Prognostic value of [^{18}F]FDG-PET/CT in multiple myeloma patients before and after allogeneic hematopoietic cell transplantation

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Abstract

Purpose Despite improved treatment options, multiple myeloma (MM) remains an incurable disease. The aim of this study was to investigate the prognostic value of positron emission tomography/computed tomography (PET/CT) using ^{18}F-2'-deoxy-2'-fluorodeoxyglucose ([^{18}F]FDG) in MM patients shortly before and ~100 days after allogeneic hematopoietic cell transplantation (allo-HCT).

Methods In this retrospective analysis, we evaluated [^{18}F]FDG-PET/CT-scans of 45 heavily pre-treated MM patients before and 27 patients after scheduled allo-HCT. All scans were qualitatively and semi-quantitatively assessed for the presence of active disease. Serological response was recorded according to International Myeloma Working Group (IMWG) criteria. Progression-free (PFS) and overall survival (OS) were correlated with different PET/CT-derived parameters, such as presence, number and maximum standardized uptake value (SUV_{max}) of focal myeloma lesions. The impact of extramedullary disease on patient outcome was also assessed.

Results PET/CT negativity -prior to or following allo-HCT- was a favorable prognostic factor for progression-free and overall survival (both, PFS and OS: pre-HSCT $p < 0.001$, post-HCT $p < 0.005$). High FDG-uptake ($SUV_{max} > 6.5$) revealed a significantly shortened survival compared to patients with a lower SUV_{max} (<6.5) (OS, 5.0 ± 1.1 m vs. not reached - longest 122.0 m; $p < 0.001$). Moreover, our data prove that a higher number (>3) of focal lesions (pre-HCT: both PFS and OS: $p < 0.001$; post-HCT PFS: $p < 0.001$, OS: $p = 0.139$) as well as the presence of extramedullary disease serve as adverse prognostic factors prior to and after allo-HCT. At response assessment after allo-HCT, [^{18}F]FDG-PET/CT had a complementary value in prognostication in addition to IMWG criteria alone.

Conclusion [^{18}F]FDG-PET/CT before and shortly after allogeneic HCT is a powerful predictor for progression-free and overall survival in MM patients.

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Keywords Multiple myeloma · Molecular imaging · FDG-PET/CT · Allogeneic hematopoietic cell transplantation

Introduction

Despite improved treatment options including so-called novel agents like proteasome inhibitors or immunomodulatory drugs and the addition of autologous stem cell transplantation in younger patients, which have resulted in prolonged progression-free and overall survival, multiple myeloma (MM) still remains an incurable disease for the vast majority of patients [1, 2].

Allogeneic hematopoietic cell transplantation (allo-HCT) holds the potential for cure by exploiting immune surveillance of myeloma cells by grafting a new immune system derived from allogeneic stem cells from a HLA-identical sibling or unrelated donor (graft-versus-myeloma effect) [3, 4]. However, it is also associated with markedly high rates of treatment-related morbidity and mortality as high as 30-50% [5]. Since outcome after allo-HCT is best in patients with low or even without any tumor burden at the time of transplant, reliable identification of suitable candidates is of utmost importance.

Different studies have demonstrated the benefit of molecular imaging using positron emission tomography/computed tomography (PET/CT) and the radiolabeled glucose analog ^{18}F-2'-deoxy-2'-fluorodeoxyglucose ([^{18}F]FDG) for diagnosis, staging and estimation of prognosis in MM patients [6–12]. However, most studies have focused mainly on early therapeutic settings prior to HCT [13–16].

In the setting of allo-HCT, characterization of patients with low or -preferably- no active tumor burden by non-invasive whole-body imaging shortly prior to transplantation could substantially aid in identification of patients most likely to benefit. Additionally, PET/CT might play a role in monitoring remission post allo-HCT. The aim of this study was to further elucidate the value of molecular imaging by [^{18}F]FDG-PET/CT before and after allogeneic hematopoietic cell transplantation.

Material and methods

All patients underwent imaging for clinical purposes and gave written informed consent to receive [^{18}F]FDG-PET/CT imaging for the purpose of restaging and assessment of disease activity. Due to the retrospective nature of this study, the local institutional review boards waived the requirement for additional approval.

Patients

Between November 2003 and May 2015, 52 patients (32 males, 20 females, age 36-67 y, mean 53.4 ± 7.0) with a history of multiple myeloma were enrolled. All patients had been heavily pre-treated with a number of various chemotherapies, including novel agents like proteasome inhibitors (e.g., bortezomib), or immunomodulatory drugs (lenalidomide and others). Radiation therapy had been administered to 27/52 patients (51.9%), 48/52 subjects (92.3%) had undergone autologous HCT. Conditioning regimens before allo-HCT differed and included fludarabine, treosulfan and anti-thymocyte globulin (ATG). Detailed patients' characteristics are displayed in Table 1 and Supplementary Table 1.

Forty-five patients underwent [^{18}F]FDG-PET/CT imaging 19 ± 14 days prior to allogeneic HCT. For 27 patients (20 from the pre-transplant cohort), post-transplant scans were available at day 91 ± 50 (range 26-233 days). For the sub-cohort of survivors (n = 15), median follow-up was 62.3 months (range 29-124) and for patients who deceased during follow-up, median time-to-death was 8.1 months (range 1-84).

Serological response was assessed according to the international Uniform Response Criteria for MM [17].

Progression-free (PFS) and overall survival (OS) were correlated to a number of PET-derived (SUV_{max}) as well as clinical parameters (albumin [available in 37/52 patients], lactate dehydrogenase [LDH; all patients], β2 microglobulin [β2M; 35/52], free immunoglobulin light chains [FLC; all patients] and creatinine [all patients]). Furthermore, interphase molecular cytogenetics based on fluorescence in situ hybridization (FISH) was performed. Presence of del(17p), t(4;14), t(14;16), t(14;20) and chromosome 1 abnormalities were considered as high-risk (26/52), all other karyotypes were classified as standard risk (17/52). For 9/52 patients, no FISH results were available.

Imaging

Pet/CT

PET/CT was performed on integrated PET/CT scanners (GE Discovery LS, GE Healthcare, Boston, MA, USA; since 2011 on Siemens Biograph mCT-S(40), Siemens, Knoxville, USA [Ulm]; Siemens Biograph mCT 64, Siemens, [Würzburg]) consisting of a lutetium oxyorthosilicate full-ring PET and a 4-, 40- or 64-slice spiral CT. [^{18}F]FDG (mean, 306 ± 31 MBq) was injected intravenously. After a period of 60 min, transmission data were acquired using contrast-enhanced spiral CT (dose modulation with a quality reference of 210 mAs, 120 kV, a 512 × 512 matrix, 5 mm slice thickness, increment of 30 mm/s, rotation time of 0.5 s, and pitch index of 0.8) including the base of the skull to the proximal thighs.

Table 1 Patients' imaging characteristics

	pre-allo HCT					post-allo HCT					
No.	PET before allo-HCT	PET-positive	IMD-FL	EMD	Serologic response before allo-HCT	PET after allo-HCT	PET-positive	IMD-FL	EMD	Serologic response after allo-HCT	PET response after allo-HCT
1	yes	yes	0	yes	CR	yes	no	0	no	CR	CR
2	yes	yes	>10	yes	SD	yes	yes	>10	yes	PD	PD
3	yes	yes	7	no	PR	yes	yes	5	no	PR	SD
4	no	–	–	–	PR	yes	yes	>10	no	n/a	n/a
5	yes	yes	>10	yes	PR	yes	yes	4	yes	VGPR	PR
6	no	–	–	–	PD	yes	yes	>10	yes	n/a	n/a
7	yes	yes	>10	no	SD	yes	yes	>10	yes	PD	PD
8	yes	yes	0	yes	PD	yes	yes	0	yes	SD	PD
9	yes	no	0	no	PR	yes	no	0	no	VGPR	CR
10	yes	yes	5	no	SD	yes	yes	5	no	VGPR	SD
11	no	–	–	–	PR	yes	yes	5	no	PR	n/a
12	yes	yes	>10	yes	PD	yes	yes	>10	yes	PD	PD
13	yes	yes	>10	yes	CR	yes	yes	>10	yes	PD	PD
14	no	–	–	–	PD	yes	yes	>10	yes	PD	n/a
15	no	–	–	–	VGPR	yes	no	0	no	CR	CR
16	yes	no	0	no	SD	yes	yes	2	no	PR	PR
17	yes	yes	3	no	VGPR	yes	no	0	no	PR	CR
18	yes	yes	>10	no	CR	yes	yes	2	no	PR	PR
19	yes	no	0	no	CR	yes	yes	0	yes	CR	PD
20	yes	yes	1	no	near CR	yes	no	0	no	PR	CR
21	yes	yes	1	no	PD	yes	no	0	no	CR	CR
22	yes	no	0	no	CR	yes	no	0	no	sCR	CR
23	yes	yes	3	yes	PR	yes	yes	3	yes	sCR	PR
24	yes	no	0	no	CR	yes	no	0	no	sCR	CR
25	no	–	–	–	PR	yes	yes	3	no	VGPR	PR
26	no	–	–	–	CR	yes	yes	2	yes	sCR	n/a
27	yes	yes	3	no	n/a	yes	no	0	no	VGPR	CR
28	yes	yes	>10	yes	PD	no	–	–	–	n/a	–
29	yes	yes	>10	yes	PD	no	–	–	–	n/a	–
30	yes	no	0	no	VGPR	no	–	–	–	sCR	–
31	yes	yes	4	no	SD	no	–	–	–	PR	–
32	yes	yes	>10	yes	PR	no	–	–	–	n/a	–
33	yes	no	0	no	PR	no	–	–	–	sCR	–
34	yes	no	0	no	CR	no	–	–	–	CR	–
35	yes	yes	0	yes	PR	no	–	–	–	CR	–
36	yes	yes	0	yes	PR	no	–	–	–	CR	–
37	yes	yes	2	no	VGPR	no	–	–	–	n/a	–
38	yes	no	0	no	PR	no	–	–	–	CR	–
39	yes	yes	2	no	PR	no	–	–	–	n/a	–
40	yes	yes	>10	no	PR	no	–	–	–	VGPR	–
41	yes	no	0	no	PR	no	–	–	–	CR	–
42	yes	no	0	no	PR	no	–	–	–	CR	–
43	yes	no	0	no	PR	no	–	–	–	PR	–
44	yes	yes	>10	no	PR	no	–	–	–	PD	–
45	yes	no	0	no	PR	no	–	–	–	CR	–

Table 1 (continued)

No.	pre-allo HCT					post-allo HCT					
	PET before allo-HCT	PET-positive	IMD-FL	EMD	Serologic response before allo-HCT	PET after allo-HCT	PET-positive	IMD-FL	EMD	Serologic response after allo-HCT	PET response after allo-HCT
46	yes	no	0	no	PR	no	–	–	–	CR	–
47	yes	no	0	no	CR	no	–	–	–	sCR	–
48	yes	no	0	no	CR	no	–	–	–	CR	–
49	yes	yes	1	no	CR	no	–	–	–	CR	–
50	yes	no	0	no	PR	no	–	–	–	sCR	–
51	yes	no	0	no	PR	no	–	–	–	CR	–
52	yes	yes	>10	no	PR	no	–	–	–	VGPR	–

Patients' imaging and serological characteristics before and after an allogeneic hematopoietic cell transplantation (allo-HCT); IMD – intramedullary disease, FL – focal lesions, EMD – extramedullary disease. (s)CR – (stable) complete remission, VGPR – very good partial response, PR – partial response, SD – stable disease, PD progressive disease. N/A: information not available

Consecutively, PET emission data were acquired in 3D-mode with a 200 × 200 matrix with 2 min emission time per bed position. After decay and scatter correction, PET data were reconstructed iteratively with attenuation correction using dedicated standard software (PETsyngo VG51C, Siemens, Erlangen, Germany, [Ulm]; HD. PET, Siemens Esoft, [Würzburg]). Standard criteria to define lesions as PET/CT positive were applied according to Zamagni et al. as previously described [13]. Briefly, presence of areas of focally increased tracer uptake within bones (compared to normal bone marrow [BM]) excluding articular processes, with or without corresponding lesions identified by CT were rated positive for multiple myeloma; alternatively, a maximum standardized uptake value of $SUV_{max} \geq 2.5$ within osteolytic lesions exceeding 1 cm in size or $SUV_{max} > 1.5$ within osteolytic lesions ranging between 0.5 and 1 cm in size were rated positive. Up to ten focal lesions (FL) were recorded. Subjects presenting with more than 10 FL were categorized into the subgroup >10 FL. Presence of extramedullary disease (EMD), defined as [^{18}F]FDG-avid lesions that were not contiguous to bone or arose in soft tissue, was described by lesion location, and the number of lesions was recorded. Paramedullary disease arising from bone was considered as a myeloma lesion but not as EMD. In parallel to medullary disease, SUV_{max} and location of the hottest extramedullary lesion were recorded.

Statistical analysis

Statistical analyses were performed using SPSS Statistics software (version 24.0; IBM Armonk, US). Quantitative values are displayed as mean ± standard deviation or median ± standard error as appropriate. Comparisons of related samples were performed using the Wilcoxon-signed rank test, whereas Chi square- or Fisher exact test was used for comparison of frequencies between independent subgroups. The Kaplan-Meier method in combination with the log-rank test was used for calculation of survival probabilities for independent subgroups. For calculation of specific predictive values of hottest lesions, ROC analysis was used. All statistical calculations were performed two-sided and a p-value <0.05 was considered to prove statistical significance.

Results

Fifty-two multiple myeloma patients with a median age of 52 years (range 36-67 y) were included. Forty-five patients received [^{18}F]FDG-PET/CT directly before and twenty-seven subjects shortly (~100 days) after scheduled allo-HCT. Overall median progression-free survival of the entire cohort was 6.8 ± 19.4 m (range: 0.9-81.7 m). Thirty-six patients died during follow-up from disease progression and one non-myeloma-related death due to pneumonia was recorded. Median overall survival was 18.6 ± 31.5 m (range: 1.6-122.0 m). Detailed characteristics of the patients including serological response and imaging parameters are summarized in Table 1 and Supplementary Table 1.

Imaging characteristics before and after Allo-HCT

Out of 45 patients who underwent [^{18}F]FDG-PET/CT before scheduled allo-HCT (pre-HCT), 27 subjects (60.0%) presented with a positive scan. In detail, exclusively intramedullary disease (IMD) was present in 15/27 subjects (55.6%), and both IMD and EMD in 8/27 patients (29.6%). In the remaining 4/27 (14.8%) subjects only EMD was recorded. Regarding EMD, lymph node and soft tissue involvement was most commonly recorded (6/27, 22.2%, respectively), followed by hepatic (2/27, 7.4%), splenic (1/27, 3.7%) and central nervous system (1/27, 3.7%) manifestations. No lesions were found in

testis. Also, 10/27 (37.0%) had 1-3 FL and 17/27 (63.0%) had more than 3 FL.

After allogeneic HCT (post-HCT), 18 out of 27 available patients (66.7%) were [^{18}F]FDG-PET positive. Four out of 18 subjects (22.2%) had 1-3 FL and 14/18 (77.8%) had more than three FL. IMD was present in 16/18 (88.9%) patients, EMD in 11/18 (61.1%). Nine out of these 18 subjects (50.0%) suffered from both intra- and extramedullary disease.

Regarding EMD, lymph node involvement was most commonly seen (9/18, 50.0%), followed by manifestations of soft tissue (7/18, 38.9%), testis (2/18, 11.1%) and brain (1/18, 5.6%). No lesions were detected in the spleen and the liver. PET negativity before or after allo-HCT turned out to be a positive prognostic factor regarding progression-free and overall survival. Pre-HCT, median PFS was 21.3 ± 8.8 m in PET$^-$ patients as compared to 4.3 ± 0.7 m in PET$^+$ patients ($p < 0.001$) and only one not MM-related (pneumonia) death of the PET$^-$ subjects occurred during follow-up (OS not reached with longest OS 122.0 m; vs. 9.5 ± 3.3 m for PET$^+$ patients; $p < 0.001$; Fig. 1a).

Post-HCT, median PFS (28.7 ± 2.6 m vs. 3.4 ± 0.4 m ($p < 0.001$)) and OS (OS not reached, longest OS 92.5 m vs. 8.7 ± 1.3 m; $p = 0.004$; Fig. 1b), were again significantly longer in a PET$^-$ group than in the PET$^+$ group.

Out of all analyzed patients, 20 (38.5%) underwent [^{18}]FDG-PET/CT before and after allo-HCT. Thereby, 8/20 (40.0%) presented with a negative PET scan after transplantation with 5/8 having had a positive scan pre-HCT.

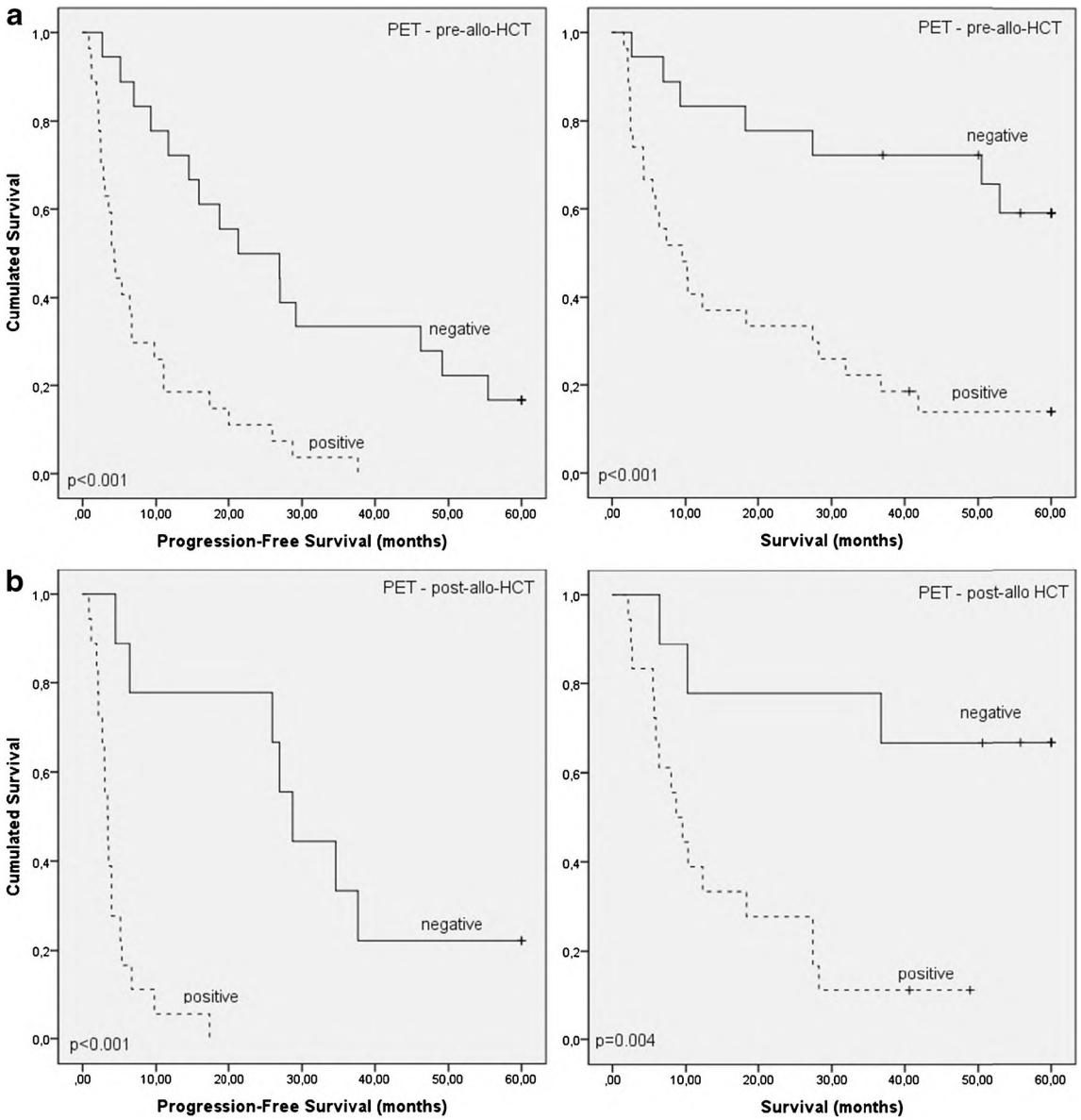


Fig. 1 Prognostic impact of [^{18}F]FDG-PET-positivity on time to progression and overall survival. Kaplan-Meier analysis of patient outcome according to presence of PET+ lesions (A) in PET scan before (A) and after (B) allo-HCT

Noteworthy, these five subjects had only a limited number of intramedullary lesions (1-3) prior to HCT.

In contrast, 12/20 (60.0%) patients were still PET$^+$ after HCT, with 10/12 (83.3%) having had FL pre-HCT and 2/12 - 16.7%) subjects displaying newly-detectable viable disease after allo-HCT. PET negativity inferred both longer PFS (26.9 ± 2.0 m vs.3.5 ± 0.8 m, $p < 0.001$) and OS (10.3 ± 2.4 m vs. not reached with longest OS 92.5 m, $p = 0.012$).

Number, location and activity of myeloma lesions

Imd

Out of the 23/45 (51.1%) patients who presented with intramedullary focal PET$^+$ lesions prior to allo-HCT, 7/23 (30.4%) subjects had 1-3 FL, the remainder >3 FL (15/23, 65.2%). Post-HCT, out of 16/27 (59.3%) patients with intramedullary focal PET$^+$ lesions, 3/16 (18.8%) subjects had 1-3 FL, the remainder (13/16, 81.2%) >3 FL.

The number of lesions proved to be a significant prognostic factor both pre- and post-HCT: In patients with ≤3 lesions. Pre-HCT, PFS was 15.8 ± 4.8 m and median survival was not reached in patients with ≤3 FL, whereas PFS was 3.0 ± 0.8 m and OS 5.9 ± 2.0 m (PFS, $p \leq 0.001$; OS, $p \leq 0.001$) in patients with >3 intramedullary FL (Fig. 2a).

Post-HCT, median PFS was 6.4 ± 12.0 m and median survival was 27.4 ± 9.0 m in patients with ≤3 lesions, whereas PFS was 3.4 ± 0.7 m and OS 8.7 ± 1.8 m (PFS, $p \leq 0.001$; OS, $p = 0.139$) in patients with >3 intramedullary FL (Fig. 2b).

Emd

Of the 12/45 (26.6%) patients with extramedullary disease, 6/12 (50.0%) subjects had 1-3 lesions, the remainder had more than three FL (6/12, 50.0%). Manifestations could be detected in 6/12 patients within soft tissue (50.0%; 4/6 - 66.7% subjects with >3 FL) and in 6/12 (50.0%) patients in lymph nodes (2/6 - 33.3% subjects with >3 FL). In spleen, liver and brain one out of eight patients (12.5%) showed a PET-positive lesion, respectively, whereas no manifestations in testis could be observed.

After allo-HCT, 11/27 (40.7%) patients showed extramedullary PET$^+$ lesions with 3/11 (27.3%) subjects having 1-3 PET$^+$ lesions and the remainder >3 FL (8/11, 72.7%). Lymph node and soft tissue manifestations were most commonly detected with lesions in 9/11 (81.8%; 3/9 - 33.3% patients with >3 FL) and 7/11 (63.6%, 4/7 - 57.1% patients with >3 FL) patients, respectively. Two out of eleven (18.2%) subjects displayed a lesion in the testis; one of eleven (9.1%) had a lesion in the brain, whereas no manifestations could be observed in the spleen and in the liver.

The number of extramedullary lesions proved to be a significant prognostic factor both before and after allo-HCT. In patients with ≤3 FL, highly significant longer PFS and OS were observed, as compared to those with >3 extramedullary FL. Pre-HCT, PFS was 11.0 ± 2.9 m and OS was 31.9 ± 14.4 m in patients with ≤3 FL, whereas PFS was 2.1 ± 1.4 m and OS 5.9 ± 5.0 m (PFS, $p = 0.005$; OS. $p = 0.011$) in patients with >3 extramedullary FL (Fig. 3a).

Post-HCT, PFS was 6.4 ± 1.6 m and OS was 27.4 ± 13.0 m in patients with ≤3 FL, whereas PFS was 3.0 ± 0.9 m and OS 5.9 ± 0.5 m (PFS, $p = 0.012$; OS, $p = 0.059$) in patients with >3 extramedullary FL (Fig. 3b). Furthermore, occurrence of EMD in soft tissue and in lymph nodes was associated with shorter PFS and OS (detailed information is provided in Table 2).

Activity of lesions

Prior to allo-HCT, hottest lesion activity in PET images, as assessed by SUV_{max} in intra- and extramedullary lesions, was correlated with PFS and OS. Using ROC analysis, cut-off values were derived to determine inferior outcome. A value of $SUV_{max} > 6.54$ was predictive for shorter overall survival (median OS 5.0 ± 1.1 m vs. not reached; $p < 0.001$), PFS was not significantly related to lesion activity ($p = 0.065$).

At restaging post allo-HCT, hottest lesion activity was also correlated with OS. A $SUV_{max} > 2.81$ was associated with a shorter overall survival (8.0 ± 2.1 m vs. not reached, $p = 0.008$). Similar to the situation prior to allo-HCT, PFS could not be related to hottest lesion activity ($p = 0.096$).

Predictive value of cytogenetics and laboratory characteristics

Unfavorable cytogenetics was associated with both shorter PFS (4.3 ± 0.7 m) and OS (8.7 ± 2.1 m; non-high-risk patients: PFS, 15.8 ± 6.6 m, $p = 0.084$; OS, not reached with longest OS 122.0 m, $p = 0.022$).

Elevated LDH values >250 U/l proved a negative prognostic factor for both shorter PFS and survival (pre-HCT: PFS, 1.2 ± 0.8 m vs. 11.0 ± 2.9 m, $p = 0.010$; OS, 2.5 ± 0.2 m vs. 28.3 ± 14.3, $p = 0.001$, post-HCT: PFS, 5.3 ± 3.4 m vs. 3.9 ± 1.1 m, $p = 0.091$; OS, 28.3 ± 15.6 m vs. 8.7 ± 2.2 m, $p = 0.275$). Due to the unbalanced group numbers for β2M, FLC, albumin and creatinine, we refrained from analysis of these data in detail, although the same trend could be observed for all three parameters, indicating that elevated levels of β2M, FLC, creatinine and low values of serum albumin result in an inferior outcome.

Complementary value of [^{18}F]-FDG-PET/CT and serological response

Combining serological and PET response post-HCT, we could observe that patients with both serological and imaging-defined complete remission (CR; 4/21; 19.1%) showed best outcomes with prolonged PFS and OS (both, not reached), closely followed by patients with CR status (4/21, 19.1%)

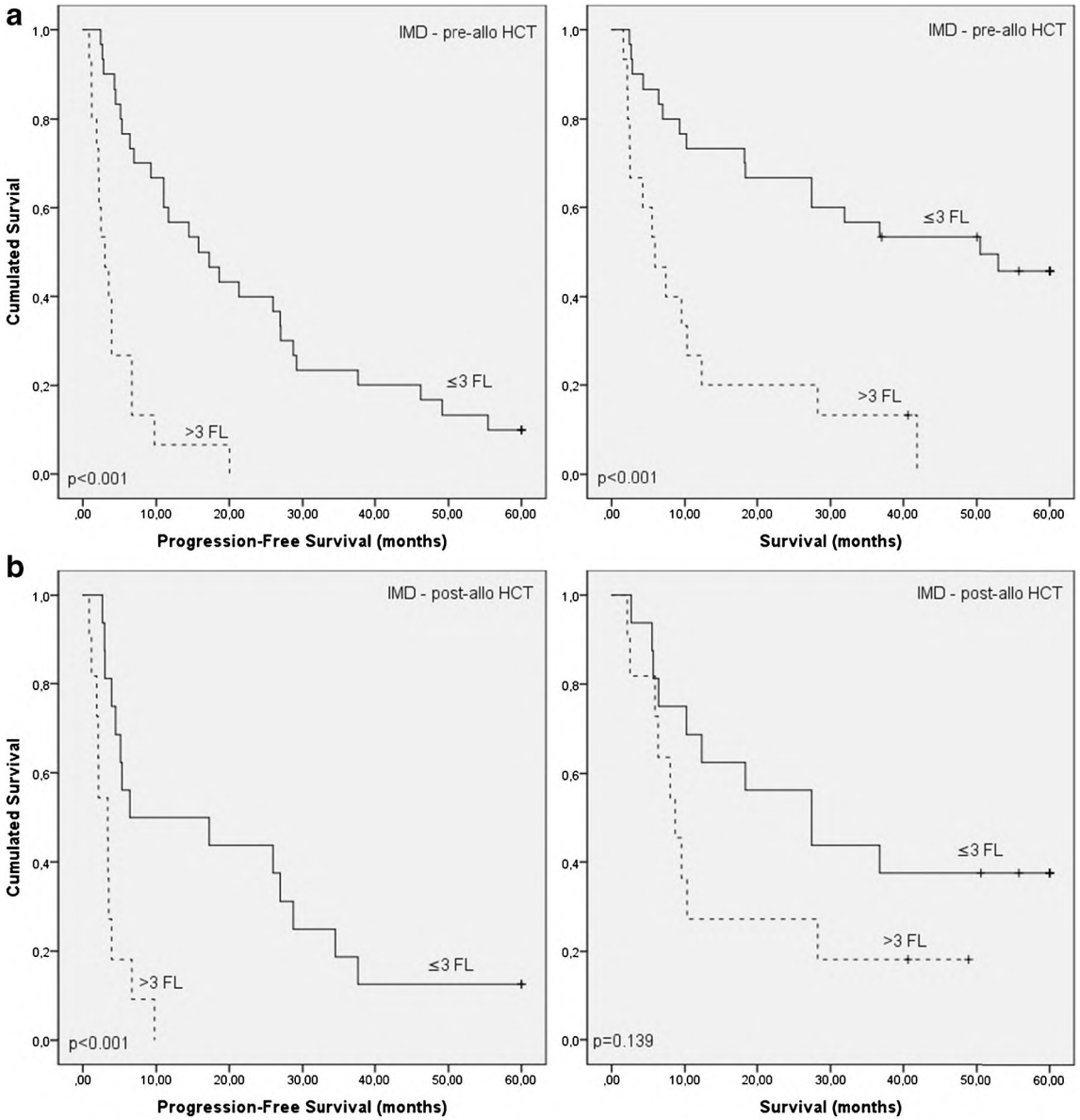


Fig. 2 Prognostic impact of number and location of intramedullary lesions on progression-free and overall survival. Kaplan-Meier analysis of outcome according to the number of PET^+ intramedullary lesions prior (A) and after (B) allo-HCT

exclusively defined by PET (PET^-/$Serology^+$; PFS 26.0 ± 11.2 m, OS not reached). In contrast, patients with both serological and metabolically active disease (11/21, 52.4%; PET^+/$Serology^+$, PFS, 3.9 ± 0.5 m, OS, 10.3 ± 3.5 m), as well as PET-positive FL in the absence of serologic disease (PET^+/$Serology^-$; 2/21; 9.5%) had a trend towards reduced progression-free and overall survival (two patients: PFS_1:2.7 m, OS_1: 2.7 m; PFS_2:17.5 m; OS_2: 18.7 m) (Fig. 4).

Discussion

Over the last years, the role of PET/CT as a state-of-the-art imaging tool for the management of MM has gained increasing importance. Several studies demonstrated the prognostic impact of this imaging technique for monitoring treatment response in MM patients in various scenarios including stem cell transplantation [13, 18–20].

In this study, we analyzed the prognostic value of [^{18}F]FDG-PET/CT in MM patients shortly before and approximately 100 days after allogeneic hematopoietic stem cell transplantation. Our data confirm that also in the specific setting of allogeneic HCT PET negativity, determined both shortly before and after transplantation of MM patients, is significantly associated with longer PFS and OS.

Notably, in addition to IMWG criteria, [^{18}F]FDG-PET/CT had an incremental value in assessing treatment response and thereby prognosis after auto-HCT: Whereas patients with both

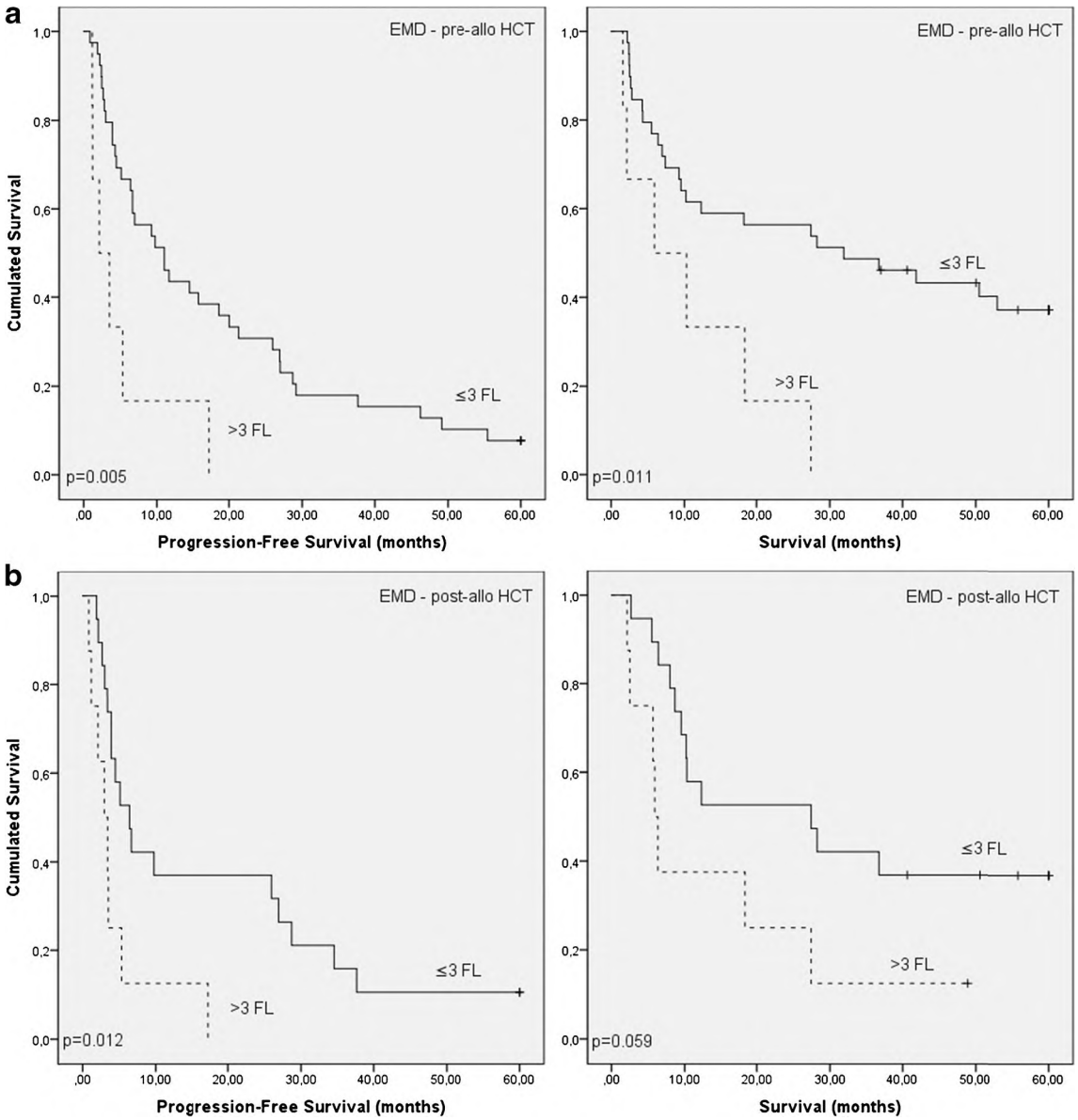


Fig. 3 Prognostic impact of extramedullary disease. Kaplan-Meier analysis of outcome according to the presence of extramedullary disease itself before (A) and after (B) allogeneic HCT

negative PET and in serologically defined complete remission had best outcomes, PET positivity –even in the presence of serologic complete response– inferred shorter PFS and OS. This complementary value of [^{18}F]FDG-PET/CT has also recently been proven in a prospective French trial which included both PET/CT imaging and assessment of minimal residual disease (MRD) by seven-color flow cytometry before maintenance therapy in newly diagnosed MM patients: In the cohort studied, PFS was higher for patients with both a normalized [^{18}F]FDG-PET/CT and a negative MRD before maintenance versus patients with either PET positivity and/or MRD positivity before maintenance (3-year PFS, 86.8% vs. 52.9%, respectively; [21]). Whereas these preliminary observations have to be taken with caution given the relatively small number of patients, the fact that patients with both [^{18}F]FDG-PET/CT–negative and serology/MRD-negative results had longer PFS (and OS) compared with those who remained positive with either technique may be of great importance for future trials and treatment strategies.

Both before as well as after allo-HCT, presence of ≥3 focal lesions and extramedullary disease, especially in soft tissue and/or lymph nodes portended a poor prognosis. With regards to metabolic activity, cut-off values for SUV_{max} of >6.54 before and > 2.81 after allo-HCT were strongly associated with inferior PFS and OS. These results are in line with reported data from our and other groups that have identified the presence of ≥3 FL, EMD and SUV_{max} > 4.2 or > 3.9 as adverse prognostic factors in both earlier as well as advanced stages of

Table 2 Extramedullary manifestation – progression-free and overall survival rates

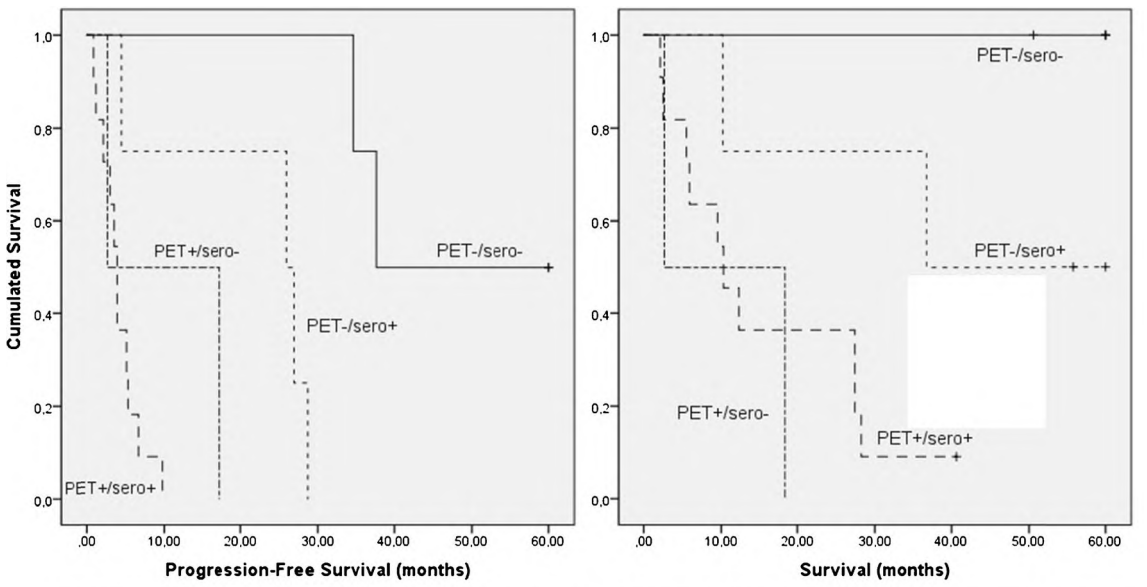
Soft tissue involvment		no	yes	p-value
Pre-HCT	PFS	11.0 ± 2.9	1.2 ± 0.6	0.002*
	OS	31.9 ± 12.0	2.5 ± 2.6	0.001*
Post-HCT	PFS	5.3 ± 1.4	2.1 ± 0.04	0.002*
	OS	27.4 ± 16.9	6.3 ± 4.8	0.071
Lymph node involvement		no	yes	p-value
Pre-HCT	PFS	9.8 ± 3.1	3.5 ± 2.1	0.052
	OS	28.3 ± 15.3	5.9 ± 9.9	0.196
Post-HCT	PFS	6.4 ± 1.6	3.4 ± 0.7	0.015*
	OS	27.4 ± 17.0	6.3 ± 0.6	0.040*

Kaplan-Meier analysis revealed significant effects (*) between patient with and without extramedullary manifestation in soft tissue and lymph nodes before and after allogeneic hematopoietic cell transplantation, PFS – Progression-free Survival, OS – Overall Survival. PFS and OS are given in months

MM [18, 19] and confirm [^{18}F]FDG-PET/CT as a robust tool for patient prognostication regardless of the clinical scenario. For example, feasibility of [^{18}F]FDG-PET/CT-based risk stratification was demonstrated in newly diagnosed MM patients [9, 13, 22] as well as after autologous and allogeneic HCT [16, 18, 20, 23]. As discussed above, given the recently published data from the IMAJEM trial, [^{18}F]FDG-PET/CT might also prove valuable for the detection of MRD in addition to serological assessment [21]. Sensitivity of PET imaging might further be improved by use tracers other than [^{18}F]FDG (e.g., [^{18}F]fluorocholine, [^{11}C]acetate or [^{11}C]methionine) which have yielded promising results in first pilot human studies [24–29]. However, more data on these new radiotracers are needed before firm conclusions can be drawn.

Regarding cytogenetics and laboratory values, we were able to correlate high risk cytogenetics to a worse prognosis, which is consolidated by former studies [30, 31]. In analogy to previous analyses, we could also verify in this cohort that elevated LDH values (>250 U/l) are significantly correlated with a positive PET/CT scan and both shorter PFS and OS [20, 32].

PET-guided analysis shortly before and after allo-HCT might allow for an optimized selection of patients likely to truly benefit from transplantation: Apart from the superior outcomes of patients who achieved metabolic complete remission after conditioning therapy, low myeloma burden with ≤3 FL prior to HCT could be transferred to PET negativity around day +100 after HCT. In analogy, patients with still metabolically active disease prior to allo-HCT are unlikely to achieve CR afterwards. Presence of active FL after transplantation suggests the prompt initiation of consolidation treatment with new drugs, administration of donor lymphocytes or reduction



p-value PFS	PET-/sero-	PET-/sero+	PET+/sero-	PET+/sero+
PET-/sero-	-	0.007	0.018	0.001
PET-/sero+		-	0.107	0.011
PET+/sero-			-	0.262
PET+/sero+				-

p-value OS	PET-/sero-	PET-/sero+	PET+/sero-	PET+/sero+
PET-/sero-	-	0.128	0.018	0.006
PET-/sero+		-	0.107	0.075
PET+/sero-			-	0.541
PET+/sero+				-

Fig. 4 Prognostic impact of serology and PET-analysis after allo-HCT on progression free and overall survival. Kaplan-Meier analysis of outcome in terms of response according serology and [^{18}F]FDG-PET. Comparison of four groups of all possible combinations: CR-status detected via PET and serology (PET−/sero.-), the non-CR status including partial response, stable and progressive disease proven via PET and serology (PET+/sero.+), as well as the combination of contrary status results PET−/sero. + and PET+/sero.-

of graft-versus-host prophylaxis. The fact that [^{18}F]FDG-PET/CT may be complimentary to MRD assessment is a very important outlook for future studies.

This study has a number of limitations. First, it is retrospective with a relatively small number of patients, which limits statistical power. Second, the time interval after allo-HCT was quite heterogeneous with a range from 26 to 233 days. [^{18}F]FDG-PET/CT scans before and after allo-HCT were not available for all patients. Third, not all positive MM lesions, especially very small extramedullary manifestations, were histologically proven, thus, there might be a false positive rate, e.g., for EMD in lymph nodes. It is not clear if and to which extent individual treatment decisions based on [^{18}F]FDG-PET/CT imaging have influenced patients' overall prognosis. Fourth, use of different PET/CT scanners at the two institutions during the time span of the study might have influenced results. Last, heterogeneity of prior treatment protocols has to be acknowledged. Particularly, the novel therapeutic options that have arisen in the last years have significantly changed treatment and prognosis of MM patients, and could therefore have confounded our results.

Nevertheless, our data provide new information on the utility of PET/CT shortly before and -in particular- around day +100 after allogeneic hematopoietic cell transplantation and add -to the existing body of evidence - the important prognostic value of [^{18}F]FDG-PET/CT in the management of MM patients. The combination of MRD assessment and molecular imaging with PET/CT early after treatment holds the potential to significantly improve and sharpen individual prognosis as well as treatment of MM patients.

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Compliance with ethical standards

Ethical approval All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Disclosure of potential conflict of interest All authors state that they have nothing to disclose.

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