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ORIGINAL ARTICLE

Pretreatment ^{18}F-FDG PET/CT combined with quantification of clonal circulating plasma cells as a potential risk model in patients with newly diagnosed multiple myeloma

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Abstract

Purpose Both ^{18}F-FDG PET/CT and clonal circulating plasma cell (CPC) quantification are emerging tools for multiple myeloma (MM) prognostication that have been validated in recent studies. This study investigated the value of PET/CT coupled with CPC quantification for MM prognostication that may contribute to future risk-adapted treatment.

Methods We retrospectively analysed the prognostic relevance of a combination of pretreatment PET/CT findings and CPC levels in 163 consecutive patients with newly diagnosed, symptomatic MM receiving novel agents during induction therapies.

Results High-risk PET/CT findings and elevated CPC levels were defined by the presence of >3 focal lesions with or without extramedullary disease and CPCs ≥0.10% of the total mononuclear cells evaluated, respectively. Subsequently, patients were divided into three groups: PET-CPC stage I included patients with no high-risk PET/CT findings and low CPC levels; stage III included patients with high-risk PET/CT findings and high CPC levels; and stage II included the remaining patients. The three groups of patients differed significantly in terms of both progression-free survival (PFS) and overall survival (OS) (median PFS: not reached [NR] and 36.4 and 15.9 months, and median OS: NR, NR, and 40.4 months for stages I, II, and III, respectively; $P < 0.001$ for both PFS and OS). This system discriminated both PFS and OS even among younger (age < 75 years) or older (≥ 75 years) patients, patients with Revised International Staging System stage II or III, and patients with or without high-risk cytogenetic characteristics. In the multivariate analysis, the PET-CPC staging system remained prognostic for both PFS and OS.

Conclusions The PET-CPC staging system predicted survival outcomes independently of established risk factors in patients with newly diagnosed MM. Pretreatment ^{18}F-FDG PET/CT assessment combined with CPC quantification may improve the prognostication of MM and facilitate the development of novel risk-adapted approaches for MM.

Keywords Circulating plasma cell · Focal lesion · Multiple myeloma · Positron emission tomography/computed tomography · Prognosis

Introduction

To date, several risk stratification systems have been developed and validated for symptomatic multiple myeloma (MM). Of these, the International Staging System (ISS) and the Revised ISS (R-ISS), which combined ISS with the status of cytogenetic abnormalities (CAs) and serum levels of lactate dehydrogenase, are the most representative [1, 2]. Despite their usefulness, the primary endpoint of the original and subsequent validation studies for the R-ISS as well as ISS was set as overall survival (OS), not progression-free survival (PFS): both systems include serum albumin levels as a major

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parameter for frailty assessment [1–4]. Therefore, these systems have not been utilized for risk-adapted intensification of therapy [5, 6]. Additionally, except CAs, there are few prognostic markers that reflect the biological features of myeloma. Accordingly, additional approaches for functional evaluation that are aimed at detection of disease aggressiveness and/or potential resistance to therapy have been explored.

There are two emerging tools for MM prognostication that have been validated in recent studies. First, whole-body combined ^{18}fluorine-fluoro-deoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is now considered to be a valuable tool not only for initial diagnosis and response assessment [7–9], but also for prognostic assessment of MM. Several previous studies have shown the prognostic significance of abnormalities detected by PET/CT in the context of known risk factors [10–14]. Although it captures the tumour burden as well, FDG-avidity provides more information for the aggressiveness of myeloma proliferation. Second, several studies have demonstrated the prognostic relevance of clonal circulating plasma cells (CPCs) in patients with symptomatic MM and related plasma cell disorders [15–17]. Additionally, the levels of CPCs have been suggested to be independent of the tumour burden and to reflect potential resistance to chemotherapy [18–20]. Both newer parameters largely reflect disease factors rather than host factors and have shown prognostic value independently of known risk factors. However, they have not yet been included in the major prognostic systems neither has their synergistic prognostic potential been explored. We hypothesized that the combination of these functional evaluation tools and further incorporation of high-risk CA data might be useful for the identification of patients who are at the highest risk of disease relapse and potentially require more intensive treatment.

Hence, we investigated the prognostic relevance of abnormal findings on pretreatment whole-body ^{18}F-FDG PET/CT in combination with the pretreatment levels of CPCs in the context of established risk factors, including high-risk CAs and the R-ISS, using a cohort of patients with newly diagnosed MM (NDMM).

Materials and methods

Study design and patients

We initially identified 167 consecutive patients with NDMM who underwent concurrent pretreatment whole-body ^{18}F-FDG PET/CT evaluation and CPC quantification and were treated with chemotherapy between January 2012 and August 2018 at Kameda Medical Centre, Kamogawa, Japan. Patient backgrounds and outcomes were reviewed from the electronic medical records. Diagnosis and treatment response were assessed using the International Myeloma Working Group criteria [21]. To maximise homogeneity of chemotherapy regimens, thereby improving the prognostic value of our analyses, we excluded patients who had been treated without novel agents (e.g., immunomodulatory agents or proteasome inhibitors) during induction therapies ($n = 4$). Ultimately, 163 patients were thus included in our analyses. All participants had provided written comprehensive informed consent not only for undergoing PET/CT scan and CPC quantification, but also for future secondary use of their clinical data including PET/CT and CPC findings and patient outcomes for retrospective studies. The study was conducted according to the Declaration of Helsinki and was approved by the review board of Kameda Medical Centre.

Acquisition and evaluation of PET/CT imaging

PET/CT imaging was performed as previously reported [9, 11, 22]. In brief, patients were injected intravenously with a standard dose of 4.3 MBq/kg ^{18}F-FDG (max 350 MBq). Sixty to seventy-five minutes after FDG injection, a whole-body CT scan and PET scan extending from the head to the mid-thigh level was obtained using nine bed positions (adjusted by height to a maximum of 12 bed positions). A CT scan was obtained initially with a voltage of 140 kV, current intensity of 150 mA, tube rotation of 0.5 s, section thickness of 3.5 mm, and pitch of 1.275:1, without an oral or intravenous contrast agent. The blood glucose level required prior to FDG administration was set to ≤150 mg/dL.

PET/CT images were evaluated by a team of experienced nuclear medicine physicians who were well versed in MM diagnosis. PET/CT positivity was defined based on previous reports [11]. Briefly, positive areas were indicated by either the presence of focal areas of detectable increased tracer uptake within bones with or without any underlying lesion identified by CT or a maximum standardized uptake value (SUVmax) ≥ 2.5 within the osteolytic CT areas exceeding 1 cm in size or ≥ 1.5 within osteolytic CT areas ranging between 0.5 and 1 cm in size. In accordance with previous reports [11], we also considered each bone marrow focal area visually detectable in at least two or more slices as a positive area regardless of the SUVmax and in the absence of any underlying lytic lesion at CT images. The numbers, locations, and SUVmax values of hypermetabolic focal lesions (FLs) were recorded.

Quantification of CPCs

Pretreatment CPC levels were detected and quantified using two-tube, seven-colour multiparametric flow cytometry. Flow cytometric analyses was performed on peripheral blood mononuclear cells isolated by Ficoll gradient, and stained with antibodies to CD19, CD38, CD45, CD56, CD138, and cytoplasmic kappa and lambda immunoglobulin light chains. Data

acquisition was performed using a Navios flow cytometer (Beckman-Coulter, Fullerton, CA, USA) and cells were analysed using Kaluza software (Beckman-Coulter, Fullerton, CA, USA). The CPCs were detected by analysis of CD19, CD38, CD45, CD56, and CD138 levels. Clonality was confirmed by light chain restriction [kappa:lambda expression ratio of >4:1 (kappa restricted) or < 1:2 (lambda restricted)] [17]. In accordance with previous reports [15, 17, 23], the target for collection was more than 150,000 cellular events. The CPCs were reported as the percentage per total mononuclear cells. Patients were considered to be negative for clonal CPCs at a sensitivity of 10^{-4} (0.01%) clonal plasma cells in all events evaluated.

Statistical analysis

Relationships between baseline characteristics and PET/CT findings in combination with CPC levels were assessed using one-way analysis of variance, the Kruskal–Wallis test, or chi-squared tests as appropriate. When necessary, variables were transformed for further analysis. Clonal CPC levels below 0.01% (negative CPCs) were treated as 0.00% in the analysis. Receiver operating characteristic (ROC) curve analysis, which predicted the highest risk of disease progression within 2 years or death within 5 years, was performed to determine the cut-off level of CPCs.

To focus on the prognostic impact of disease factors of myeloma, the primary and secondary endpoints of this study were set as PFS and OS, respectively. The probability of PFS and OS was estimated using the Kaplan–Meier method and was compared using the log-rank test. The prognostic impact of PET/CT and CPCs was evaluated using univariate and multivariate Cox proportional-hazards analyses. Variables that showed *P* values <0.1 on univariate analysis were further tested in the multivariate analysis. Consequently, the multivariate Cox regression model was adjusted for age and the R-ISS score. A two-tailed *P* value <0.05 was considered statistically significant. Statistical analysis was performed using R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic and baseline patient characteristics

Baseline clinical characteristics of all patients are summarized in Table 1. The median age of the patients was 74.1 (interquartile range (IQR): 66.3–80.8) years. The median observation period was 27.5 (IQR: 12.8–46.8) months. The prevalence of high-risk CAs (del(17p), t(4;14), or t(14;16) detected by interphase fluorescence in situ hybridisation) was consistent with previous reports [2, 4].

A total of 105 (64.4%) patients showed abnormal finding(s) on PET/CT. The prevalence of PET/CT findings that have been suggested to carry negative prognostic impact showed a distribution consistent with previous reports [11, 14]; the presence of >3 FLs, SUVmax >4.2, and extramedullary diseases (EMDs) was observed in 77 (47.2%), 79 (48.5%), and 10 (6.1%) patients, respectively. All patients with EMDs had >3 FLs.

Consistent with previous reports [15], there were 98 (60.1%) patients whose CPCs were detectable. The median level of CPCs was 0.07% (IQR: 0.00–0.38%).

Defining high-risk PET/CT findings and determination of the optimal cut-off level of CPCs

As previously described [10, 11], the presence of >3 FLs, SUVmax >4.2, and EMDs were all prognostic for both PFS and OS in our cohort (Figs. S1, S2, and S3, respectively). The ROC curve analysis suggested that the optimal cut-off level of CPCs was 0.10% for predicting the highest risk of both disease progression within 2 years and death within 5 years (Fig. S4). Thus, patients were divided into two groups with lower (< 0.10%) or higher (≥ 0.10%) CPCs. Patients with higher CPCs showed both significantly shorter PFS and OS than those with lower CPCs (Fig. S5).

In the multivariate analysis, the presence of >3 FLs and higher CPCs remained prognostic for both PFS and OS (Table 2A). Considering these findings in addition to the fact that the patients with EMDs were included in patients with >3 FLs, the high-risk PET/CT findings in this study were defined as the presence of >3 FLs with or without EMDs.

Combined assessment using PET/CT findings and CPC levels predicts survival outcomes

We divided patients into three groups according to the presence or absence of high-risk PET/CT findings and elevated CPC levels (PET-CPC staging system) as follows: stage I included patients with no high-risk PET/CT findings and lower CPC levels; stage III included patients with high-risk PET/CT findings and higher CPC levels; and stage II included patients with either high-risk PET/CT findings or higher CPC levels but not both.

A comparison of the baseline clinical characteristics across patients with different PET-CPC stages is also summarized in Table 1. Patients in stage II were older than those in stages I and III. PET-CPC stages showed significant associations with almost all myeloma-related parameters, including disease stages and the prevalence of high-risk CAs, whereas there were no significant differences across the three stages of treatment (including autologous stem cell transplantation and maintenance therapy) or treatment response.

Table 1 Baseline clinical characteristics of all patients and comparison of patient groups categorized according to the presence of high-risk PET/CT findings and elevated clonal circulating plasma cell levels

Clinical factors	All cohorts	PET-CPC staging system†			*P*-value
	n = 163	Stage I (−/−) *n* = 53 (32.5%)	Stage II (+/−) *n* = 67 (41.1%)	Stage III (+/+) *n* = 43 (26.4%)	
Age, years [median (IQR)]	74.1 (66.3, 80.8)	71.2 (66.2, 78.4)	77.1 (69.8, 83.4)	71.2 (65.2, 76.4)	0.008
Sex, male (%)	81 (49.7)	26 (49.1)	36 (53.7)	19 (44.2)	0.61
Heavy chain type, IgG (%)	85 (52.1)	30 (56.6)	32 (47.8)	23 (53.5)	0.61
Albumin, g/dL [median (IQR)]	3.2 (2.7, 3.8)	3.7 (3.3, 4.0)	3.0 (2.6, 3.5)	3.1 (2.5, 3.7)	0.001
Beta 2-microglobulin, mg/L [median (IQR)]	5.4 (3.0, 8.6)	3.1 (2.2, 4.6)	6.1 (4.1, 8.9)	8.0 (4.1, 15.2)	<0.001
Creatinine, mg/dL [median (IQR)]	0.96 (0.71, 1.74)	0.79 (0.64, 1.16)	0.97 (0.82, 1.94)	1.20 (0.83, 2.66)	0.001
Haemoglobin, g/dL [median (IQR)]	9.6 (8.3, 11.4)	10.9 (9.6, 12.4)	9.2 (7.9, 10.6)	9.2 (7.9, 10.4)	<0.001
LDH, high (%)	50 (30.7)	8 (15.1)	19 (28.4)	23 (53.5)	<0.001
High-risk CA (%)	38 (23.3)	5 (9.4)	12 (17.9)	21 (48.8)	<0.001
Del(17p)	15 (9.2)	3 (5.7)	4 (6.0)	8 (18.6)	0.045
t(4;14)	18 (11.0)	2 (3.8)	7 (10.4)	9 (20.9)	0.028
t(14;16)	5 (3.1)	0 (0.0)	1 (1.5)	4 (9.3)	0.020
ISS, stage III (%)	88 (54.0)	9 (17.0)	45 (67.2)	34 (79.1)	<0.001
R-ISS, stage III (%)	46 (28.2)	2 (3.8)	18 (26.9)	26 (60.5)	<0.001
D-S, stage III (%)	102 (62.6)	14 (26.4)	50 (74.6)	38 (88.4)	<0.001
CPCs, % [median (IQR)]	0.07 (0.00, 0.38)	0.00 (0.00, 0.02)	0.08 (0.00, 0.27)	0.95 (0.25, 5.05)	<0.001
CPCs, ≥ 0.1% (%)	76 (46.6)	0 (0.0)	33 (49.3)	43 (100)	<0.001
BM PCs, % [median (IQR)]	16.0 (6.1, 35.1)	6.1 (3.0, 11.9)	19.8 (9.6, 34.7)	37.3 (18.2, 53.8)	<0.001
CD56-positivity (%)	122 (74.8)	39 (73.6)	52 (77.6)	31 (72.1)	0.78
Findings on whole body PET/CT (%)					
Positive	105 (64.4)	18 (34.0)	44 (65.7)	43 (100)	<0.001
FLs, > 3	77 (47.2)	0 (0.0)	34 (50.7)	43 (100)	<0.001
SUVmax, > 4.2	79 (48.5)	13 (24.5)	33 (49.3)	33 (76.7)	<0.001
EMDs	10 (6.1)	0 (0.0)	3 (4.5)	7 (16.3)	0.003
Induction regimen (%)					
Novel agent use	163 (100)	53 (100)	67 (100)	43 (100)	1.0
Doublet	55 (33.7)	16 (30.2)	27 (40.3)	12 (27.9)	0.32
Triplet	108 (66.3)	37 (69.8)	40 (59.7)	31 (72.1)	
ASCT recipients (%)	47 (28.8)	15 (28.3)	16 (23.9)	16 (37.2)	0.32
Best response, VGPR or better (%)	114 (69.9)	38 (71.7)	49 (73.1)	27 (62.8)	0.48
Maintenance after VGPR or better (%)††	89 (78.1)	29 (76.3)	38 (77.6)	22 (81.5)	0.87
Outcome (%)					
Alive	123 (75.5)	52 (98.1)	49 (73.1)	22 (51.2)	0.001
Dead	40 (24.5)	1 (1.9)	18 (26.9)	21 (48.8)	

Abbreviations: ASCT, autologous stem cell transplantation; BM, bone marrow; CA, cytogenetic abnormality; CPC, circulating plasma cell; D-S, Durie–Salmon; EMDs, extramedullary diseases; FLs, focal lesions; IQR, interquartile range; ISS, International Staging System; LDH, lactate dehydrogenase; PCs, plasma cells; PET/CT, positron emission tomography/computed tomography; R-ISS, revised International Staging System; SUVmax, maximum standardized uptake value; VGPR, very good partial response

† Patients are divided into three groups: Stage I, non-high-risk PET/CT findings and lower CPC levels (−/−); Stage III, high-risk PET/CT findings and higher CPC levels (+/+); and Stage II, either high-risk PET/CT findings or higher CPC levels but not both (+/−)

†† *n* = 114 (Stage I, *n* = 38; Stage II, *n* = 49; and Stage III, *n* = 27)

Kaplan–Meier survival curves of PFS and OS according to the PET-CPC stages are shown in Fig. 1. The three groups of patients categorized by the PET-CPC system differed significantly in terms of survival duration (median PFS: not reached [NR] and 36.4 and 15.9 months for stages I, II, and III, respectively; $P < 0.001$ for all stage I vs. II, stage I vs. III, and stage II vs. III; median OS: NR, NR, and 40.4 months for stages I, II, and III,

Table 2 Multivariate Cox regression analysis predicting progression-free and overall survival

Variables	PFS		OS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
A.				
Age, ≥70 years	–	–	2.46 (1.18–5.10)	0.016
R-ISS, stage III	2.45 (1.32–4.58)	0.004	5.05 (1.93–13.2)	<0.001
CPCs, ≥0.1%	3.13 (1.78–5.50)	<0.001	2.39 (1.17–4.91)	0.017
FLs on PET/CT, >3	2.49 (1.31–4.71)	0.005	2.53 (1.09–5.85)	0.030
SUVmax, >4.2	1.14 (0.66–1.97)	0.65	1.36 (0.66–2.78)	0.40
B.				
Age, ≥70 years	–	–	2.54 (1.23–5.26)	0.012
R-ISS, stage III	1.65 (0.88–3.12)	0.12	3.78 (1.41–10.1)	0.008
PET-CPC staging system†	2.95 (1.97–4.43)	<0.001	2.67 (1.58–4.50)	<0.001

Abbreviations: CI, confidence interval; CPCs, circulating plasma cells; FLs, focal lesions; HR, hazard ratio; OS, overall survival; PET/CT, positron emission tomography/computed tomography; PFS, progression-free survival; R-ISS, revised International Staging System; SUVmax, maximum standardized uptake value

† PET-CPC staging system includes high-risk PET/CT findings (FLs on PET/CT, > 3) and CPCs ≥0.1%, with each parameter scoring 1 point and thus creating a staging system ranging from I to III

respectively; $P = 0.001$, <0.001, and 0.012 for stage I vs. II, stage I vs. III, and stage II vs. III, respectively). Among patients in PET-CPC stage II, no significant difference in both PFS and OS was detected between patients with high-risk PET/CT findings and patients with elevated CPC levels.

The prognostic performance of the PET-CPC system in the context of established risk factors

To confirm the availability of the PET-CPC staging system, we examined the prognostic performance of the system in the context of age, the R-ISS, and high-risk CAs. Notably, the

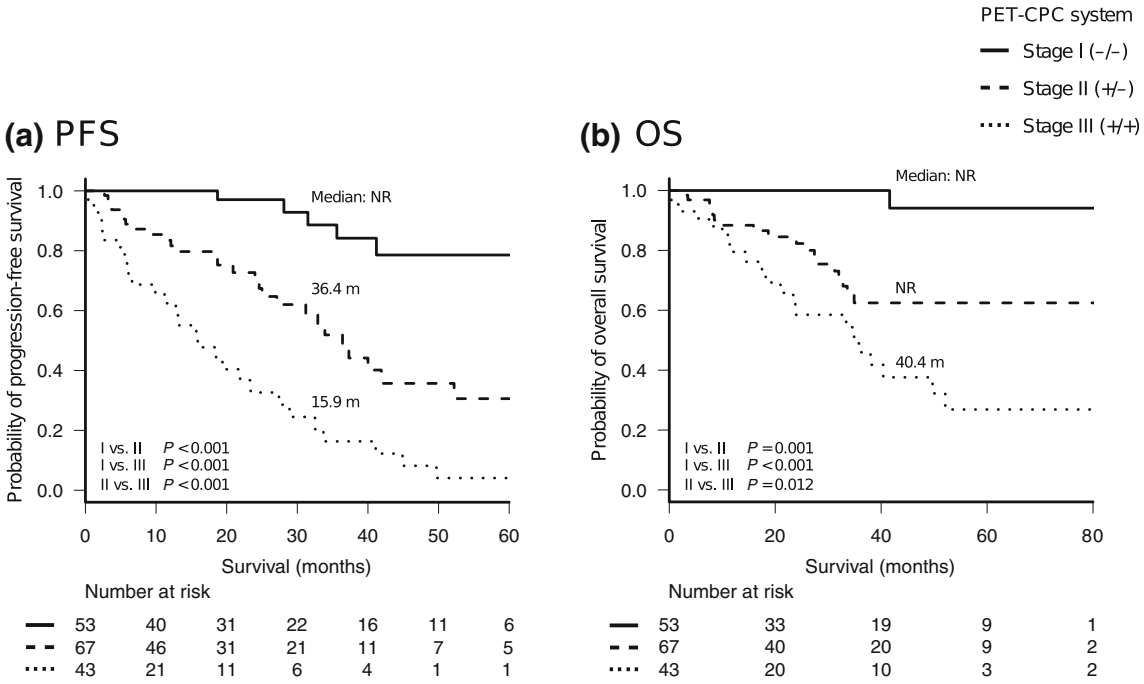

Fig. 1 Survival according to the PET-circulating plasma cell (PET-CPC) staging system. (**a**) Progression-free survival (PFS) and (**b**) overall survival (OS) across patients with different stages. Patients are divided into three groups: stage I included patients with no high-risk PET/CT findings and lower CPC levels (−/−); stage III included patients with high-risk PET/CT findings and higher CPC levels (+/+); and stage II included patients with either high-risk PET/CT findings or higher CPC levels, but not both (+/−)

system showed excellent discrimination of PFS curves across the three groups among both younger (age < 75 years) and older (≥75 years) subjects (Fig. S6). Similarly, the system clearly discriminated PFS curves among patients with R-ISS stage II (Fig. S7A). Most patients with R-ISS stage III (45 of the 47 patients: 95.6%) were categorized into PET-CPC stage II ($n = 18$) or III ($n = 27$), and the former patients showed significantly longer PFS than the latter patients (Fig. S7B). The PET-CPC system also discriminated PFS curves among patients with and without high-risk CAs (Fig. 2). Patients with PET-CPC stage III who harboured concomitant high-risk CAs showed an exceptionally short PFS (median: 11.2 months).

In the multivariate analysis, the PET-CPC staging system retained its prognostic significance for both PFS and OS even after adjustment for age and the R-ISS (Table 2B).

Discussion

In the present study, we validated the prognostic value of pretreatment ^{18}F-FDG PET/CT as well as CPC quantification, and further revealed that the combination of these two emerging approaches robustly stratified NDMM prognosis independently of established prognostic factors. To the best of our knowledge, the association between PET/CT findings and CPC levels and the prognostic relevance of the combination of these parameters have not been reported.

Consistent with several previous studies [11, 13, 14], PET/CT showed that its prognostic performance was independent of those of other powerful prognostic parameters. Although earlier studies have suggested that SUVmax >4.2 had a significant prognostic impact [11], a more recent study detected no clear SUVmax cut-off that was predictive of survival outcomes [14]. Our analysis revealed that the SUVmax value was not predictive of both PFS and OS in the multivariate analysis. Accordingly, our definition of the high-risk PET/CT findings harmonized with the results of recent studies [13, 14]. Recently, Italian Myeloma criteria for PET Use (IMPeTUs) have been defined to harmonise the interpretation of PET/CT findings in MM [24, 25]. Although the authors of these studies emphasise that the criteria are not yet ready for clinical application, we speculate that they will be widely applied in clinical trials as well as in real-life clinical settings for the initial evaluation and response assessment of MM. Therefore, future studies that explore the association between PET/CT findings defined by the IMPeTUs criteria and CPC levels would also be of particular interest.

CPC levels have also been suggested to reflect a different disease biology due to their association with cytogenetic abnormalities [26], increased angiogenesis [18], and lower expressions of integrins and adhesion molecules [20]. In addition, evaluation of CPCs is emerging as an attractive modality for non-invasive risk stratification [17, 23]. These backgrounds led us to select CPCs as a partner of PET/CT for establishing a novel risk model that is dedicated to effectively

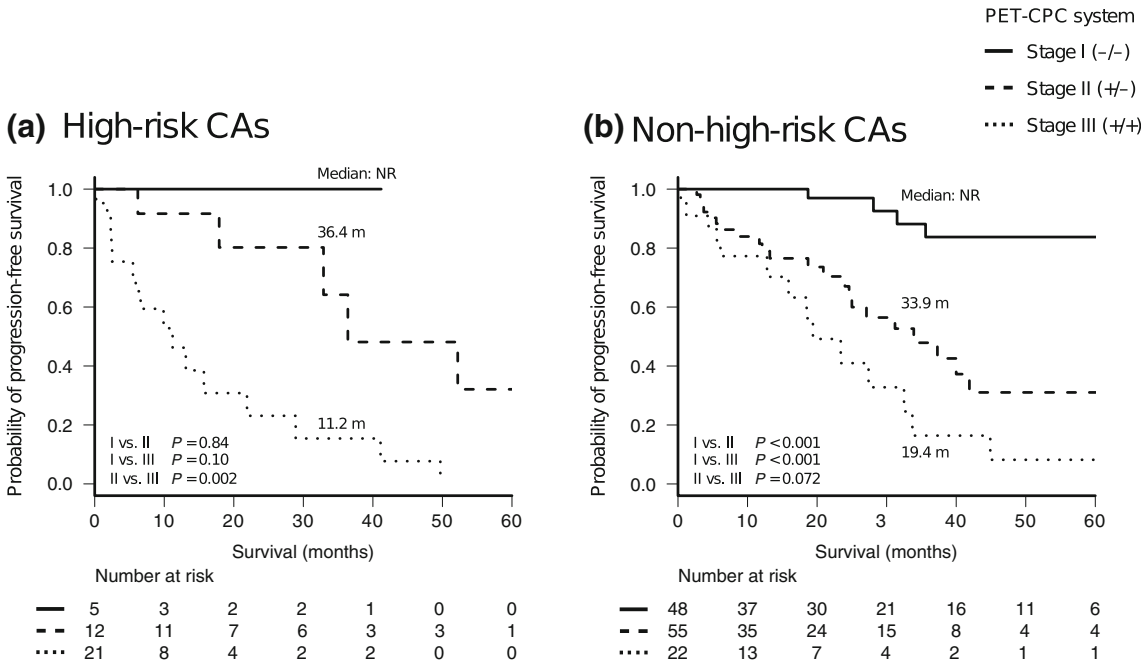

Fig. 2 Progression-free survival (PFS) according to the PET-circulating plasma cell (PET-CPC) staging system in patients with different cytogenetic profiles. PFS according to the PET-CPC staging system in patients (**a**) with or (**b**) without high-risk cytogenetic abnormalities (CAs). High-risk CAs denote del(17p), t(4;14), and t(14;16) detected using interphase fluorescence in situ hybridisation.

detecting differences in disease biology. Thus, in this study, we focused on the PFS as a primary endpoint using a cohort of patients receiving novel targeted agents included in induction regimens. The cut-off level of CPCs (0.10%) was substantially coincident with that used in a previous report [15].

Intriguingly, many patients showed a discrepancy between the prevalence of high-risk PET/CT findings and CPC levels (patients with PET-CPC stage II), and had an intermediate risk for disease progression between patients with PET-CPC stage I and III. These findings suggested that these two parameters might reflect slightly different biological features of myeloma in addition to the tumour burden, and that they might be complementary to each other, working synergistically as a prognostic marker. We speculate that PET/CT might reflect aggressiveness of myeloma clone proliferation as well as tumour burden, while elevated CPC levels might reflect an independency of myeloma clones from the bone marrow microenvironment by the loss of homing or anchoring, which might confer a resistance to chemotherapy [20]. Importantly, the prognostic performance of the PET-CPC system was independent of high-risk CAs or the R-ISS, the most powerful known prognostic factors, suggesting that the PET-CPC system may be used to complement and improve the established stratification strategies. Contrary to the R-ISS, PET/CT and CPCs are fundamentally independent of patient frailty, as is the case with high-risk CAs. Therefore, the identification of patients at exceptionally high risk using this system (i.e., patients with PET-CPC stage III with high-risk CAs) could provide an opportunity for interventions with alternative treatment, including the early use of newer agents, tandem autologous stem cell transplantation, or chimeric antigen receptor T cells [27]. The identification of this highest-risk group could improve risk-adapted approaches that have previously failed to improve outcomes [28, 29].

We noted that patients with PET-CPC stage II were older than those with stage III. This might be associated with the high incidence of high-risk CAs among patients with PET-CPC stage III: t(4;14) and t(14;16) are considered primary genetic events in plasma cell disorders, and are known to correlate with disease progression and a younger age among patients with symptomatic MM [30–34]. In our real-world cohort in an aging society, this association might have been intensified by the inclusion of patients with a wide age range. Despite this age difference as well as the absence of significant differences in treatment, patients with PET-CPC stage III showed significantly poorer survival outcomes, emphasizing the prognostic impact of the concomitant high-risk PET findings in patients with elevated CPC levels. Furthermore, we confirmed the successful prognostic performance of the PET-CPC system in both younger and older subjects, suggesting that our findings may be reproducible in real-life clinical settings in general. Future prospective studies with less heterogeneous patient cohorts receiving more uniform treatments are needed.

The present study is limited by its retrospective nature and heterogeneous treatments. It was conducted at a single institute without a validation analysis in independent cohorts. Despite these study limitations, our results highlighted a novel approach for prognostic assessment using a simple combination of two promising, non-invasive approaches. We believe that these findings carry unique clinical and biological significance.

In conclusion, our findings demonstrated that the combined assessment of pretreatment ^{18}F-FDG PET/CT and CPCs was useful for risk stratification in patients with NDMM. The prognostic performance of the PET-CPC staging system was independent of established risk factors and further incorporation of high-risk CAs into this system contributed to the identification of patients at extremely high risk of disease relapse, suggesting that this system may potentially be available for improvement of known risk stratification strategies as well as for establishment of future risk-adapted treatment modification strategies. Further studies are warranted to validate our results and to elucidate detailed mechanisms of our new insights.

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Author contributions YA conceived, designed, and initiated the study, collected data, performed all statistical analyses, wrote the manuscript, and provided patient care. KN, HK, AK, DM, and MT provided patient care. EO and TO interpreted the PET/CT images. KM supervised the study and provided patient care. All authors reviewed and approved the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies 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.

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