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Association of FISH cytogenetic risk and baseline PET/CT findings with early treatment response and disease progression in patients with newly diagnosed multiple myeloma

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ABSTRACT

Aims: To evaluate the association of fluorescence in situ hybridization (FISH)-defined cytogenetic risk and baseline positron emission tomography/ computed tomography (PET/CT) findings with early treatment response and early disease progression in patients with newly diagnosed multiple myeloma (MM).

Methods: Seventy patients with newly diagnosed MM were included in this retrospective study. Clinical characteristics, International Staging System (ISS) and Revised ISS (R-ISS) stage, lactate dehydrogenase (LDH) level, FISH-defined cytogenetic risk, and baseline PET/CT parameters, including the number of focal lesions, maximum standardized uptake value (SUV max), extramedullary disease, bone marrow involvement, and metabolic risk group, were recorded. Treatment responses after the second and fourth cycles were evaluated. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method, and exploratory associations with PFS were assessed using Cox proportional hazards regression.

Results: According to baseline PET/CT, 81.4% of patients were classified as having a metabolically high-risk disease. Compared with the metabolically low-risk group, patients in the metabolically high-risk group achieved significantly higher rates of very good partial response (VGPR) after the second cycle (49.1% vs. 15.4%, p=0.032) and ≥VGPR after the fourth cycle (64.9% vs. 23.1%, p=0.011). However, progression rates did not differ significantly between the two groups (p=0.675). Although response rates and progression frequency were numerically higher in the FISH high-risk group, these differences did not reach statistical significance. Kaplan–Meier analysis demonstrated longer PFS in female patients (p=0.001); ≥VGPR after the fourth cycle was not significantly associated with PFS (p=0.116). In the multivariable Cox model (13 PFS events), female gender remained significantly associated with PFS (HR=0.067, 95% CI 0.008–0.569, p=0.013), although the estimate was unstable because of the very limited number of events. The 1-year PFS and OS rates were 86% and 92%, respectively.

Conclusion: In this exploratory cohort, the study-specific PET/CT metabolic risk classification was associated with deeper early treatment responses but not with short-term disease progression. FISH-defined cytogenetic risk was not significantly associated with early response or progression. Given the short follow-up duration, limited number of events, and lack of external validation of the metabolic risk classification, these findings should be considered preliminary and do not establish the independent prognostic value of PET/CT or FISH-defined risk.

Keywords: Multiple myeloma, PET/CT, in situ hybridization; fluorescence, progression-free survival, treatment outcome

INTRODUCTION

Multiple myeloma (MM) is a plasma cell malignancy characterized by clonal expansion of abnormal plasma cells within the bone marrow, resulting in monoclonal immunoglobulin production and progressive end-organ damage. Representing approximately 10% of hematologic malignancies, MM predominantly affects older individuals, with a median age at diagnosis of approximately 65–70 years.[1,2] MM is a biologically heterogeneous disease, and cytogenetic and molecular abnormalities are among the most important determinants of prognosis. Fluorescence in situ hybridization (FISH) is routinely used to identify recurrent high-risk chromosomal abnormalities; however, patients with similar cytogenetic profiles may still experience markedly different clinical outcomes, indicating that additional prognostic markers are required.

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Beyond cytogenetic evaluation, functional imaging has become an important component of the initial assessment of patients with MM. Among available imaging modalities, 18F-FDG PET/CT provides valuable information regarding tumor metabolic activity and disease distribution. Baseline PET/CT findings, including a high number of focal lesions, elevated SUVmax, and extramedullary disease, have been associated with adverse clinical outcomes. Previous studies have identified prognostically relevant SUVmax thresholds ranging from approximately 3.9 to 4.2. In addition, diffuse or mixed bone marrow FDG uptake patterns have been reported to be associated with inferior progression-free and overall survival (OS). However, the optimal combination of these parameters and their cutoff values has not been universally standardized. Consequently, PET/CT has emerged not only as a staging tool but also as a potential biomarker of disease burden and biological aggressiveness.[3-9]

Depth of response following induction therapy has also emerged as an important prognostic marker in patients with newly diagnosed MM. Several studies have demonstrated that achieving a very good partial response (VGPR) or better after induction therapy is associated with prolonged progression-free survival (PFS) and OS.[10]

Although both cytogenetic abnormalities and PET/CT findings have individually demonstrated prognostic value, evidence regarding their combined contribution to predicting early treatment response and disease progression remains limited. A better understanding of how these complementary risk assessment tools interact may improve early risk stratification and support individualized treatment strategies. Therefore, the present study aimed to investigate the relationship between FISH-defined cytogenetic risk, baseline 18F-FDG PET/CT findings, early treatment response, and short-term disease progression in patients with newly diagnosed MM.

METHODS

This study was approved by the Non-interventional Ethics Committee of İzmir City Hospital (Date: 29.04.2026, Decision No: 2026/280). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective, single-center study included patients newly diagnosed with MM at tertiary referral center, between December 2023 and October 2025. The data cut-off date for follow-up and survival analyses was May 15, 2026. Only patients who underwent both FISH cytogenetic analysis and baseline 18F-FDG PET/CT at diagnosis were eligible for inclusion. The diagnosis of MM was established according to the International Myeloma Working Group (IMWG) criteria.

Patients without baseline PET/CT imaging, unavailable FISH cytogenetic results, or incomplete early treatment response data were excluded.

Demographic characteristics, myeloma subtype, International Staging System (ISS) stage, Revised International Staging System (R-ISS) stage, serum lactate dehydrogenase (LDH) level, FISH cytogenetic findings, treatment regimens, autologous stem cell transplantation (ASCT) status, treatment responses, and follow-up data were retrospectively retrieved from the institutional electronic medical records. Serum LDH levels above the institutional upper limit of normal (233 U/L) were considered elevated. Treatment responses were assessed according to the IMWG response criteria. Responses after the second and fourth cycles of induction therapy were recorded. Achievement of a VGPR or better (≥VGPR) after the fourth cycle was defined as an early deep response. Disease progression included all progression events documented during the follow-up period.

FISH analysis was performed on unselected bone marrow aspirate samples obtained at diagnosis, without CD138-positive plasma cell enrichment. Patients harboring any of the following cytogenetic abnormalities were classified as having high-risk cytogenetics: del(17p), t(4;14), t(14;16), deletion 1p, and/or gain of chromosome 1q. Patients without these abnormalities were classified as having standard-risk cytogenetics.

Baseline 18F-FDG PET/CT was performed in all patients at diagnosis and interpreted by experienced nuclear medicine physicians. The number of focal lesions, maximum standardized uptake value (SUVmax), presence of extramedullary disease, and diffuse bone marrow involvement were recorded. The metabolic risk classification used in the present study was adapted from the high-risk PET/CT features described by Terao et al.[7], who defined high-risk findings as the presence of more than three focal lesions, SUVmax >4.2, or extramedullary disease. For the present analysis, an SUVmax cutoff of >4 was selected as a pragmatic approximation of the >3.9 prognostic threshold reported by Bartel et al.[9] In addition, diffuse bone marrow involvement was incorporated into the composite classification based on the findings of Li et al,[8] who demonstrated that diffuse or mixed bone marrow FDG uptake patterns were independently associated with inferior progression-free and OS. Accordingly, patients were classified as having metabolically high-risk disease if at least one of the following features was present: more than three focal lesions, SUVmax >4, extramedullary disease, or diffuse bone marrow involvement. Patients without any of these findings were classified as having metabolically low-risk disease. This study-specific composite classification was used for exploratory risk stratification and was not intended to represent an established or externally validated clinical risk score.

The primary endpoint was to evaluate the association of baseline PET/CT findings and FISH-defined cytogenetic risk with early treatment response, including VGPR after the second cycle and ≥VGPR after the fourth cycle. Secondary endpoints were disease progression, PFS, and OS. PFS was defined as the time from diagnosis to disease progression or death from any cause, whichever occurred first. Patients alive and progression-free at last follow-up were censored at the date of last examination. OS was defined as the time from diagnosis to death from any cause.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). A two-sided p value of <0.05 was considered statistically

significant. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Descriptive statistics are presented as mean±standard deviation or median (range), as appropriate. Categorical variables are expressed as frequencies and percentages. Comparisons between categorical variables were performed using the Pearson χ^2 test or Fisher's exact test, as appropriate. Survival outcomes were estimated using the Kaplan–Meier method and compared using the log-rank test. Variables with a p value <0.25 in the univariable analysis, together with clinically relevant variables, were entered into the multivariable Cox proportional hazards regression model using the enter method. Hazard ratios (HRs) with 95% confidence intervals, regression coefficients (B), standard errors (SE), and corresponding p values are reported.

RESULTS

A total of 70 patients with newly diagnosed MM were included in the study. The mean age was 65.0±9.2 years, and 36 (51.4%) patients were female. IgG was the most common myeloma subtype (44.3%), followed by free light chain (27.1%) and IgA myeloma (25.7%). According to the ISS, 20.0% of patients had stage I disease, 42.9% had stage II disease, and 37.1% had stage III disease. Based on the R-ISS, most patients (60.0%) were classified as stage II, whereas 27.1% had stage III disease.

Elevated serum LDH levels were observed in 23 patients (32.9%), and 21 patients (30.0%) were classified as having high-risk cytogenetics based on FISH analysis. Baseline PET/CT demonstrated more than three focal lesions in 48 patients (68.6%) and an SUV max >4 in 44 patients (62.9%). Extramedullary disease was detected in 19 patients (27.1%), whereas diffuse bone marrow involvement was observed in 33 patients (47.1%). Overall, 57 patients (81.4%) were classified as having metabolically high-risk disease according to the predefined PET/CT criteria. Baseline clinical and disease characteristics are summarized in Table 1.

Most patients (61/70, 87.1%) received a initial regimen based on bortezomib, cyclophosphamide, and dexamethasone (VCD), whereas the remaining initial treatment regimens were heterogeneous and represented by small patient numbers. Subsequent regimen modifications were frequently response-adapted following assessment after the second treatment cycle.

Treatment responses and clinical outcomes are presented in Table 2. After the second cycle of induction therapy, 30 patients (42.9%) achieved a VGPR, 37 (52.9%) achieved a partial response (PR), and only three patients had stable disease (SD) or progressive disease (PD). Following the fourth treatment cycle, the VGPR rate increased to 57.1%, while PR and PD were observed in 37.1% and 5.7% of patients, respectively. Overall, 40 patients (57.1%) achieved an early deep response (≥VGPR) after the fourth cycle.

During follow-up, 39 patients (55.7%) underwent ASCT. Disease progression occurred in 10 patients (14.3%), and six patients (8.6%) died; three deaths occurred after progression and three without documented prior progression. Thus, 13 PFS events (18.6%) were observed. At last follow-up, 64 patients (91.4%) were alive and 57 (81.4%) were alive and progression-free.

Table 1. Baseline clinical and disease characteristics of the patients

Parameter	n	%
Myeloma subtype		
IgG kappa	18	25.7
IgG lambda	13	18.6
IgA kappa	9	12.9
IgA lambda	9	12.9
IgM lambda	1	1.4
Free kappa	14	20.0
Free lambda	5	7.1
Non-secretory	1	1.4
ISS Stage		
Stage I	14	20.0
Stage II	30	42.9
Stage III	26	37.1
R-ISS Stage		
Stage I	9	12.9
Stage II	42	60.0
Stage III	19	27.1
Serum LDH		
Normal	47	67.1
Elevated	23	32.9
FISH-defined cytogenetic risk		
Standard	49	70.0
High	21	30.0
>3 focal lesions on baseline PET/CT		
Yes	48	68.6
No	22	31.4
SUVmax >4 on baseline PET/CT		
Yes	44	62.9
No	26	37.1
Extramedullary disease		
Present	19	27.1
Absent	51	72.9
Bone marrow involvement on PET/CT		
Present	33	47.1
Absent	37	52.9
Metabolically high-risk disease		
Yes	57	81.4
No	13	18.6

IgG: Immunoglobulin G, ISS: International Staging System, R-ISS: Revised International Staging System, LDH: Lactate dehydrogenase, FISH: Fluorescence in situ hybridization, SUVmax: Maximum standardized uptake value, IgA: Immunoglobulin A, IgM: Immunoglobulin M, PET/CT: Positron emission tomography/computed tomography

The median follow-up duration was 15.3 months (range, 3.6–29.1 months). Median PFS and OS were not reached during the study period. The estimated 1-year PFS and OS rates were 86% and 92%, respectively (Figure).

PFS and OS were compared according to gender, myeloma subtype, PET/CT findings, serum LDH level, FISH-defined cytogenetic risk, and depth of response after the fourth treatment cycle. Kaplan–Meier analysis demonstrated significantly longer PFS in female patients than in male patients (p=0.001). No significant differences in PFS were observed for the remaining variables, including ≥VGPR after the fourth cycle (p=0.116).

Table 2. Treatment response and clinical outcomes

Parameter	n	%
Response after the second cycle		
VGPR	30	42.9
PR	37	52.9
SD	2	2.9
PD	1	1.4
Response after the fourth cycle		
VGPR	40	57.1
PR	26	37.1
PD	4	5.7
≥VGPR after the fourth cycle		
Yes	40	57.1
No	30	42.9
Autologous stem cell transplantation (ASCT)		
Yes	39	55.7
No	31	44.3
Disease progression*		
Present	10	14.3
Absent	60	85.7
Vital status		
Alive	64	91.4
Dead	6	8.6

ASCT: Autologous stem cell transplantation, PD: Progressive disease, PFS: Progression-free survival, PR: Partial response, SD: Stable disease, VGPR: Very good partial response.*Death without prior progression: 3 (4.3%), PFS events: 13 (18.6%)

None of the evaluated variables showed a statistically significant association with OS. Because all female patients and all patients with extramedullary disease remained alive throughout follow-up, comparative OS analyses could not be performed for these subgroups.

Univariable and multivariable Cox regression analyses were performed to identify factors associated with PFS and OS. In the univariable analysis, gender was the only variable significantly associated with PFS. Male patients had a significantly higher risk of disease progression or death than female patients (HR=14.7, 95% CI 1.9-113.4, p=0.010). However, only one PFS event occurred among 36 female patients, compared with 12 events among 34 male patients. Therefore, the hazard ratio had a wide confidence interval and should be interpreted cautiously. Achievement of ≥VGPR after the fourth cycle was not significantly associated with PFS (HR=0.42, 95% CI 0.14-1.28, p=0.127). FISH-defined cytogenetic risk, PET metabolic risk, SUV max, number of focal lesions, extramedullary disease, and bone marrow involvement on PET/CT were not significantly associated with PFS. No significant prognostic factor for OS was identified in the univariable analysis.

A multivariable Cox proportional hazards model including age, gender, myeloma subtype, FISH-defined cytogenetic risk, SUVmax, and achievement of ≥VGPR after the fourth cycle identified female gender as the only variable significantly associated with PFS (HR=0.067, 95% CI 0.008-0.569, p=0.013). However, only 13 PFS events (10 progressions and three deaths without prior progression) were available for the six covariates included in the model, corresponding to approximately 2.2 events per variable, and only one event occurred among female patients. Therefore, the model was at substantial risk of overfitting, and its hazard ratios, standard errors, and p values should be considered unstable and exploratory. Accordingly, p values approaching the conventional significance threshold were not interpreted as evidence of prognostic associations. The results of the multivariable Cox regression analysis are summarized in Table 3.

Table 3. Multivariable Cox regression analysis for progression-free survival

Variable	B	SE	Wald χ^2	HR	95% CI	p
Age	0.056	0.042	1.763	1.058	0.974–1.149	0.184
Gender (female vs. male)	-2.710	1.095	6.130	0.067	0.008–0.569	0.013
FISH-defined cytogenetic risk (high vs. standard)	1.193	0.664	3.231	3.298	0.898–12.111	0.072
Baseline SUVmax (>4 vs. ≤4)	0.544	0.725	0.564	1.723	0.416–7.131	0.453
≥VGPR after the fourth cycle (yes vs. no)	-0.874	0.641	1.861	0.417	0.119–1.465	0.173
Myeloma subtype (non-IgG vs. IgG)	1.193	0.698	2.921	3.296	0.839–12.943	0.087

HR: Hazard ratio, SE: Standard error, VGPR: Very good partial response, SUVmax: Maximum standardized uptake value

Treatment responses according to FISH-defined cytogenetic risk are presented in Table 4. Although patients with high-risk cytogenetics showed numerically higher VGPR rates after both the second cycle (52.4% vs. 38.8%, p=0.307) and the fourth cycle (66.7% vs. 53.1%, p=0.429), neither difference reached statistical significance. Likewise, the distribution

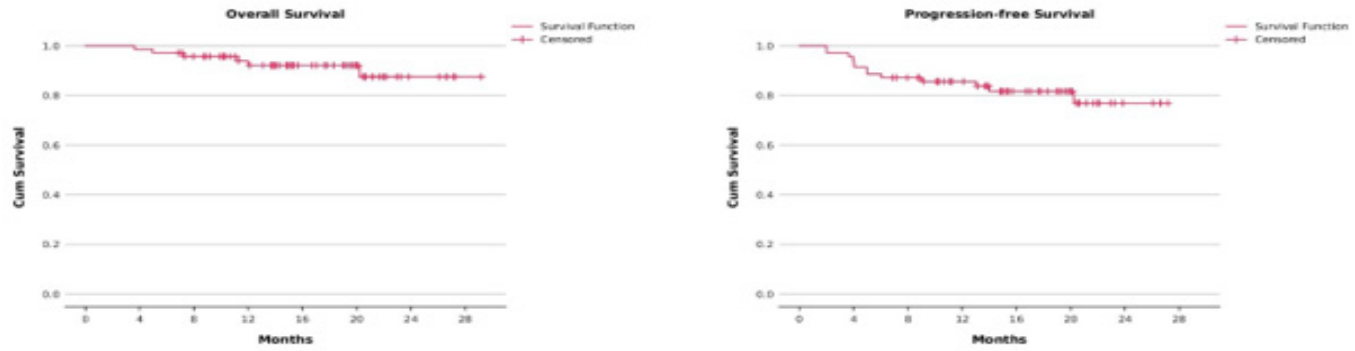


Figure. Kaplan–Meier curves for overall survival (left) and progression-free survival (right)

Table 4. Comparison of treatment response and disease progression according to FISH-defined cytogenetic risk

Parameter	Standard-risk cytogenetics (n=49, 70.0%)	High-risk cytogenetics (n=21, 30.0%)	OR (95% CI)	p
VGPR after the second cycle, n (%)	19 (38.8%)	11 (52.4%)	1.74 (0.62–4.87)	0.307
≥VGPR after the fourth cycle, n (%)	26 (53.1%)	14 (66.7%)	1.77 (0.61–5.14)	0.429
Response after the fourth cycle				
PD, n (%)	2 (4.1%)	2 (9.5%)	—	0.263
PR, n (%)	21 (42.9%)	5 (23.8%)	—	
VGPR, n (%)	26 (53.1%)	14 (66.7%)	—	
Disease progression during follow-up, n (%)	5 (10.2%)	5 (23.8%)	2.75 (0.70–10.77)	0.154

OR: Odds ratio, CI: Confidence interval, PD: Progressive disease, PR: Partial response, VGPR: Very good partial response

of treatment responses after the fourth cycle did not differ significantly between the two cytogenetic risk groups (p=0.263). Disease progression occurred more frequently in the high-risk cytogenetic group than in the standard-risk group (23.8% vs. 10.2%; OR=2.75, 95% CI: 0.70–10.77), although this difference was not statistically significant (p=0.154).

When patients were stratified according to PET/CT metabolic risk (Table 5), those with metabolically high-risk disease had significantly higher VGPR rates after the second treatment cycle (49.1% vs. 15.4%; OR=5.31, 95% CI: 1.08–26.14; p=0.032) and significantly higher ≥VGPR rates after the fourth cycle (64.9% vs. 23.1%; OR=6.17, 95% CI: 1.52–25.01; p=0.011) than patients with metabolically low-risk disease. In addition, the overall response distribution after the fourth cycle differed significantly between the two groups (p=0.005), indicating deeper treatment responses in patients with metabolically high-risk disease. However, the incidence of disease progression did not differ significantly between the metabolically low- and high-risk groups (7.7% vs. 15.8%; OR=2.25, 95% CI: 0.26–19.52; p=0.675).

Table 5. Comparison of treatment response and disease progression according to baseline PET/CT metabolic risk

Parameter	Metabolically low-risk disease (n=13, 18.6%)	Metabolically high-risk disease (n=57, 81.4%)	OR (95% CI)	p
VGPR after the second cycle, n (%)	2 (15.4%)	28 (49.1%)	5.31 (1.08–26.14)	0.032*
≥VGPR after the fourth cycle, n (%)	3 (23.1%)	37 (64.9%)	6.17 (1.52–25.01)	0.011*
Response after the fourth cycle				
VGPR, n (%)	3 (23.1%)	37 (64.9%)	—	
PR, n (%)	10 (76.9%)	16 (28.1%)	—	
PD, n (%)	0 (0%)	4 (7.0%)	—	0.005*
Disease progression during follow-up, n (%)	1 (7.7%)	9 (15.8%)	2.25 (0.26–19.52)	0.675

OR: Odds ratio, CI: Confidence interval, PET/CT: Positron emission tomography/computed tomography, PD: Progressive disease, PR: Partial response, VGPR: Very good partial response. The overall distribution of response categories after the fourth cycle was compared using the two-sided Fisher–Freeman–Halton exact test. *p<0.05

DISCUSSION

This study examined whether baseline metabolic imaging and cytogenetic risk assessment provide complementary information for predicting early therapeutic outcomes in newly diagnosed MM. Although metabolically high-risk patients achieved deeper responses during induction therapy, FISH-defined cytogenetic risk alone was not associated with early response or short-term progression. Female gender remained associated with longer PFS after multivariable adjustment, although this estimate was unstable, whereas ≥VGPR was not significantly associated with PFS.

Baseline 18F-FDG PET/CT has become an important imaging modality for risk stratification in MM because it provides functional information beyond conventional morphologic assessment.[11] Previous studies have demonstrated that a high number of focal lesions, elevated SUVmax, diffuse bone marrow uptake, and extramedullary disease may be associated with inferior survival outcomes.[9,12] In contrast, metabolically high-risk patients in our cohort achieved deeper early responses. High FDG uptake may reflect a large population of viable, metabolically active plasma cells capable of rapid cytoreduction. Conversely, low FDG avidity does not necessarily indicate indolent disease, because low hexokinase-2 expression may result in low-avidity or false-negative PET/CT findings.[13] Metabolically and secretory-active plasma cells may also be more dependent on cellular proteostasis and therefore initially more susceptible to proteasome inhibitor-based treatment, although these pathways were not directly evaluated in our study.[14]

Moreover, rapid response may coexist with aggressive and clonally heterogeneous disease, allowing treatment-resistant subclones to persist despite substantial initial cytoreduction. Previous studies have similarly reported that high-risk patients may be more likely to achieve an early response and that rapid responders may have higher LDH levels and inferior long-term outcomes.[15-17] Therefore, the observed early response may reflect initial treatment sensitivity rather than favorable disease biology.

Despite the superior early response observed in the metabolically high-risk group, progression rates did not differ significantly between the two metabolic risk groups. This apparent dissociation raises the possibility that rapid initial cytoreduction may not translate into durable disease control. In addition, treatment was selected according to clinical judgment rather than assigned within a standardized prospective protocol and could be modified according to the interim response. Therefore, differences in initial treatment selection, regimen intensity, and subsequent response-adapted modifications may have contributed to the observed early response. Longer follow-up and prospective studies using standardized treatment approaches are required to clarify whether this association reflects disease biology, treatment-related factors, or both.

High-risk cytogenetic abnormalities identified by FISH are well-established adverse prognostic factors in MM and are incorporated into current risk stratification systems.[1,18,19] In the present study, patients with high-risk cytogenetics demonstrated numerically higher response rates and a higher frequency of disease progression; however, none of these differences reached statistical significance. The limited sample size and the relatively small number of PFS events are the most likely explanations for these findings. In addition, FISH analysis was performed on unselected bone marrow aspirate samples without CD138-positive plasma cell enrichment. This may have reduced the sensitivity for detecting cytogenetic abnormalities, particularly in samples with a low plasma cell proportion or hemodilution, and may have resulted in some high-risk patients being misclassified as having standard-risk cytogenetics. Such misclassification could have attenuated the observed associations between FISH-defined risk and clinical outcomes.

Female gender was associated with longer PFS in both univariable and multivariable analyses. However, previous studies have reported conflicting results regarding the prognostic effect of gender in MM.[20,21] In our cohort, only one PFS event occurred among female patients, compared with 12 among male patients, resulting in a wide confidence interval around the hazard ratio. Therefore, this estimate is statistically unstable and may overestimate the true association; it should be considered hypothesis-generating, must be interpreted cautiously, and requires confirmation in larger cohorts.

Achievement of a deep response after induction therapy has consistently been associated with improved survival in previous studies.[16,17,22] In our cohort, ≥VGPR after the fourth treatment cycle was not significantly associated with PFS (log-rank p=0.116; multivariable HR=0.42, 95% CI 0.12–1.47, p=0.173), although fewer PFS events occurred among these patients (5/40 vs. 8/30). The limited number of events likely precluded the detection of an association reported in larger studies, and this finding should not be interpreted as evidence for or against a prognostic effect of response depth.

Limitations

Several limitations should be considered when interpreting our findings. The retrospective single-center design and relatively small cohort limit the generalizability of the results. Restricting inclusion to patients with available baseline PET/CT and FISH results may have introduced selection bias. The small metabolically low-risk subgroup (n=13) also reduced the precision of response estimates. These factors may have contributed to the observed association between high metabolic risk and deeper early responses. More importantly, the median follow-up duration was only 15.3 months, with only 13 PFS events (10 progressions and three deaths without progression) and six deaths in total; consequently, median PFS and OS were not reached. The survival analyses, particularly the multivariable Cox regression model, were therefore substantially underpowered and should be considered exploratory. Specifically, the model included six covariates for 13 PFS events, yielding approximately 2.2 events per variable. This low event-to-variable ratio creates a substantial risk of overfitting and unstable effect estimates. Therefore, neither the absence of statistically significant associations nor p values close to 0.05 should be used to draw definitive prognostic conclusions regarding the evaluated PET/CT or cytogenetic variables. Treatment selection was based on clinical judgment, and treatment modifications after the second cycle were frequently guided by the interim response. Therefore, the recorded four-cycle treatment sequence represented a post-baseline, response-dependent variable rather than a uniform baseline covariate. In addition, the small and highly imbalanced treatment subgroups precluded reliable adjustment for treatment regimen in conventional multivariable models. Consequently, residual confounding related to treatment selection and regimen intensity cannot be excluded. In addition, performing FISH without CD138-enriched plasma cell sorting may have reduced the detection of cytogenetic abnormalities and resulted in misclassification of some patients as cytogenetically standard risk. MRD assessment was unavailable and could not be incorporated into the prognostic evaluation. Finally, the metabolic risk classification used in this study was a study-specific composite adapted from previously reported adverse PET/CT features and has not been externally validated. Findings based on this classification should therefore be interpreted as exploratory and require confirmation in independent cohorts.

Despite these limitations, the study also has several strengths. To our knowledge, few studies have simultaneously evaluated FISH-defined cytogenetic risk and a composite metabolic risk classification based on baseline PET/CT findings in relation to early treatment response. Furthermore, all patients underwent baseline PET/CT before treatment initiation, and treatment responses were evaluated using uniform criteria, providing a uniformly assessed real-world cohort.

Our findings suggest that metabolic information obtained from baseline PET/CT may complement conventional cytogenetic risk assessment during the initial treatment period. Although metabolically high-risk disease was associated with a higher likelihood of achieving a deep early response, neither PET/CT metabolic risk nor FISH-defined cytogenetic risk was significantly associated with short-term disease progression. Larger prospective studies with longer follow-up are needed to clarify the combined prognostic value of metabolic imaging and cytogenetic risk assessment in newly diagnosed MM.

CONCLUSION

Baseline PET/CT and FISH-defined cytogenetic risk may provide complementary information during the initial assessment of newly diagnosed MM. Metabolically high-risk disease was associated with deeper early treatment responses but was not significantly associated with short-term disease progression, whereas FISH-defined cytogenetic risk was not associated with early response or progression in this cohort. However, the short follow-up duration and limited numbers of progression and death events preclude definitive conclusions regarding PFS, OS or the independent prognostic value of these variables. Therefore, the survival findings should be considered preliminary and require validation in larger prospective studies with longer follow-up.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Non-interventional Ethics Committee of İzmir City Hospital (Date: 29.04.2026, Decision No: 2026/280).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: MKY; Design: MKY; Control: ZNÖ, OB; Resources: MKY, ÖA, FAY; Materials: MKY, ÖA, FAY; Data Collection and/or Processing: MKY, ÖA, FAY; Analysis and/or Interpretation: MKY; Literature Review: MKY; Writing the Article: MKY; Critical Review: MKY, ÖA, FAY, ZNÖ, OB.

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