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ORIGINAL ARTICLE

^{18}F-FDG PET/CT is useful for determining survival outcomes of patients with multiple myeloma classified as stage II and III with the Revised International Staging System

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Abstract

Purpose This study evaluated the prognostic role of ^{18}F-FDG PET/CT at baseline in patients with newly diagnosed multiple myeloa (MM) and evaluated the prognostic relevance of ^{18}F-FDG PET/CT for each stage according to the Revised International Staging System (R-ISS).

Method We retrospectively analyzed the records of 167 patients with newly diagnosed MM. ^{18}F-FDG PET/CT was performed prior to induction therapy in patients with newly diagnosed MM.

Results In the total cohort, the presence of more than three hypermetabolic focal lesions (FLs) or extramedullary disease (EMD) on baseline PET/CT was associated with significantly inferior progression-free survival (PFS) and overall survival (OS) than other patients. Because most patients (91%) with EMD had more than three FLs, PET/CT positivity was defined as the presence of more than three FLs or the presence of EMD. In multivariate analyses, PET/CT positivity was an independent predictor of PFS and OS in all patients. Fifty-five patients (46.1%) with R-ISS II were PET/CT-positive at baseline and had significantly shorter PFS and OS. PET/CT positivity was also correlated with poor PFS and OS in patients with R-ISS III.

Conclusion ^{18}F-FDG PET/CT was an independent predictor of survival outcomes in patients with newly diagnosed MM. In addition, performing ^{18}F- FDG PET/CT at diagnosis may be useful for determining the survival outcomes of MM patients with R-ISS II and III.

Keywords Multiple myeloma · Positron emission tomography · Prognosis · Revised International Staging System

Introduction

Multiple myeloma (MM) is a malignant disorder of plasma cells, characterized by its clonal expansion within the bone marrow and overproduction of monoclonal immunoglobulin in the blood [1]. Some studies have demonstrated that MM is a clonally heterogeneous disorder at diagnosis and that clonal evolution occurs during disease progression [2–4]. Therefore, despite considerable improvements in the treatment of MM, it remains an incurable disease with a wide range of survival outcomes. Various prognostic systems have been suggested to accurately determine the prognosis of MM. The Revised International Staging System (R-ISS) was suggested recently by the International Myeloma Working Group (IMWG) to improve risk stratification compared with the standard International Staging System (ISS) [5]. The R-ISS is based on the ISS stages, cytogenetic abnormalities and the serum lactate dehydrogenase (LDH) level at diagnosis; it has been validated in an analysis of an independent cohort of unselected patients with MM [6, 7] . However, stage II increased problematically and a more heterogeneous population is included in stage II by applying the R-ISS [8].

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has become a standard imaging technique for staging work-ups and

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predicting prognosis in several types of hematologic malignancies, particularly lymphomas [9]. ^{18}F-FDG PET/CT is useful for detecting bone lesions in patients with MM, with sensitivity and specificity reported in the range of 80–100% [10–12]. The number of FDG-avid focal lesions (FLs), the presence of extramedullary disease (EMD), and the maximum standardized uptake value (SUVmax) are reliable prognostic ^{18}F-FDG PET/CT parameters in MM at diagnosis, before allogeneic stem cell transplantation, and at relapse or progression [13–16]. Therefore, ^{18}F-FDG PET/CT has been increasingly used to predict prognosis in patients with MM.

In this study, we evaluated the prognostic impact of ^{18}F-FDG PET/CT at baseline in all patients with newly diagnosed MM and evaluated the prognostic relevance of ^{18}F-FDG PET/CT at each disease stage according to the R-ISS.

Patients and methods

Patients

This retrospective study included 167 patients with newly diagnosed MM between February 2012 and March 2017 at Chonnam National University Hwasun Hospital. Patients who underwent ^{18}F-FDG PET/CT at the initial diagnosis were included. Patients diagnosed with monoclonal gammopathy of undetermined significance, smoldering MM, amyloidosis, and plasma cell leukemia were excluded. Patients with an active infection at the time of diagnosis were also excluded from this study. This study was approved by the Institutional Review Board of Chonnam National University Hwasun Hospital in accordance with the Declaration of Helsinki.

^{18}F-FDG PET/CT and image analysis

All patients underwent ^{18}F-FDG PET/CT using a Discovery ST PET/CT system (GE Healthcare, Milwaukee, WI, USA), consisting of a bismuth germanate full scanner and a 16-detector-row CT scanner. The patients fasted for at least 6 h prior to intravenous administration of ^{18}F-FDG (7.4 MBq per body weight) to ensure a serum glucose level below 7.2 mmol/l. About 60 min after ^{18}F-FDG was administered, transmission data were acquired using low-dose CT (120 kV, automated from 10 to 130 mA, a 512 × 512 matrix, a 50-cm field of view (FOV), a 3.75-mm slice thickness, and a rotation time of 0.8 s), extending from the base of the skull to the proximal thigh. Immediately after CT acquisition, PET emission scans were acquired from the same anatomic locations with a 15.7-cm axial FOV acquired in two-dimensional mode with a 128 × 128 matrix [17]. The CT data were used for attenuation correction. The images were reconstructed using a conventional iterative algorithm (OSEM). A workstation (AW Volume Share™) that provided multi-planar reformatted images was also used for image display and analysis.

Definitions and response assessment

A FL at diagnosis was defined as focally increased FDG uptake greater than the physiologic bone marrow or liver uptake, with or without any underlying lesion [10]. EMD was defined as FDG-avid soft tissue that was not contiguous to bone. The PET/CT scans were read by two nuclear medicine physicians who had no knowledge of the subjects or their clinical information.

The ISS or the R-ISS was used to assess clinical disease at diagnosis. The IMWG uniform response criteria were used to assess the response to treatment.

Statistical analysis

Pearson's χ^2 test and the Mann–Whitney U test were used for discrete and continuous variables respectively, to compare the characteristics of the patients. Covariates with a P-value < 0.05 in univariate analyses were included in the Cox proportional hazards regression model. Progression-free survival (PFS) was calculated from the start of treatment until disease progression or death from any cause. Overall survival (OS) was defined as the period from the date of diagnosis until the date of the last follow-up or death from any cause. PFS and OS were evaluated using Kaplan–Meier estimates and compared using the log-rank test. The relative risk of an event and the 95% confidence interval (95% CI) were estimated using a Cox proportional hazard model. All statistical computations were performed using SPSS v.21 (SPSS, Chicago, IL, USA). A P-value < 0.05 was considered significant.

Results

Patient population

The baseline clinical characteristics of the 167 patients are summarized in Table 1. The median age of all patients was 67 years (range, 34–79 years), and 59.9% were older than 65 years. The most prevalent type of M-protein was IgG (62.3%), and 19.2% of the patients were light chain disease. Among the patients, 28 (16.8%) had severe renal insufficiency (serum creatine ≥ 2 mg/dl).

Overall, 104 patients (62.3%) received a proteasome inhibitor-containing regimen as the first-line chemotherapy. The combinations were: bortezomib, melphalan, and prednisolone; bortezomib, cyclophosphamide, and prednisolone; bortezomib and dexamethasone; or carfilzomib, melphalan, and prednisolone. Forty-three patients (25.7%) received an

Table 1 Baseline clinical characteristics of all patients ($n = 167$)

Variables	
Median age, years (range)	67.0 (34.0–79.0)
≥ 65 years, *n* (%)	100 (59.9)
Sex, *n* (%)	
Male	92 (55.1)
Female	75 (44.9)
Immunoglobulin (Ig) type, *n* (%)	
IgG	104 (62.3)
IgA	31 (18.6)
Light chain only	32 (19.2)
International Staging System (ISS), *n* (%)	
I	26 (15.6)
II	64 (38.3)
III	77 (46.1)
Revised-ISS, *n* (%)	
I	22 (13.2)
II	115 (68.9)
III	30 (18.0)
ECOG PS ≥ 2, *n* (%)	20 (12.0)
LDH > (1 × ULN), *n* (%)	38 (22.8)
ALC ≤ 1.1 × 10^9/l, *n* (%)	16 (9.6)
Serum creatinine ≥2 mg/dl, *n* (%)	28 (16.8)
Hemoglobin <10 g/dl, *n* (%)	90 (53.9)
Frontline treatment, *n* (%)	
IMiD-based	43 (25.7)
Proteasome inhibitor-based	104 (62.3)
IMiD+proteasome inhibitor	19 (11.4)
Daratumumab-based	1 (0.6)
Performance of ASCT, *n* (%)	47 (28.1)

Abbreviations: *n* number, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *LDH*, lactate dehydrogenase, *ULN* upper limit of the normal value, *ALC* absolute lymphocyte count, *IMiD* immunomodulating drugs; *ASCT* autologous stem cell transplantation

immunomodulatory drug-based regimen as the first-line therapy: thalidomide, cyclophosphamide, and dexamethasone or lenalidomide and dexamethasone. Nineteen patients (11.4%) were treated with bortezomib, thalidomide, and dexamethasone. One patient (0.6%) was treated with daratumumab, bortezomib, melphalan, and prednisolone. Forty-seven patients (28.1%) underwent autologous stem cell transplantation (ASCT).

Baseline ^{18}F-FDG PET/CT and survival outcomes

A total of 102 patients (61.1%) had at least one FL at diagnosis, and 44.9% had more than three FLs. The median SUVmax in patients with FLs was 4.8 (range, 2.6–46.1). EMD was present in 13.2% of all patients. Because most patients (91%) with EMD had more than three FLs, PET/CT positivity was defined as the presence of more than three FLs or the presence of EMD. Seventy-seven patients (46.1%) were PET/CT-positive at baseline. The C-reactive protein level was higher (0.550 vs 0.245 mg/l, $P = 0.004$) and the serum albumin level was lower in the PET/CT-positive group (3.5 vs 3.6 g/dl, $P = 0.040$). Patients who were PET/CT-positive had a significantly lower complete remission rate after first-line therapy compared with those who were PET/CT-negative (15.6% vs 34.4%, $P = 0.007$).

Over the median follow-up duration of 24.4 months, 91 patients (54.4%) had progressed and 36 (21.5%) had died by the time of the last follow-up visit. The median PFS was 23.6 months (95% CI, 18.0–29.2 months) and the median OS was not reached. Patients with more than three FLs had significantly inferior PFS and OS compared with patients with three or fewer FLs (PFS, 15.4 vs 29.7 months, $P < 0.001$; OS, 43.3 months vs not reached, $P = 0.009$, Fig. 1a, b). The presence of EMD was also prognostic for PFS and OS (PFS, 14.8 vs 24.6 months, $P = 0.011$; OS, 23.5 months vs. ot reached, Fig. 1c, d). Patients with more than three FLs or EMD (PET/CT-positive) had significantly poorer survival outcomes than those who were PET/CT-negative (PFS, 15.4 vs 30.1 months, $P < 0.001$; OS, 43.3 months vs not reached, $P = 0.004$, Fig. 1e, f).

In the univariate analysis (Table 2), five clinical factors were significantly associated with PFS, including an age ≥ 65 years, R-ISS, Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2, thrombocytopenia, and PET/CT positivity. In addition, the following clinical factors were significantly associated with OS in the univariate analysis: R-ISS III, ECOG PS ≥ 2, and PET/CT positivity.

A Cox multivariate analysis for PFS and OS was performed (Table 3). PET/CT positivity (HR 2.832, 95% CI 1.813–4.422, $P < 0.001$), R-ISS III (HR 3.295, 95% CI 1.257–8.637, $P = 0.015$), and thrombocytopenia (HR 1.961, 95% CI 1.233–3.121, $P = 0.004$) were significantly associated with PFS. In addition, PET/CT positivity (HR 2.629, 95% CI 1.297–5.329, $P = 0.007$), R-ISS stage III (HR 2.696, 95% CI 1.280–5.680, $P = 0.009$), and an ECOG PS ≥2 (HR 3.174, 95% CI 1.461–6.895, $P = 0.004$) were significantly associated with OS.

Comparison of the ISS and R-ISS

Using the ISS, 15.6% of patients were classified as stage I, 38.3% as stage II, and 46.1% as stage III. By applying the R-ISS, 13.2% of patients were classified as stage I, 68.9% as stage II, and 18.0% as stage III. The ISS was not prognostic for PFS or OS when applied to all 167 patients ($P = 0.091$ and $P = 0.160$ respectively, Fig. 2a, b). However, median PFS and

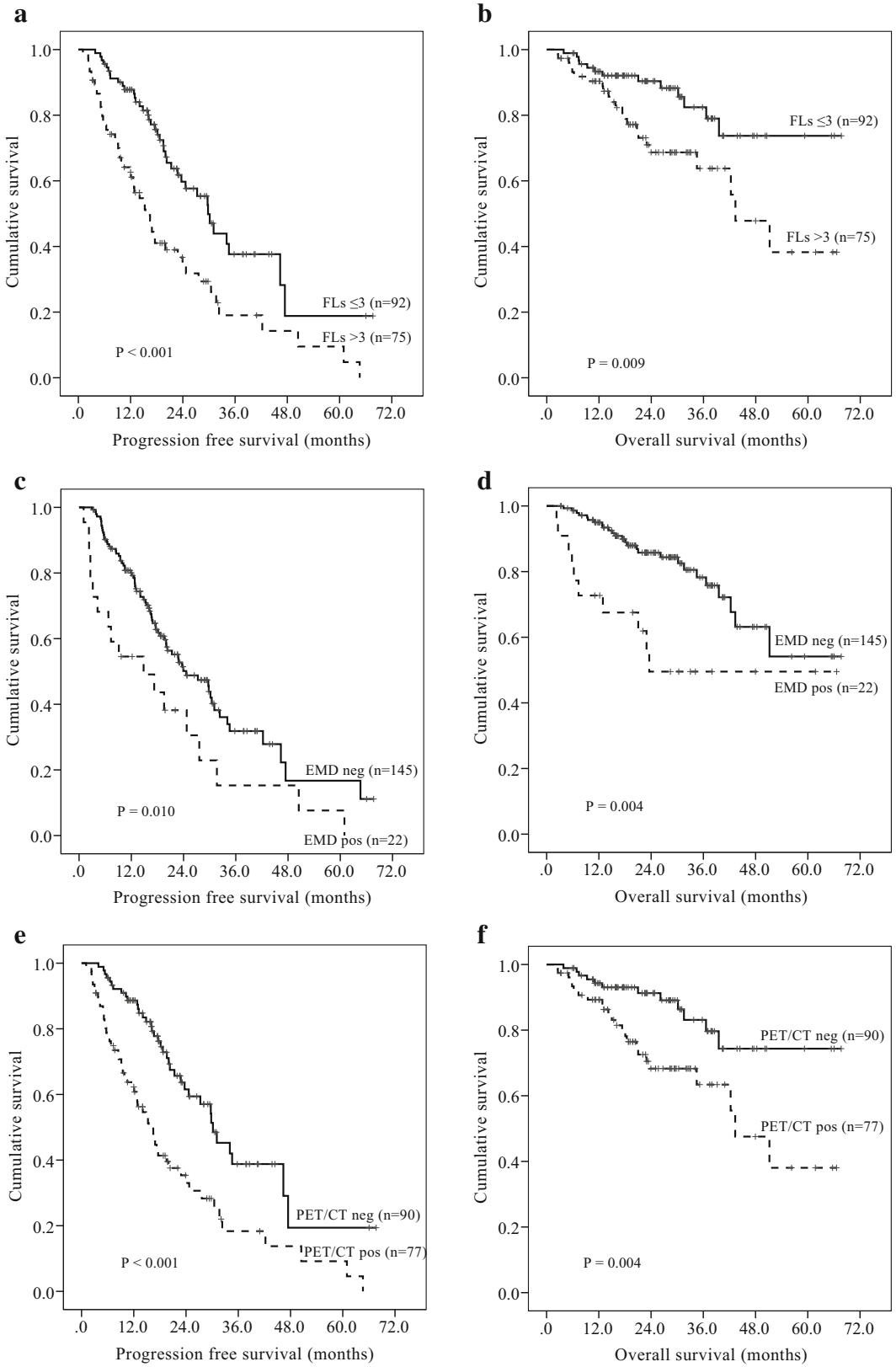

Fig. 1 Kaplan–Meier survival curves for progression-free survival (PFS) and overall survival (OS) according to hypermetabolic focal lesions (*FLs*, **a**, **b**), the presence of extramedullary disease (*EMD*, **c**, **d**), and ^{18}F-FDG-PET/CT positivity (**e**, **f**) at baseline

Table 2 Univariate analysis for progression-free survival and overall survival (n = 167)

	PFS		OS	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age ≥ 65 years	1.578 (1.017–2.448)	0.042	1.379 (0.697–2.727)	0.356
Male	0.942 (0.623–1.425)	0.779	0.838 (0.433–1.622)	0.599
ECOG PS ≥ 2	2.081 (1.150–3.767)	0.015	3.810 (1.780–8.155)	0.001
ALC ≤ 1.1×10^9/l	1.148 (0.593–2.224)	0.682	1.126 (0.397–3.194)	0.823
Platelets < 150×10^9/l	1.798 (1.161–2.783)	0.009	1.677 (0.841–3.342)	0.142
Hemoglobin < 10 g/dl	1.394 (0.916–2.120)	0.121	1.339 (0.685–2.620)	0.393
Serum calcium ≥ 10.2 g/dl	1.014 (0.581–1.768)	0.962	1.142 (0.474–2.752)	0.768
Serum creatinine ≥ 2 mg/dl	1.126 (0.668–1.899)	0.656	0.884 (0.367–2.132)	0.784
Serum albumin < 3.5 g/dl	1.420 (0.939–2.147)	0.096	1.559 (0.810–3.000)	0.184
Serum β2-microglobulin > 5.5 mg/l	1.361 (0.897–2.065)	0.147	1.542 (0.799–2.978)	0.197
R-ISS II[a]	2.693 (1.150–6.302)	0.022	4.644 (0.629–34.295)	0.132
R-ISS III[a]	4.071 (1.592–10.409)	0.003	9.954 (1.270–78.032)	0.029
PET positivity	2.410 (1.583–3.669)	<0.001	2.650 (1.323–5.307)	0.006

Abbreviations: *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *ALC* absolute lymphocyte count, *R-ISS* Revised International Staging System, *PET* positron emission tomography

[a] R-ISS I is the reference

OS times were significantly different depending on the three R-ISS groups. The median PFS according to the R-ISS was 31.6 months for stage I, 23.6 months for stage II, and 16.6 months for stage III ($P = 0.009$, Fig. 2c). The median OS was not reached for R-ISS I or II; it was 31.5 months for R-ISS III ($P = 0.016$, Fig. 2d).

Prognostic impact of ^{18}F-FDG PET/CT in each stage of R-ISS

Twelve of 22 patients (54.5%) with R-ISS I were PET/CT-positive. Among patients with R-ISS I, there were no significant differences in PFS or OS according to PET/CT positivity ($P = 0.734$ and $P = 0.527$ respectively, Fig. 3a, b). Among patients with R-ISS II and III, 53 patients (46.1%) and 12 patients (40%) were PET/CT-positive (Fig. 4). PET/CT-positive patients with R-ISS II had significantly inferior PFS and OS compared with those who were not PET/CT-positive (PFS, 15.4 vs 29.7 months, $P = 0.001$; OS, 43.3 months vs not reached, $P = 0.020$, Fig. 3c, d). In addition, PET/CT-positive patients with R-ISS III had significantly inferior PFS and OS compared with those who were not PET/CT-positive (PFS, 4.9 vs 22.7 months, $P < 0.001$; OS, 21.0 months vs not reached, $P = 0.008$, Fig. 3e, f).

Table 3 Multivariate analysis for progression- free survival and overall survival

	Progression-free survival	
	Hazard ratio (95% CI)	*P*-value
Age ≥ 65 years	1.530 (0.937–2.499)	0.089
ECOG PS ≥ 2	1.473 (0.766–2.834)	0.245
PET/CT positivity	2.832 (1.813–4.422)	<0.001
R-ISS II[a]	2.213 (0.944–5.188)	0.068
R-ISS III[a]	3.295 (1.257–8.637)	0.015
Platelets < 150×10^9/l	1.961 (1.233–3.121)	0.004
	Overall survival	
	Hazard ratio (95% CI)	*P*-value
ECOG PS ≥ 2	3.174 (1.461–6.895)	0.004
R-ISS III[a]	2.696 (1.280–5.680)	0.009
PET/CT positivity	2.629 (1.297–5.329)	0.007

[a] R-ISS I is the reference

Discussion

In this study, ^{18}F-FDG PET/CT was a reliable imaging tool to predict the survival of patients with newly diagnosed MM. Patients who had more than three FLs or EMD on the baseline PET/CT had a significantly lower response rate after induction therapy, and significantly poorer PFS and OS compared with those who were not PET/CT-positive. Several previous studies have reported the prognostic relevance of ^{18}F-FDG PET/CT in patients with newly diagnosed MM and relapse or refractory MM. In the first large prospective study evaluating the prognostic role of ^{18}F-FDG PET/CT in 239 patients with newly diagnosed MM, PET/CT imaging was associated with adverse clinical factors, such as high levels of β2-microglobulin, C-reactive protein, LDH, and a high risk gene expression profile; and the presence of more than three FLs and EMD was an independent predictor associated with inferior survival outcomes [13]. In another prospective study of patients treated

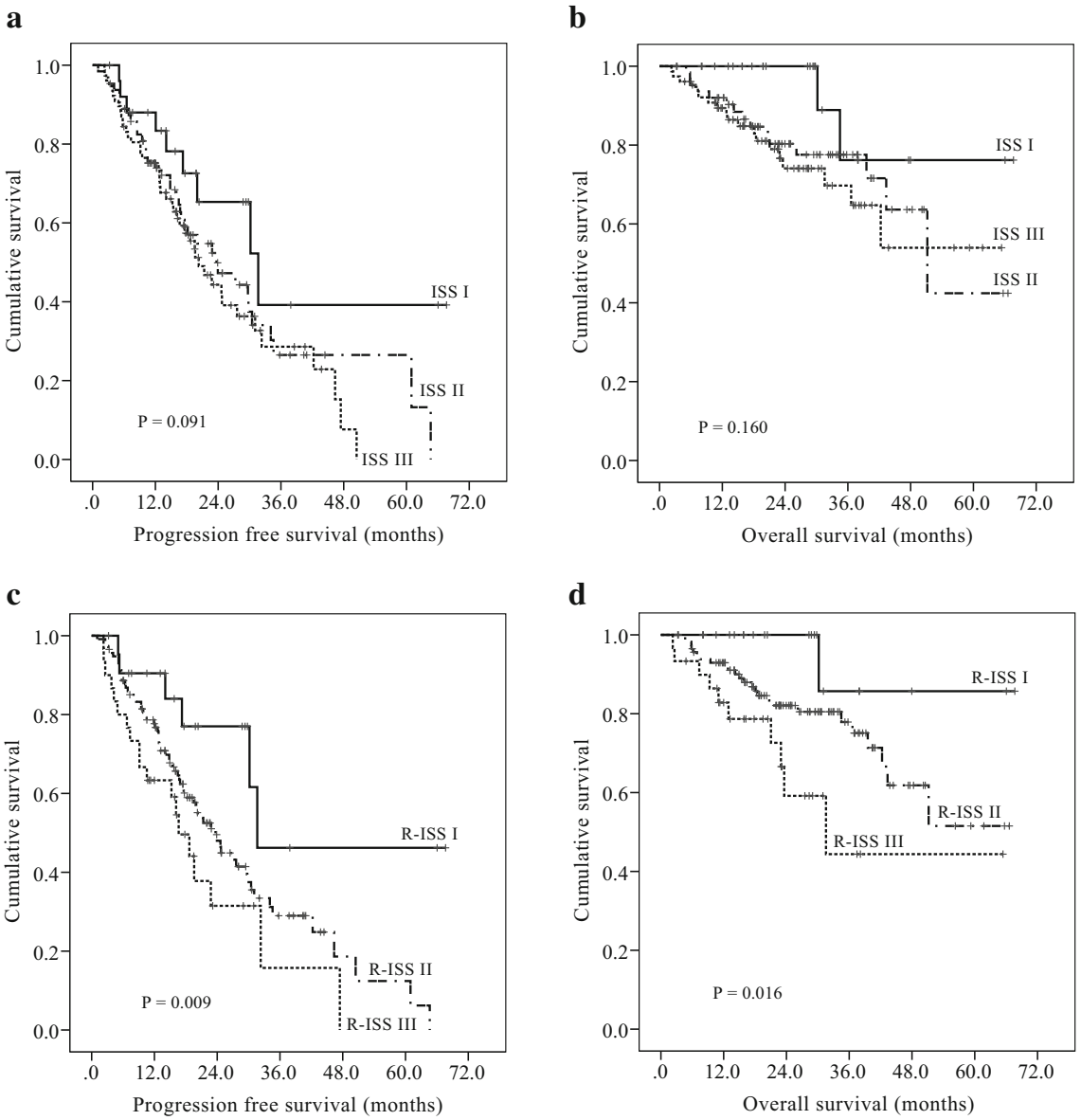

Fig. 2 Kaplan–Meier survival curves for PFS and OS according to the International Staging System (*ISS*, **a**, **b**) and Revised ISS (*R-ISS*. **c**, **d**) in all patients ($n = 167$)

with thalidomide and dexamethasone induction therapy followed by double ASCT, the SUVmax (> 4.2), number of FLs (> 3), and the presence of EMD at baseline were significantly associated with inferior PFS and OS [18]. Other studies have suggested that volume-based parameters, such as metabolic tumor volume and total lesion glycolysis, are promising tools for predicting survival of patients with MM [19, 20]. However, a major limitation in these reports is the lack of uniformity or reliable criteria for interpreting the PET/CT results. The IMWG recently suggested that a high number of FLs (> 3) or the presence of EMD are reliable prognostic indicators in the consensus criteria for PET/CT interpretation [10]. Our data reconfirmed the usefulness of these parameters for predicting PFS and OS in a real-world setting.

In addition, this study demonstrated that ^{18}F-FDG PET/CT significantly improved the prognostic value of the R-ISS in patients with MM. The R-ISS was developed to stratify patients into homogeneous survival subgroups by classifying those with ISS stage I and a poor prognosis, and patients with ISS stage III and a better prognosis, into stage II; this was based on data from 3060 patients with newly diagnosed MM who were enrolled in 11 international clinical trials. The R-ISS provides prognostic value independent of age or the treatment received and is more robust than the original ISS [5]. The R-ISS had a prognostic role in an independent cohort of unselected patients with MM [6, 7, 21]. However, a major limitation of the R-ISS is that stage II increased problematically and included a more heterogeneous population in terms of survival

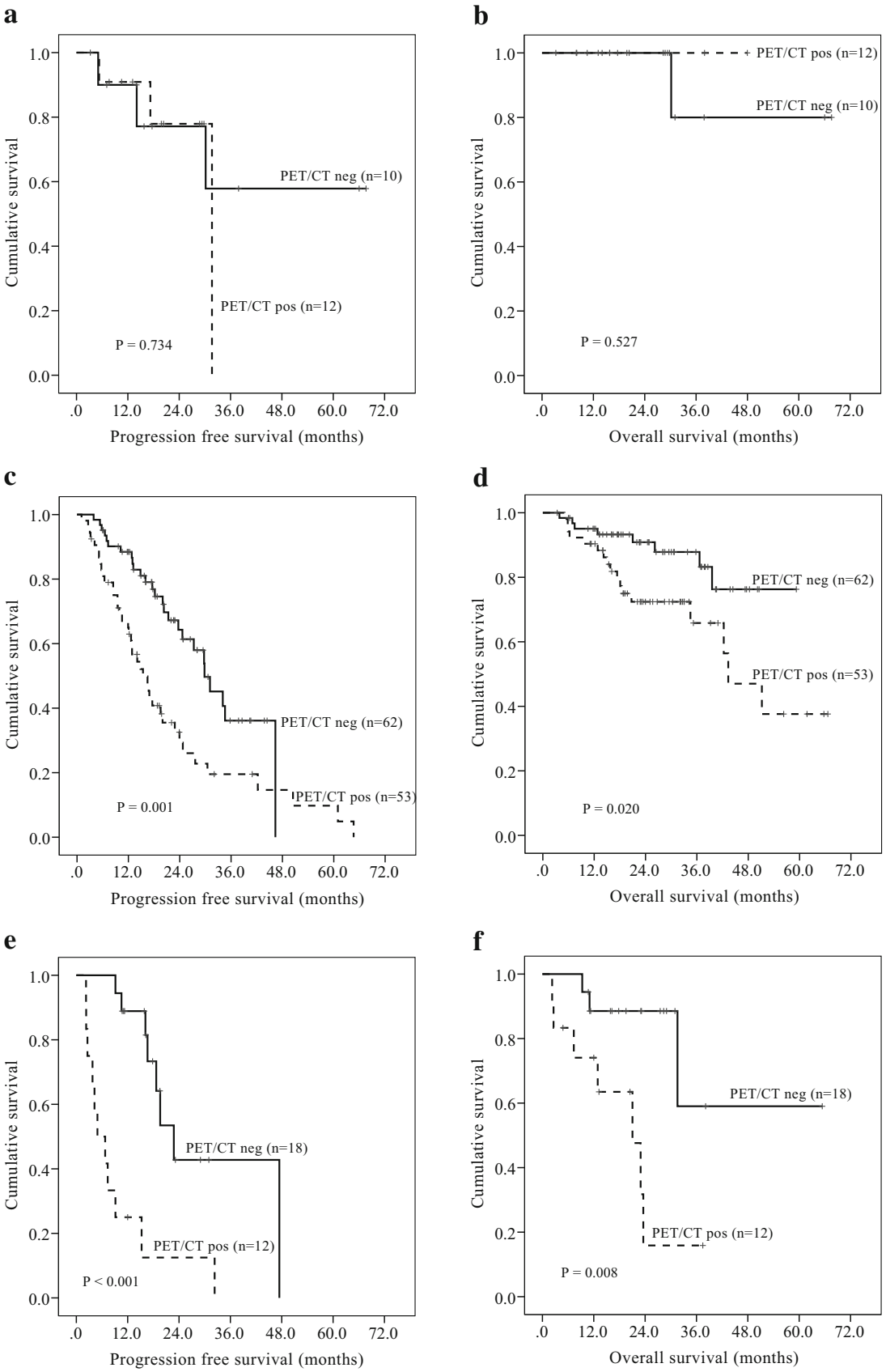

Fig. 3 Kaplan–Meier survival curves for PFS and OS according to ^{18}F-FDG PET/CT positivity for each distinct stage of R-ISS

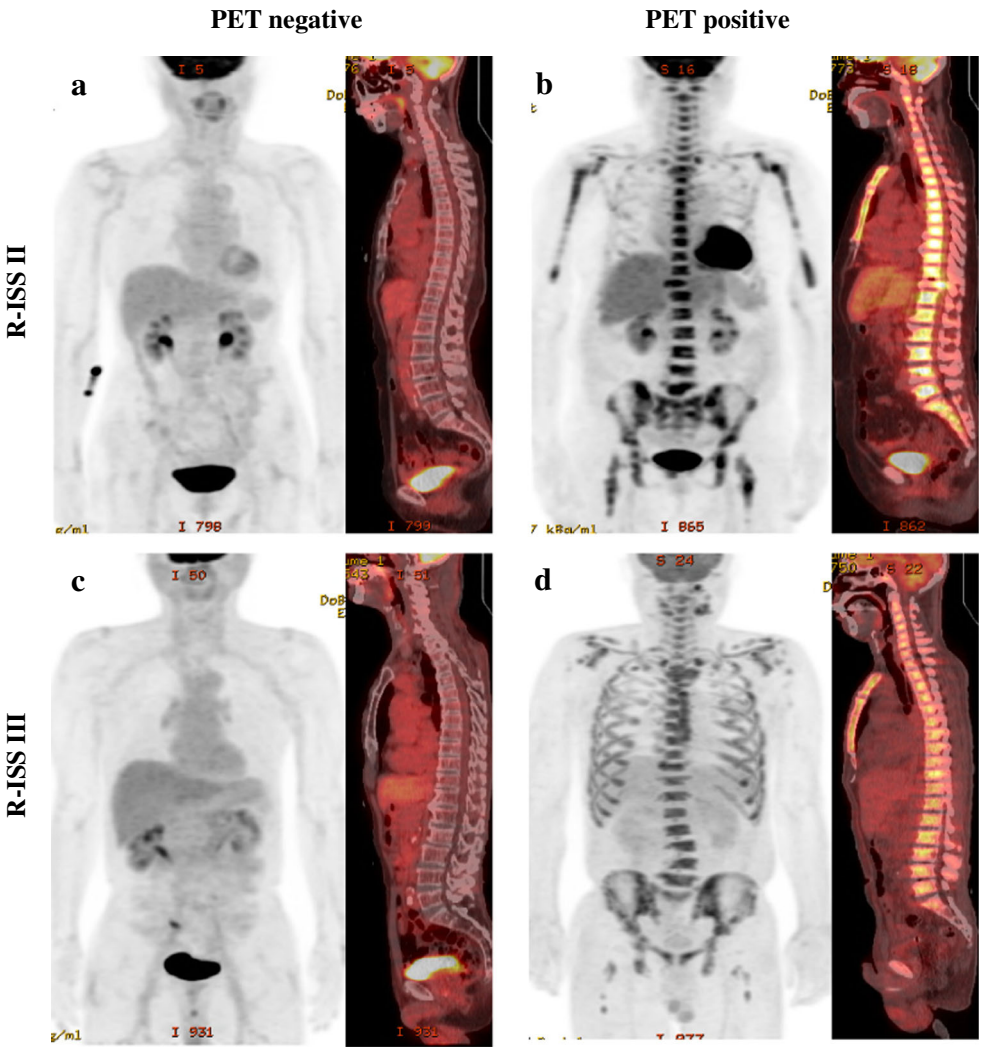

Fig. 4 Representative cases with patients with R-ISS II (**a**, **b**) and III (**c**, **d**) according to ^{18}F-FDG-PET/CT positivity

outcomes. By applying the R-ISS, stage II included 1.7–1.9 fold more patients than the ISS. This finding suggests that more reliable prognostic factors are needed to clarify the prognosis of patients with stage II. In our study, about half of the patients with stage II were PET/CT-positive and had poor PFS and OS, similar to those of patients with stage III. Among the patients with stage III, PET/CT-positive patients had significantly inferior PFS and OS than PET/CT-negative patients. These results show that PET/CT is useful for determining the survival outcomes of patients with R-ISS II and III.

Some limitations of our study should be discussed. First, we did not evaluate patient responses using ^{18}F-FDG PET/CT after induction therapy. ^{18}F-FDG PET/CT is an excellent tool to monitor the response to treatment over other imaging techniques because of its ability to evaluate the metabolic activity of clonal proliferating plasma cells. In a previous study, the persistence of more than three FLs on day 7 after induction therapy was an early predictor of poor survival outcome [22]. In another study, negativity on PET/CT after ASCT was associated with superior PFS and OS compared with PET/CT positivity [18]. Second, some patients with extensive disease may have negative results on ^{18}F-FDG PET/CT. One study reported that PET false-negativity was observed in 11% of patients with MM and was associated with low hexokinase-2 expression [23]. Additional conditions leading to false-negativity include hyperglycemia, recent steroid treatment, or the presence of small lytic lesions in the skull close to the brain. However, we did not check for false-negativity in this study. Third, a whole body scan was not performed due to reimbursement-related issues, and high uptake lesions in the skull and lower limbs were missing in this study. In addtion, our study population was heterogeneous in terms of age, initial treatment, and the performance of stem cell transplantation.

In conclusion, the R-ISS had more significant prognostic value than the ISS in patients with MM. In addition, the presence of more than three FLs or EMD on the baseline ^{18}F-FDG PET/CT was an independent predictor of poor PFS and OS. PET/CT-positive patients with R-ISS II or III correlated with poor PFS and OS. Therefore, ^{18}F-FDG PET/CT was useful for discriminating the survival outcomes of patients with R-ISS II and III.

Author contributions S.H.J. and J.J.L. designed the study and S.H.J. prepared the manuscript; S.Y.K., J.J.M., and H.S.M. performed the image analysis; S.Y.A., S.Y.J., S.S.L., M.R.P., D.H.Y., J.S.A., and H.J.K. critically reviewed the manuscript. All authors have read and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest.

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 Declaration of Helsinki and its later amendments or comparable ethical standards.

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