Standardization of 18F-FDG-PET/CT According to Deauville Criteria for Metabolic Complete Response Definition in Newly Diagnosed Multiple Myeloma

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Abstract

Purpose

18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is currently the standard technique to define minimal residual disease (MRD) status outside the bone marrow (BM) in patients with multiple myeloma (MM). This study aimed to define criteria for PET complete metabolic response after therapy, jointly analyzing a subgroup of newly diagnosed transplantation-eligible patients with MM enrolled in two independent European randomized phase III trials (IFM/DFCI2009 and EMN02/HO95).

Patients and Methods

Two hundred twenty-eight patients were observed for a median of 62.9 months. By study design, PET/CT scans were performed at baseline and before starting maintenance (premaintenance [PM]). The five-point Deauville scale (DS) was applied to describe BM (BM score [BMS]) and focal lesion (FL; FL score [FS]) uptake and tested a posteriori in uni- and multivariable analyses for their impact on clinical outcomes.

Results

At baseline, 78% of patients had FLs (11% extramedullary), 80% with an FS ≥ 4. All patients had BM diffuse uptake (35.5% with BMS ≥ 4). At PM, 31% of patients had visually detectable FLs (2% extramedullary), 24% and 67.7% of them with an FS of 3 and ≥ 4, respectively. At PM, 98% of patients retained residual BM diffuse uptake, which was significantly lower than at baseline (mainly between BMS 2 and 3, BMS was ≥ 4 in only 8.7% of patients). By both uni- and multivariable analysis, FS and BMS < 4 were associated with prolonged progression-free survival (PFS) and overall survival (OS) at PM (OS: hazard ratio [HR], 0.6 and 0.47, respectively; PFS: HR, 0.36 and 0.24, respectively)

Conclusion

FL and BM FDG uptake lower than the liver background after therapy was an independent predictor for improved PFS and OS and can be proposed as the standardized criterion of PET complete metabolic response, confirming the value of the DS for patients with MM.

Introduction

18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) integrated with computed tomography (CT) accurately and sensitively detects myeloma bone or extramedullary disease (EMD) lesions, assessing tumor metabolic activity and monitoring response to treatment, by distinguishing active and inactive (eg, fibrotic) disease.1-3 Several studies have linked PET-positive lesions after therapy with poor prognosis,4-7 even upon complete remission.8,9

Context

Key Objectives

18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is currently the preferred imaging technique for evaluating response to therapy. However, there is yet no standardization on image criteria and cutoffs for positivity or negativity. This joint analysis on two prospective imaging substudies of 228 patients with newly diagnosed multiple myeloma (MM) is the first attempt to define PET complete metabolic response (CMR) after therapy and to apply the Deauville scale (DS) to patients with MM without predefined cutoffs.

Knowledge Generated

On the basis of our results, the reduction of focal lesion and bone marrow uptake lower than the liver uptake (DS score of < 4) after therapy can be proposed as the standardized definition of PET CMR after therapy, confirming the value of DS in MM.

Relevance

In this analysis, we identified standardized criteria to define PET CMR after therapy and redefined International Myeloma Working Group PET response criteria in order to achieve an overall harmonization among different clinical trials and worldwide routine use of FDG-PET/CT in clinical practice.

Recent sensitive techniques (cellular, molecular, and imaging based) and highly effective novel agents have changed the definition of response, introducing concepts such as depth of response and minimal residual disease (MRD).10 As a result of bone marrow (BM) plasma cell patchy infiltration, possible EMD escape, and multiple myeloma (MM) spatial heterogeneity,9,11,12 evaluation of both the extramedullary compartment and BM is required to ensure tumor complete eradication.

FDG-PET/CT is currently the preferred imaging technique for evaluating response to therapy.2 The prognostic value of PET/CT has proved complementary to MRD evaluation within the BM by flow cytometry.6,9 As with BM techniques, imaging criteria standardization and cutoffs for positivity and negativity are crucial to ensure data reproducibility and harmonization among clinical trials.

The current study aims to prospectively define FDG-PET/CT complete metabolic response (CMR) after therapy in a joint analysis of a subgroup of transplantation-eligible patients with newly diagnosed MM (NDMM) enrolled in two independent European randomized phase III trials (IFM/DFCI2009 and EMN02/HO95; ClinicalTrials.gov identifiers: NCT01309334 and NCT01134484, respectively).13,14

Patients and Methods

Patients and Treatment Protocols

Two hundred twenty-eight transplant-eligible patients with NDMM enrolled in the imaging substudies of IFM/DFCI2009 and EMN02/HO95 were analyzed. IFM/DFCI2009 prospectively evaluated the combination of eight cycles of lenalidomide, bortezomib, and dexamethasone (RVD) versus RVD plus autologous stem-cell transplantation (ASCT), followed by lenalidomide maintenance.13 EMN02/HO95 prospectively compared single versus double ASCT versus proteasome inhibitor–based intensification therapy after three to four cycles of bortezomib-based induction therapy and consolidation therapy versus no consolidation, followed by lenalidomide maintenance.14

Both IFM/DFCI2009 and EMN02/HO95 were approved by local ethics committees. All patients provided informed consent.

Imaging Substudy Characteristics

Eighteen and eight centers participated in the ancillary imaging substudies of IFM/DFCI2009 and EMN02/HO95, respectively. The Imaging Young Myeloma (IMAJEM) substudy (ClinicalTrials.gov

identifier: NCT01309334) compared axial magnetic resonance imaging (MRI) and FDG-PET/CT at diagnosis, after three cycles of induction therapy, and before maintenance, with a primary end point of baseline bone lesion detection rate and a secondary end point of prognostic impact of the imaging techniques on progression-free survival (PFS) and overall survival (OS) after three cycles and before maintenance.6 PET/CT images were acquired according to local protocols and, after anonymization, centrally and blindly reviewed on a dedicated workstation (Imagys, Keosys, France) by two expert nuclear medicine physicians. Whole-body PET/CT (top of head to feet, arms alongside body) was performed using standard procedures6 at baseline, within 3 and 4 weeks upon induction treatment, and 3 and 4 weeks after ending therapy or ASCT (see Data Supplement for further details, online only).

The EMN02/HO95 imaging substudy aimed prospectively to evaluate FDG-PET/CT at diagnosis, after four cycles of induction therapy, and before maintenance. The two primary end points were to assess the prognostic significance of PET/CT at diagnosis and after therapy and to standardize PET/CT evaluation by centralized imaging revision and definition of interpretation criteria.15 Whole-body PET/CT (including skull, upper limbs, and femurs) was locally performed using standard procedures2 at baseline, at least 10 days after induction treatment, and 3 months after last ASCT or intensification or consolidation therapy15 (see Data Supplement for further details). Each PET scan was reinterpreted a posteriori by blinded independent central review, managed by WIDEN (DiXit, Turin, Italy) and conducted by a panel of five expert nuclear medicine physicians.

Joint Analysis and DS Application

The primary objective was to standardize PET/CT evaluation and to define criteria for PET CMR after therapy (PET MRD definition) by testing the prognostic impact of such criteria on PFS. To this end, only baseline and premaintenance (PM) scans were considered. The secondary objective was to confirm the prognostic impact of PET parameters on OS, as previously shown.6,15

All PET/CT scans were acquired according to the European Association of Nuclear Medicine PET procedures guidelines for FDG studies16 and reported following the Italian Myeloma Criteria for PET Use (IMPeTUs; elaborated within the EMN02/HOVON95 trial).17 In particular, BM metabolic state, focal lesions (FLs; number and metabolic state), and EMD (site, number, and metabolic state) were checked and reported. FDG uptake degree was visually quantified in the target lesion according to the 5-point Deauville scale (DS) adopted for PET scans in lymphomas (FL score [FS]) and in the BM out of FLs (BM score [BMS]).18,19 Furthermore, semiquantitative measures were obtained in physiologic areas corresponding to reference organs, liver, and mediastinal blood pool (MBP) using a spherical volume of interest (VOI) with radius > 3 cm in the central portion of the liver, far away from its edge, and a VOI within the aorta lumen, carefully avoiding the vessel wall or calcification areas for MBP. Semiquantitative parameters, such as liver and MBP mean and maximum standardized uptake value (SUVmax) and BM SUVmax of the hottest lesion per macro area, were annotated and used to reinforce visual analysis interpretation, especially in borderline cases. Median BM SUVmax was defined in the lumbar vertebrae L3 to L5 (excluding FLs in this region). PET positivity was considered for any uptake in FLs, BM, or EMD > DS1 (DS1=no uptake), either at baseline or PM. The impact of each parameter on PFS and OS was evaluated by univariable and multivariable (MV) analyses.

Statistical Analysis

Basic characteristics and PET parameter data sets from the imaging substudies of both trials were merged together. A thorough data quality assessment before statistical analysis ensured data integrity and data set consistency. Data set homogeneity, especially for inference variables, was checked either by Fisher's exact test, to compare frequency distributions, or by the Mann-Whitney U test and t tests for nonnormal or normal continuous distributions, respectively. Regarding potential selection bias, no arbitrary criteria were applied, but consecutive patients enrolled in the participating centers

guaranteeing compliance with PET protocol were included. Analyses were adjusted for possible differences in outcome between the studies.

Descriptive statistics, including mean, median, minimum, maximum, and interquartile range (IQR), were provided for continuous variables to describe distributions with position indexes. The graphical method was adopted to evaluate normal distribution, whereas only medians and IQRs were reported for nonnormal distributed variables. Absolute and relative frequencies were provided for categorical variables. In both trials, PET scans were scheduled at least at baseline and PM. Results were then tabulated and stratified according to those time points.

PFS and OS time-to-event end points were estimated using the Kaplan-Meier method, first from the date of starting induction therapy, according to each trial design, and then by the landmark approach from the PM time frame. Survival univariable and MV semiparametric Cox regression models were adopted to estimate hazard ratios (HRs) and to identify independent predictors of prolonged PFS or OS outcomes. To minimize any difference between the studies, Cox regression models were stratified by trial. According to the MV step forward approach, only patient characteristics and DS scores with $P \leq .1$ at univariable analysis were tested to fit the MV model, and only those covariates confirming $P < .05$ were included in the final model. The following variables were tested first in the univariable model and subsequently in the MV analysis: age; sex; serum hemoglobin, albumin, calcium, platelet, lactate dehydrogenase, and β2-microglobulin levels; International Staging System (ISS) or Revised-ISS stage; presence of baseline cytogenetic abnormalities; and presence of FL, EMD, or BM uptake and DS score, both at baseline and PM. During MV analysis, the goodness of fit was evaluated, considering the number of observations and events per variable, the concordance and R2 measurements, and the Akaike information criterion (AIC) parameters. Multiple testing adjustment was considered, but given the limited number of dependent comparisons and the explorative nature of this study, type II error control was privileged.

Response to treatment and disease progression were assessed according to the international uniform response criteria in both trials.20 The maximally selected rank statistics method21 was adopted to find the best prognostic cutoff value applied to PET/CT characteristics and DS score ordinal data. Considering literature knowledge and clinical judgment, those values were then revised to define the best clinically relevant cutoff value applicable to an independent patient population.22

Analyses were conducted using R language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria). $P = .05$ was the cutoff for two-sided P value statistical significance. All CIs were reported as 95% CIs.

Results

Patient Characteristics

Two hundred twenty-eight patients (134 from the IFM/DFCI2009 trial and 94 from the EMN02/HO95 trial) were included in this analysis. Main patient characteristics at study entry are listed in Table 1; patients were representative of the whole series (data not shown). Median age was 59 years (IQR, 53-62 years); 15.8% and 11.5% of patients had ISS and Revised-ISS stage III disease, respectively. Fluorescence in situ hybridization–detected high-risk cytogenetics [t(4;14), del(17p), and/or t(14;16)] on CD138+ BM plasma cells were present in 14% of patients. According to trial design, 57% of patients were randomly assigned to the transplantation arm and 43% to the bortezomib intensification arm (54% in IFM/DFCI2009 v 24% in EMN02/HO95). The best PM response rates were similar in the two trials (complete response, 36.7%; very good partial response, 82.5%).

Imaging Characteristics at Baseline and PM

At baseline, 78% of patients had visually detectable FLs, with a median SUVmax of 5 (IQR, 3.6-7.5). FS was 2 in 2.3%, 3 in 15.7%, 4 in 48.3%, and 5 in 33.7% of patients. Diffuse uptake in the BM was scored as 2 (10.1%), 3 (54.4%), 4 (28.1%), or 5 (7.4%). Median BM SUVmax was 3.11 (IQR, 2.45-4.25). Both median FL and BM SUVmax values were slightly higher in IFM/DFCI2009 than in EMN02/HO95 (5.7 v 4.2 [P < .001] and 3.7 v 2.68 [P < .001], respectively), whereas reference MBP and liver mean SUVs (Table 2) and distribution of FS, BMS, and EMD (11% of patients) were similar between studies.

At PM, 31% of patients had visually detectable FLs, with a median SUVmax of 3.67 (IQR, 2.71-5.02). EMD persisted in 2% of patients. The uptake in residual FLs was scored as 2 (8.1%), 3 (24.2%), 4 (58%), or 5 (9.7%). Ninety-eight percent of patients showed a residual diffuse uptake in BM that was significantly decreased from baseline (BMS of 2 in 52.8%, BMS of 3 in 38.5%, BMS of 4 in 8.2%, and BMS of 5 in 0.5% of patients); in 85% of patients, the BMS decreased from ≥ 4 at baseline to < 4 at PM. Median BM SUVmax was 2.3 (IQR, 1.80-3.08; Table 2). None of the patients with an FS of 2-3 had a BMS > 4. Again, both median FL and BM SUVmax values were slightly higher in IFM/DFCI2009 than in EMN02/HO95 (5.37 v 3.07 [P < .001] and 2.60 v 1.85 [P < .001], respectively). Finally, significantly more patients in the EMN02/HO95 trial had an FS of 3 (36.9% v 4.2% in IFM/DFCI2009, P < .001), whereas BMS of 2 and 3 were equally distributed between the trials (Table 2). Globally, after therapy, 53.5% and 71.2% of patients obtained an FS and BMS < 3, respectively, and 79% and 91.4% of patients obtained an FS and BMS < 4, respectively. Approximately 20% of patients with a BMS and/or FS < 4 at baseline showed an increase in the same scores to ≥ 4 at PM.

PM PET/CT Prognostic Relevance and Cutoff Definition

To verify the prognostic relevance in terms of PFS and OS of each DS score and define a posteriori the best clinically relevant positivity and negativity cutoffs, we performed univariable analyses of all the different scores for both FLs and BM at landmark time PM (Data Supplement). Both FS and BMS < 4 were strong predictors for prolonged PFS (FS < 4 v ≥ 4: median PFS, 40 v 26.6 months, respectively; HR, 0.6; 95% CI, 0.38 to 0.95; P = .0307; BMS < 4 vs ≥ 4: median PFS, 44.9 v 26.6 months, respectively; HR, 0.48; 95% CI, 0.25 to 0.92; P = .028) and OS (FS < 4 v ≥ 4: OS estimate at 60 months, 77.7% v 64.1%, respectively; HR, 0.48; 95% CI, 0.25 to 0.92; P = .0276; BMS < 4 v ≥ 4: OS estimate at 60 months, 76.7% v 52.1%, respectively; HR, 0.29; 95% CI, 0.13 to 0.65; P = .0029; Table 3). DS score ≤ 3 was associated with prolonged PFS and OS in FLs but not in the BM (Table 3), likely because of the reactive changes in BM often linked to treatment. DS score of 4 was associated with PFS and OS for FLs and BM. We considered DS score of 4 to represent the optimal cutoff for a PET CMR after treatment (Fig 1). FS < 4 retained prognostic relevance only for PFS in the subgroup of patients not receiving a transplantation (Appendix Fig A1, online only).

Table 3. Univariable Analysis of Premaintenance PET/CT Parameters Predicting for Prolonged Progression-Free Survival and Overall Survival

In a Cox MV analysis, FS and BMS < 4 were independent predictors of prolonged PFS (FS: HR, 0.60; 95% CI, 0.37 to 0.95; P = .030; BMS: HR, 0.50; 95% CI, 0.26 to 0.97; P = .041) and OS (FS: HR, 0.36; 95% CI, 0.17 to 0.74; P = .005; BMS: HR, 0.24; 95% CI, 0.09 to 0.63; P = .004; Table 4). By both

univariable and MV analysis, FS < 4 was representative of outcomes in both subpopulations deriving from the IFM/DFCI2009 (data not shown) and the EMN02/HO95 trials (Table 5 and 6).

Discussion

In this joint analysis of two prospective imaging substudies on 228 transplantation-eligible patients with NDMM studied at baseline and after treatment with FDG-PET/CT, we identified standardized criteria to define PET CMR after therapy. The International Myeloma Working Group (IMWG) recently introduced an MRD subcategory to their response criteria10,23 based on BM molecular or cellular techniques and also on imaging, as a result of the well-known patchy infiltration of BM plasma cells and the presence of spatial heterogeneity, with possible coexistence of different disease clones in the BM and in FLs.4,6,7,9,11,12,24-27 To ensure complete tumor eradication, the extramedullary compartment, in addition to the BM, must be assessed.

To evaluate response to therapy, functional rather than morphologic imaging techniques are preferred.2,3 Several studies have demonstrated a prognostic role for 18F-FDG-PET–positive lesions after therapy.4-9,28 The complementarity between imaging (either FDG-PET/CT or whole-body [WB] diffusion-weighted imaging [DWI] MRI) and BM techniques in defining the prognosis of patients was demonstrated using flow cytometry (10−46 and 10−59 sensitivity). As with BM techniques, standardization of imaging criteria and the definition of cutoff values for positivity and negativity is highly important for data reproducibility and harmonization among clinical trials, allowing routine use in clinical practice.

To the best of our knowledge, although PET/CT scans were performed at different centers, none used advanced reconstruction algorithms, which were not yet available, so this is the first attempt to define PET CMR after therapy and to apply the DS to patients with MM by jointly analyzing two prospective clinical trials without predefined cutoff values and investigating the impact of each parameter on outcomes. We previously demonstrated the applicability of DS criteria to MM in an initial cohort of 86 patients (IMPeTUs), proving the reproducibility of the scores, especially DS score of 4, and the agreement among reviewers.16 Here, we confirm that FDG-PET/CT is a reliable predictor of outcomes in patients with NDMM, particularly those receiving ASCT. Reduction of FDG uptake after therapy, in both FLs and BM, was an independent predictor of durable disease control and prolonged OS. Applying the DS score to both FLs and BM, we found that nearly all patients (98.5%) showed some FDG uptake in the BM, with a low DS score (2 or 3) not being associated with survival outcomes, probably indicating BM reconstitution after therapy. Conversely, only 31% of patients showed a residual uptake after therapy in FLs, mainly distributed among DS scores of 3 and 4. In both BM and FLs, a DS score of 4 (with liver as reference) provided the strongest prediction for PFS and OS. Overall, 79% and 91% of patients achieved a CMR in FLs and the BM, respectively. On the basis of these results, we believe that reduction of FL and BM uptake lower than the liver (DS score < 4) can be proposed as the standardized definition of PET CMR after therapy within new PET response criteria (Table 7). These criteria could be used to refine the definition of PET CMR and PET response criteria proposed by the IMWG. To date, few indications to interpret FDG-PET/CT after therapy have been proposed or validated.29,30 Total lesion glycolysis, metabolic tumor volume, and textural features are other methods proposed to assess the amount of active disease and its changes after therapy.30 Again, quantitative dynamic PET has been proposed to define metabolic response to therapy.31 However, there is yet no consensus about the suitable delineation approach for deriving volume-based measurement in clinical practice, and much work is needed in setting up clinical trials.

Regardless of interpretation, it should be acknowledged that both false-positive and false-negative results (related to hyperglycemia, recent corticosteroid administration, lack of the hexokinase enzyme32,33) may occur with FDG-PET/CT. In such patients, FDG-PET/CT is not appropriate to evaluate metabolic response to therapy. Other PET/CT tracers, targeting different metabolic pathways or receptors expressed by PCs, have been preliminarily investigated in a few patients with MM or in mouse models.34 However, limited availability of these newer tracers, interpatient tumor heterogeneity, and lack of prognostic data and standard reporting prevent definite conclusions. Alternatively, DWI-MRI, a sensitive tool for direct imaging of the BM,35 may be used. Initial experience on patients with MM in different disease phases showed WB-DWI-MRI to be highly sensitive, both early on and after treatment36,37; however, specificity issues are still an issue. Recently, an expert panel of radiologists, medical physicists, and hematologists provided guidelines for DWI-MRI to promote standardization among different sites.38 To date, we lack homogeneous and prospective data on the comparison between DWI-MRI and FDG-PET/CT in evaluating response to therapy.

In conclusion, our results confirm that FDG-PET/CT is a reliable predictor of long-term outcomes after therapy in transplantation-eligible patients with NDMM. The DS has been shown to be applicable and representative for the outcomes of patient with MM. On the basis of our results, we propose the liver background as a reference to identify PET CMR after therapy. If validated in independent prospective series of patients, these criteria could refine the definition of PET CMR and PET response criteria proposed by the IMWG in imaging MRD response criteria.10 Upcoming prospective clinical trials, extensively applying MRD techniques at the BM level and imaging, will help to establish concordance between CMR and BM MRD and confirm their complementarity.

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TABLE 1. Patient Characteristics at Baseline and Response Status

Characteristic	Overall	France (IFM/DFCI2009)	Italy (EMN02/H095)	*P*
Total No. of patients	228	134	94	
Median age, years (IQR)	59 (53-62)	59 (53-62)	58 (53-62)	.573
Random assignment				< .001
Bortezomib intensification	93 (42.5)	72 (54.1)	21 (24.4)	
ASCT	126 (57.5)	61 (45.9)	65 (75.6)	
ISS stage				.424
I	103 (45.2)	57 (42.5)	46 (48.9)	
II	89 (39.0)	57 (42.5)	32 (34.0)	
III	36 (15.8)	20 (14.9)	16 (17.0)	
R-ISS stage				.135
I	58 (29.0)	27 (23.5)	31 (36,5)	
II	119 (59.5)	74 (64.3)	45 (52.9)	
III	23 (11,5)	14 (12,2)	9 (10.6)	
Median LDH, U/L (IQR)	31.00 (166-337)	211.80 (159-327)	263.50 (179-365)	.093
LDH > upper limit	39 (17.6)	25 (19.1)	14 (15.6)	.591
High-risk cytogenetics FISH[a]	6 (14.0)	11 (10.7)	15 (18.1)	.202
Median B_2M, mg/L (IQR)	3.20 (2.40-4.45)	3.25 (2.61-4.48)	3.10 (2.21-4.38)	.405
$B_2M \geq 3.5$ mg/L	91 (41.4)	52 (41.3)	39 (41.5)	1.000
$B_2M \geq 5.5$ mg/L	35 (15.4)	19 (14.3)	16 (17.0)	.581
Median albumin, g/dL (IQR)	3.86 (3.45-4.26)	3.77 (3.39-4.23)	3.95 (3.50-4.40)	.034
Albumin < 3.5 g/dL	63 (27.6)	42 (31.3)	21 (22.3)	.176
Median platelets, $\times 10^9$/L (IQR)	232.00 (189.5-282.5)	233.00 (194.0-279.0)	225.50 (176.3-282.8)	.400
Platelets $\leq 150 \times 10^9$/L	25 (11.0)	15 (11.3)	10 (10.6)	1.000
Best response ≥ VGPR	146 (82.5)	78 (80.4)	68 (85.0)	.552
Best response ≥ CR	65 (36.7)	34 (35.1)	31 (38.8)	.641

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: B_2M, β_2-microglobulin; IQR, interquartile range; ASCT, autologous stem-cell transplantation; CR, complete response; FISH, fluorescence in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; R-ISS, Revised International Staging System; VGPR, very good partial response.

[a]Defined by one or more of the following abnormalities: del(17p), t(4;14), and/or t(14;16).

Table 1. Patient Characteristics at Baseline and Response Status

TABLE 2. PET/CT Results at Baseline and Premaintenance

Measure	Overall	France (IFM/DFCI2009)	Italy (EMN02/H095)	*P*
Baseline				
No. of patients	228	134	94	
Presence of FLs[a]	178 (78.1)	99 (73.9)	79 (84.0)	.096
Presence of EMD	25 (11.0)	13 (9.7)	12 (12.8)	.521
Median BM SUV_{max} (IQR)	3.11 (2.45-4.25)	3.70 (2.90-4.97)	2.68 (2.19-3.42)	< .001
Median FL SUV_{max} (IQR)	5.00 (3.60-7.50)	5.70 (4.45-8.45)	4.23 (2.87-6.29)	< .001
Median liver SUV_{max} (IQR)	3.24 (2.79-3.90)	3.28 (2.80-3.90)	3.21 (2.69-3.90)	.335
Median mediastinum mean SUV (IQR)	1.56 (1.33-1.80)	1.54 (1.37-1.72)	1.58 (1.27-1.86)	.677
Presence of FL uptake, DS score[a]	178 (78.1)	99 (73.9)	79 (84.0)	.075
2	4 (2.3)	0 (0.0)	4 (5.0)	.043
3	28 (15.7)	18 (18.2)	10 (12.7)	.304
4	86 (48.3)	45 (45.5)	41 (51.9)	.659
5	60 (33.7)	36 (36.3)	24 (30.4)	.274
Presence of BM uptake, DS score[a]	228	134	94	.024
2	23 (10.1)	8 (6.0)	15 (16.0)	.591
3	124 (54.4)	75 (56.0)	49 (52.1)	.655
4	64 (28.1)	36 (26.8)	28 (29.8)	.010
5	17 (7.4)	15 (11.2)	2 (2.1)	—
Premaintenance				
No. of patients	199	119	80	
Presence of FL uptake, DS score[a]	62 (31.2)	24 (20.2)	38 (47.5)	< .001
2	5 (8.1)	0 (0.0)	5 (13.2)	.010
3	15 (24.2)	1 (4.2)	14 (36.9)	< .001
4	36 (58.0)	20 (83.3)	16 (42.1)	.578
5	6 (9.7)	3 (12.5)	3 (7.9)	.686
Presence of BM uptake, DS score[a]	195 (98.5)	118 (100)	77 (96.3)	.064
2	103 (52.8)	63 (53.5)	40 (51.9)	.666
3	75 (38.5)	43 (36.4)	32 (41.6)	.344
4	16 (8.2)	11 (9.3)	5 (6.5)	.597
5	1 (0.5)	1 (0.8)	0 (0.0)	—
Median BM SUV_{max} (IQR)	2.30 (1.80-3.08)	2.60 (2.10-3.40)	1.85 (1.54-2.51)	< .001
Median FL SUV_{max} (IQR)	3.67 (2.71-5.02)	5.37 (4.20-6.93)	3.07 (2.30-3.85)	< .001

NOTE. Data presented as No (%) unless otherwise indicated.

Abbreviations: BM, bone marrow; CT, computed tomography; DS, Deauville scale; EMD, extramedullary disease; FL, focal lesion; IQR, interquartile range; PET, positron emission tomography; SUV_{max}, maximum standardized uptake value.

[a]Only a Deauville scale score > 1 was considered as positive for presence of FLs and/or BM uptake.

Table 2. PET/CT Results at Baseline and Premaintenance

TABLE 3. Univariable Analysis of Premaintenance PET/CT Parameters Predicting for Prolonged Progression-Free Survival and Overall Survival

Survival	HR	95% CI	*P*
Progression-free survival			
BMS < 3	1.09	0.74 to 1.62	.6625
BMS < 4	0.48	0.25 to 0.92	.0277
FS < 3	0.62	0.40 to 0.96	.0307
FS < 4	0.60	0.38 to 0.95	.0302
Overall survival			
BMS < 3	0.93	0.51 to 1.73	.8270
BMS < 4	0.29	0.13 to 0.65	.0029
FS < 3	0.47	0.25 to 0.89	.0199
FS < 4	0.48	0.25 to 0.92	.0276

Abbreviations: BMS, bone marrow score; CT, computed tomography; FS, focal score; HR, hazard ratio; PET, positron emission tomography.

Table 3. Univariable Analysis of Premaintenance PET/CT Parameters Predicting for Prolonged Progression-Free Survival and Overall Survival

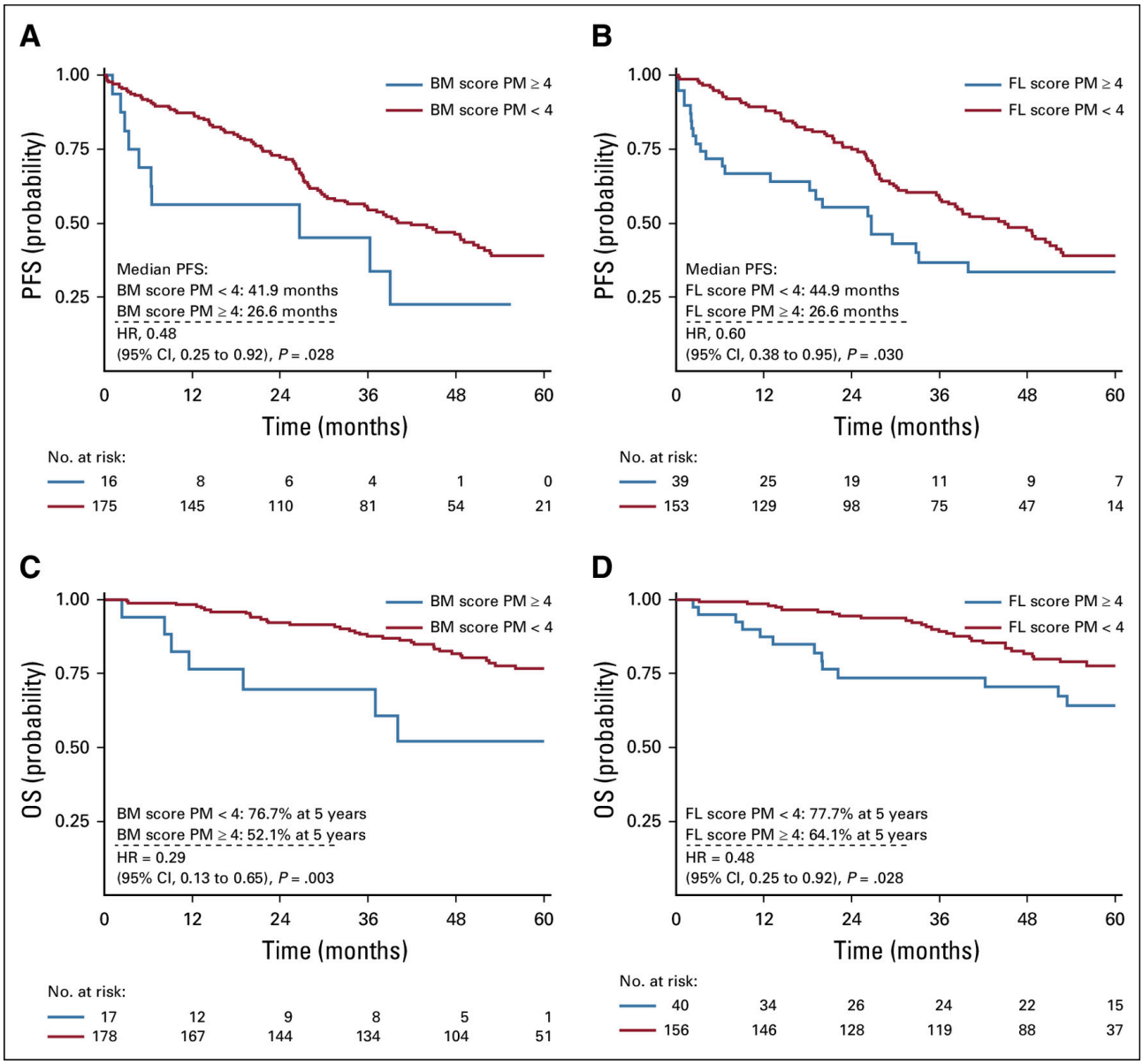

Fig 1. Progression-free survival (PFS) according to premaintenance (PM) positron emission tomography (PET)/computed tomography (CT) (A) bone marrow (BM) and (B) focal lesion (FL) scores. Overall survival (OS) according to PM PET/CT (C) BM and (D) FL scores. HR, hazard ratio.

TABLE 4. Multivariable Cox Regression Analysis of Premaintenance PET/CT Parameters and Baseline Variables Predicting for Prolonged Progression-Free and Overall Survival

Survival	HR	95% CI	*P*
Progression-free survival			
BMS < 4	0.50	0.26 to 0.97	.041
FS < 4	0.60	0.37 to 0.95	.030
Overall survival			
BMS < 4	0.25	0.10 to 0.66	.005
FS < 4	0.34	0.16 to 0.70	.004
Platelets ≥ 150,000/μL	0.33	0.14 to 0.78	.012

Abbreviations: BMS, bone marrow score; CT, computed tomography; DS, Deauville scale; FL, focal lesion; FS, focal score; HR, hazard ratio; PET, positron emission tomography.

Table 4. Multivariable Cox Regression Analysis of Premaintenance PET/CT Parameters and Baseline Variables Predicting for Prolonged Progression-Free and Overall Survival

TABLE 5. Univariable Analysis in the EMN02/HO95 Subgroup Population: Premaintenance PET/CT Parameters

Survival	HR	95% CI	*P*
Progression-free survival			
BMS < 4	0.73	0.17 to 3.09	.67
FS < 3	0.47	0.23 to 0.97	.041
FS < 4	0.51	0.23 to 1.11	.091
DS FL $SUV_{max} \leq 3.0$	0.36	0.14 to 0.92	.033
Overall survival			
BMS < 4	0.33	0.07 to 1.47	.15
FS < 3	0.26	0.10 to 0.72	.009
FS < 4	0.28	0.11 to 0.74	.010
DS FL $SUV_{max} \leq 3.0$	0.42	0.13 to 1.30	.13

Abbreviations: BMS, bone marrow score; CT, computed tomography; DS, Deauville scale; FL, focal lesion; FS, focal score; HR, hazard ratio; PET, positron emission tomography; SUV_{max}, maximum standardized uptake value.

Table 5. Univariable Analysis in the EMN02/HO95 Subgroup Population: Premaintenance PET/CT Parameters

TABLE 6. Multivariable Cox Regression Analysis in the EMN02/HO95 Subgroup Population of Premaintenance PET/CT Parameters and Baseline Variables Predicting for Prolonged Progression-Free and Overall Survival

Survival	HR	95% CI	*P*
Progression-free survival (model 1: n = 71; n = 28 events)			
FS < 4	0.46	0.21 to0.98	.044
LDH ≤ upper limit	0.38	0.16 to0.90	.028
Overall survival (model 2: n = 72; n = 17 events)			
FS < 4	0.21	0.073 to 0.59	.003
Absence of del(17p)	0.19	0.039 to 0.94	.041
Platelet count ≥ 150,000/μL	0.25	0.079 to 0.76	.015

Abbreviations: CT, computed tomography; FS, focal score; HR, hazard ratio; LDH, lactate dehydrogenase; PET, positron emission tomography.

Table 6. Multivariable Cox Regression Analysis in the EMN02/HO95 Subgroup Population of Premaintenance PET/CT Parameters and Baseline Variables Predicting for Prolonged Progression-Free and Overall Survival

TABLE 7. Proposed Refinement of PET Response Criteria After Therapy

PET Response After Therapy	Response Criteria
Complete metabolic response	Uptake ≤ liver activity in BM sites and FLs previously involved (including extramedullary and paramedullary disease [DS score 1-3])
Partial metabolic response	Decrease in number and/or activity of BM/FLs present at baseline, but persistence of lesion(s) with uptake > liver activity (DS score 4 or 5)
Stable metabolic disease	No significant change in BM/FLs compared with baseline
Progressive metabolic disease	New FLs compared with baseline consistent with myeloma

Abbreviations: BM, bone marrow; DS, Deauville scale; FL, focal lesion; PET, positron emission tomography.

Table 7. Proposed Refinement of PET Response Criteria After Therapy

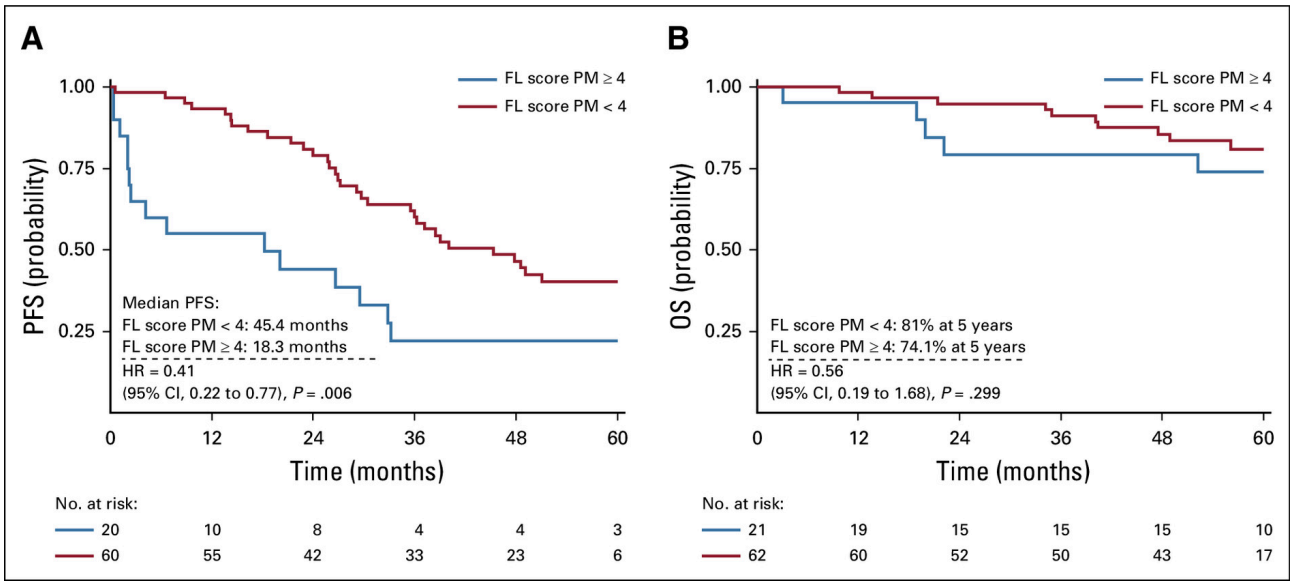

Fig A1. (A) Progression-free survival (PFS) and (B) overall survival (OS) according to premaintenance (PM) positron emission tomography (PET)/computed tomography (CT) focal lesion (FL) scores in the subgroup of patients who did not receive autologous stem-cell transplantation. HR, hazard ratio.