligible, patients, a finding herein reported for the first time.

In a multivariate analysis, a baseline SUV_{max} value >4.2 was identified as one of the leading variables adversely affecting PFS and OS, along with ISS stage 3 and failure to achieve CR upon first-line treatment. The presence of all these factors identified a small subgroup of patients (10%) with very poor prognosis who may possible require alternative treatment strategies.

Importantly, in both younger and elderly multiple myeloma patients in CR after treatment, PET/CT negativity predicted for a significantly longer PFS and OS in comparison with the same group of patients who remained PET positive, thus contributing to a more accurate evaluation of CR beyond the conventionally defined level outside the bone marrow.

PET/CT may usefully be employed during the follow-up phase to monitor the small subgroup of patients with persistent high glucose metabolism after first-line treatment (12%) in order to detect otherwise unidentifiable skeletal progression.

On the basis of our results, integrating PET/CT scanning into the algorithm of multiple myeloma staging and follow-up after treatment may improve disease management.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: E. Zamagni, K. Mancuso, M. Cavo
Development of methodology: K. Mancuso, A. Pezzi
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E. Zamagni, C. Nanni, K. Mancuso, B. Zannetti, A. Brioli, S. Rocchi
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E. Zamagni, K. Mancuso, A. Pezzi, G. Marzocchi, M. Cavo
Writing, review, and/or revision of the manuscript: E. Zamagni, P. Tacchetti, A. Pezzi, L. Pantani, A. Brioli, I. Rizzello, S. Fanti, M. Cavo
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Mancuso, A. Pezzi, B. Zannetti, I. Rambaldi
Study supervision: S. Fanti, M. Cavo
Other (performed the research and helped in collecting data): C. Terragna, E. Borsi
Other (material support): M. Martello

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