REGULAR ARTICLE

blood advances

# Utility of PET/CT in assessing early treatment response in patients with newly diagnosed multiple myeloma

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**Key Points**

- A negative PET/CT signal at 6 months is associated with improved survival outcomes in patients with newly diagnosed MM.
- The PET/CT result at 6 months adds significant prognostic value to the biochemical response.

Multiple myeloma (MM) is a plasma cell malignancy that is characterized by diverse clinical presentations. Although biochemical assessment of disease activity is commonly used to monitor treatment response, findings on magnetic resonance imaging and positron emission tomography (PET)/computed tomography (CT), among other imaging modalities, have proven to harbor prognostic value. We sought to corroborate these findings by examining the prognostic significance of fluorodeoxyglucose PET/CT scanning in the setting of newly diagnosed MM. We retrospectively analyzed 195 patients with a PET/CT available at diagnosis and at 6 months posttreatment to examine their value as an adjuvant metric to conventional hematologic responses in terms of time to next treatment (TTNT) and overall survival (OS). The median TTNT and OS for the entire cohort were 24.6 months (95% confidence interval [CI], 20.4-29.1) and 79 months (95% CI, 63.1-119.1), respectively. When comparing PET/CT negative (−) with PET/CT positive (+) patients, we found significantly prolonged median TTNT (55.2 vs 17.8 months, $P < .0001$) and OS (unreached vs 60.8 months, $P < .0001$) in the former group. We then examined the additive value of PET/CT on the hematologic response achieved at 6 months and found that PET/CT (−) is associated with significantly increased median TTNT and OS for the very good partial response (VGPR) group and the less than VGPR group. Importantly, PET/CT retained prognostic significance after adjusting for multiple other predictive variables. We conclude that a PET/CT (−) at 6 months confers a significant prognostic advantage for patients with newly diagnosed MM and adds significant value to the hematologic response assessment.

## Introduction

Multiple myeloma (MM) is a malignancy of plasma cells that accounts for 1% of all cancers and is the second most common hematologic malignancy after lymphoma. The unique secretory nature of plasma cells allows for accurate disease burden monitoring throughout the disease course, because patients who manage to substantially decrease their monoclonal protein (M-protein) levels enjoy prolonged progression-free survival (PFS) and overall survival (OS).[1] Hematologic response in the posttreatment setting is determined by a combination of the plasma cells in the bone marrow (BM) and the M-protein

Submitted 13 January 2022; accepted 20 February 2022; prepublished online on *Blood Advances* First Edition 2 March 2022; final version published online 29 April 2022. DOI 10.1182/bloodadvances.2022007052.

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level in the blood or urine (by protein electrophoresis and immunofixation). As much as these parameters play an important prognostic role, they are restricted in their ability to account for the entire spectrum of possible MM presentations. For instance, the heterogeneous infiltration of the BM from the malignant clone introduces the possibility of a false-negative interpretation, because blind BM biopsies may miss areas of the skeleton with the greatest burden of disease.[2] In addition, MM exhibits variable secretory and biologic behavior, resulting in many patients having suboptimal trajectories, despite achieving deep conventionally defined hematologic responses.[3,4]

As a result, the International Myeloma Working Group (IMWG) has incorporated imaging in the routine work-up of patients with MM to determine the extent of disease at diagnosis and posttreatment.[5] Acceptable methods include whole-body computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT, which are complementary to the standard disease assessment because they allow for detection of medullary disease and extramedullary disease (EMD), the latter of which is a known adverse prognostic finding in MM.[6,7] Additionally, imaging is the only avenue for monitoring disease in patients with oligosecretory and nonsecretory myeloma.

MRI and $^{18}$F-fluorodeoxyglucose (FDG) PET/CT are sensitive methods for disease assessment in the BM and outside of the marrow (EMD).[8,9] Although very helpful in the initial evaluation of patients with MM, and especially for diffuse BM infiltration, MRI may have difficulty distinguishing residual disease after treatment.[10] PET/CT relies on the combination of morphologic information provided by CT and the functional metabolic information provided by PET. The CT component determines the presence of lytic lesions, generalized osteopenia, fractures, and extramedullary extension of disease. The PET component highlights the metabolic activity of each lesion and, thus, helps to adjudicate the initial extent of BM involvement and the response to therapy, because lytic lesions can remain stable for prolonged periods, despite a good response to treatment. PET/CT results are commonly reported with the standardized uptake values (SUVs), and the lesion with the most intense uptake is noted. Although the maximum SUV (SUVmax) is an important indicator of disease burden, it is still influenced by patient-specific factors (eg, weight), and more standardized methods are needed for accurate comparisons between patients.

At diagnosis, the presence of >3 metabolically active lesions and an SUV >4.2 has been consistently associated with inferior outcomes.[11-13] PET/CT is also relevant in the posttreatment setting, and studies have shown the prognostic significance of decreased metabolic activity after induction therapy (as early as 7 days from the start of treatment).[14,15] This is also true in the posttransplant setting; Kaddoura et al showed significantly increased PFS and OS for patients who achieve a negative PET/CT (−) response near day 100 (12.4 vs 24 months for PFS, $P < .0001$; and 47.2 vs 100 months for OS, $P < .001$).[16] Prognostic significance was also observed for patients undergoing allogeneic stem cell transplantation.[17] Nevertheless, patients are still primarily followed by biochemical methods; despite the general concordance with PFS and OS, unexpected results are often seen. Our study aimed to corroborate these findings and evaluate the additive value of PET/CT in the conventional hematologic response for patients with MM following initial induction treatment.

## Patients and methods

### Patients

This retrospective cohort study included all patients with newly diagnosed MM seen at the Mayo Clinic from 2004 to 2020 who had an FDG PET/CT examination available with radiologic interpretation at baseline and at ~6 months (range, 2-9 months) after diagnosis. Approval for this study was obtained from the Mayo Clinic Institutional Review Board, and informed consent was obtained from all patients for review of their medical records.

First, we assessed the results of both PET/CTs for the entire cohort. Positivity and negativity were reported as per the IMWG guidelines. PET/CT negativity (−) was defined as the disappearance of every area of increased FDG uptake found at baseline, or a decrease in uptake to less than mediastinal blood pool activity, or a decrease in metabolic activity to less than that of surrounding normal tissue. Conversely, patients with residual disease at the 6-month mark were categorized as "progressed," if the PET/CT showed new areas of increased FDG metabolism, or as "positive," if the existing lesions did not entirely disappear. This study included real-world patients with considerable variability in the radiologic interpretations of the scans; as a result, SUVs were not consistently available for analysis. We then determined the hematologic response achieved at the time of the second PET/CT, based on the IMWG response criteria.[5] Complete response (CR) was defined as negative immunofixation in the serum and urine and <5% plasma cells in the BM (for patients who had a BM biopsy at the time of evaluation), in addition to negative electrophoresis in blood and urine. Very good partial response (VGPR) was defined as serum and urine M-protein detectable by immunofixation but not on electrophoresis or >90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours. For patients who did not have an evaluable M-protein at baseline (serum M-spike <1 g/dl, urine M-spike <200 mg/24 hours), serum-free light chains were monitored for disease assessment. Lastly, the percentage of BM plasma cells was used for patients with <10 mg/dl of involved light chain at baseline. CR was defined as <5% of plasma cells in the second BM (BM) biopsy for these patients.

### Statistical analysis

Baseline clinical characteristics were collected for the entire cohort, and comparisons were made for the 2 subgroups [PET/CT positive (+) vs PET/CT (−)] using the Student $t$ test for continuous variables and the $\chi^2$ test for categorical values. The end points of the study were time to next treatment (TTNT), measured from the date of diagnosis to change or intensification of treatment, and OS, measured from the date of diagnosis to death from any cause with censoring performed at the time of the last contact. A Kaplan-Meier model was used to estimate median TTNT and OS and for image production. Statistical significance in TTNT and OS for all tests performed was determined using a 2-sided log-rank test. The Cox proportional-hazards model was used for multivariable analyses, which included known unfavorable risk factors, such as high-risk fluorescence in situ hybridization (FISH), EMD at diagnosis, and high International Staging System (ISS) score, to test for retained prognostic significance of PET/CT at the 6-month mark. All statistical analyses were performed using R version 4.1.1 (R Foundation for Statistical Computing, https://www.R-project.org/). A $P$ value < .05 was used to determine statistical significance.

**Table 1. Baseline characteristics of the entire cohort**

| | Negative PET/CT at 6 mo (n = 50) | Positive PET/CT at 6 mo (n = 145) | Total (N = 195) | *P* |
|---|---|---|---|---|
| **Age, y** | | | | .170 |
| Mean | 59.4 | 61.7 | 61.1 | |
| Median | 59.7 | 61.8 | 61.1 | |
| Range | 28.5-81.8 | 37.2-89.2 | 28.5-89.2 | |
| **Race** | | | | .584 |
| Black | 0 (0.0) | 2 (1.4) | 2 (1.0) | |
| White | 45 (90.0) | 131 (90.3) | 176 (90.3) | |
| Other | 2 (4.0) | 8 (5.5) | 10 (5.1) | |
| **LDH (μ/L)** | | | | .367 |
| Mean | 177 | 204.5 | 197.1 | |
| Median | 147 | 166 | 162 | |
| Range | 52-575 | 84-1507 | 52-1507 | |
| **EMD** | | | | .332 |
| No | 40 (80.0) | 106 (73.1) | 146 (74.9) | |
| Yes | 10 (20.0) | 39 (26.9) | 49 (25.1) | |
| **Sex** | | | | .504 |
| Female | 14 (28.0) | 48 (33.1) | 62 (31.8) | |
| Male | 36 (72.0) | 97 (66.9) | 133 (68.2) | |
| **Serum M-spike (g/dL)** | | | | .876 |
| Mean | 1.5 | 1.5 | 1.5 | |
| Median | 0.7 | 0.6 | 0.6 | |
| Range | 0-6.3 | 0-10.6 | 0-10.6 | |
| **ISS score** | | | | .745 |
| 1 | 18 (40.9) | 59 (44.4) | 77 (43.5) | |
| 2 | 19 (43.2) | 49 (36.8) | 68 (38.4) | |
| 3 | 7 (15.9) | 25 (18.8) | 32 (18.1) | |
| **High-risk FISH** | | | | .406 |
| No | 29 (80.6) | 87 (73.7) | 116 (75.3) | |
| Yes | 7 (19.4) | 31 (26.3) | 38 (24.7) | |
| **Depth of response** | | | | **<.001** |
| CR | 24 (48.0) | 30 (20.7) | 54 (27.7) | |
| non-CR | 26 (52.0) | 115 (79.3) | 141 (72.3) | |
| **Transplant** | | | | **.022** |
| No | 36 (72.0) | 125 (86.2) | 161 (82.6) | |
| Yes | 14 (28.0) | 20 (13.8) | 34 (17.4) | |

Unless otherwise indicated, data are n (%).
LDH, lactate dehydrogenase.
Bold text indicates *P* values with statistical significance at the 95% level.

## Results

We identified 195 patients with MM who underwent PET/CT with radiologic interpretation at diagnosis and at ~6 months after study entry. The median follow-up of the entire cohort was 80.6 months (interquartile range, 49.4-117.2), and the median TTNT and OS following initiation of treatment were 24.6 months (95% confidence interval [CI], 20.4-29.1) and 79 months (95% CI, 63.1-119.1), respectively. The median age at the time of diagnosis was 61 years; 49 (25.1%) patients had EMD (definition included soft tissue masses that did not arise from a known bone lesion and pure EMD [ie, liver, lymph node, renal invasion]) on their initial evaluation, and 38 (24.7%) patients had a high-risk FISH abnormality [del17p, t(4;14), t(14;16), t(14;20), or TP53 deletion]. In our cohort, 137 (70.2%) patients received stem cell transplantation as part of their treatment, but only 34 (17.4%) had their transplant before the second PET/CT examination. Among the entire cohort, the most common regimen used for induction was lenalidomide, bortezomib, and dexamethasone (28.7%), followed by cyclophosphamide, bortezomib, and dexamethasone (22.5%), and lenalidomide plus dexamethasone (22.2%). Most of the remaining patients were exposed to different combinations of an immunomodulator and a proteasome inhibitor. Table 1 summarizes the baseline clinical characteristics of the cohort.

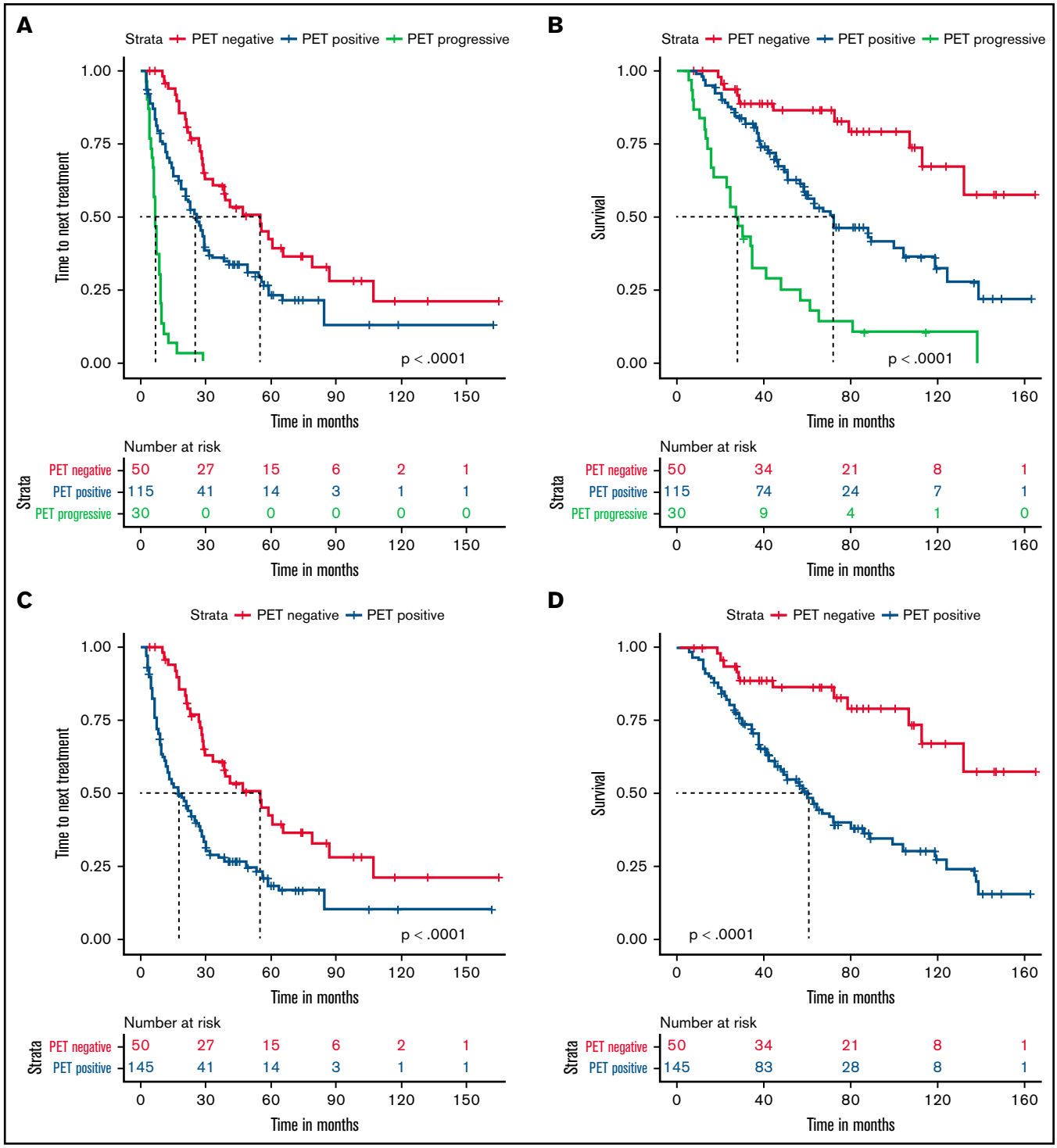


**Figure 1. Kaplan-Meier plots for TTNT and OS comparisons based on PET/CT scan findings for the entire cohort.** TTNT (A) and OS (B) for the entire cohort. TTNT (C) and OS (D) for the entire cohort with PET/CT (+) patients analyzed together.

With regard to PET/CT status, 50 (25.6%) patients had a negative PET/CT at the 6-month mark, and 145 (74.6%) patients had detectable disease, including 30 (15.3%) patients with signs of progression. Diagnostic PET/CT was negative for 8 patients (4.1%). The median interval between the diagnostic and subsequent PET/CT was 5.3 months (interquartile range, 4-7 months). For PET/CT (−) patients, the median interval between the first and second examinations was 6 months,

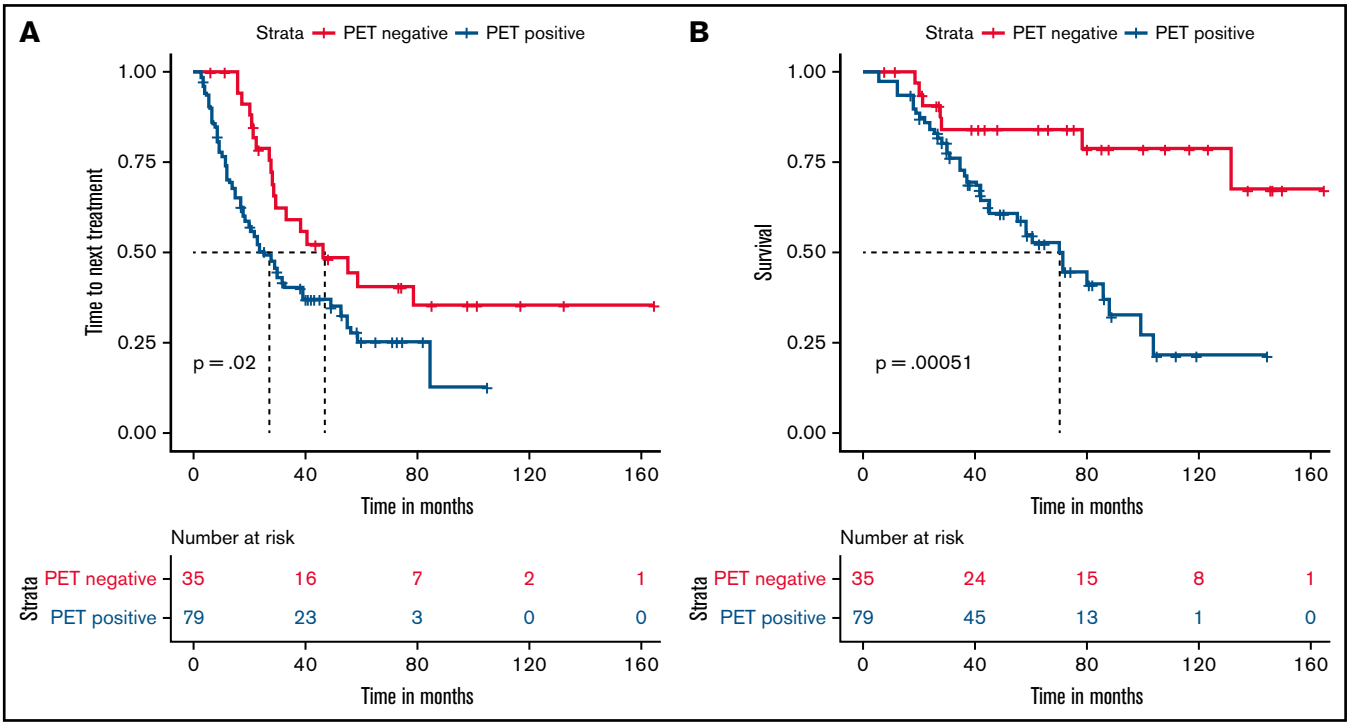


**Figure 2. Kaplan-Meier plots for TTNT and OS comparisons based on PET/CT scan findings for the VGPR or better response group.** TTNT (A) and OS (B) for patients with VGPR or better response.

whereas it was 5 months for PET/CT (+) patients ($P$ = .048). The distribution of the interval between the 2 examinations was as follows: 49 patients had both of their PET/CT examinations within 4 months (7 negative and 42 positive), 94 patients had their PET/CT examinations between 4 and 7 months apart (27 negative and 67 positive), and 52 patients underwent follow-up PET/CT >7 months after the first (16 negative and 36 positive).

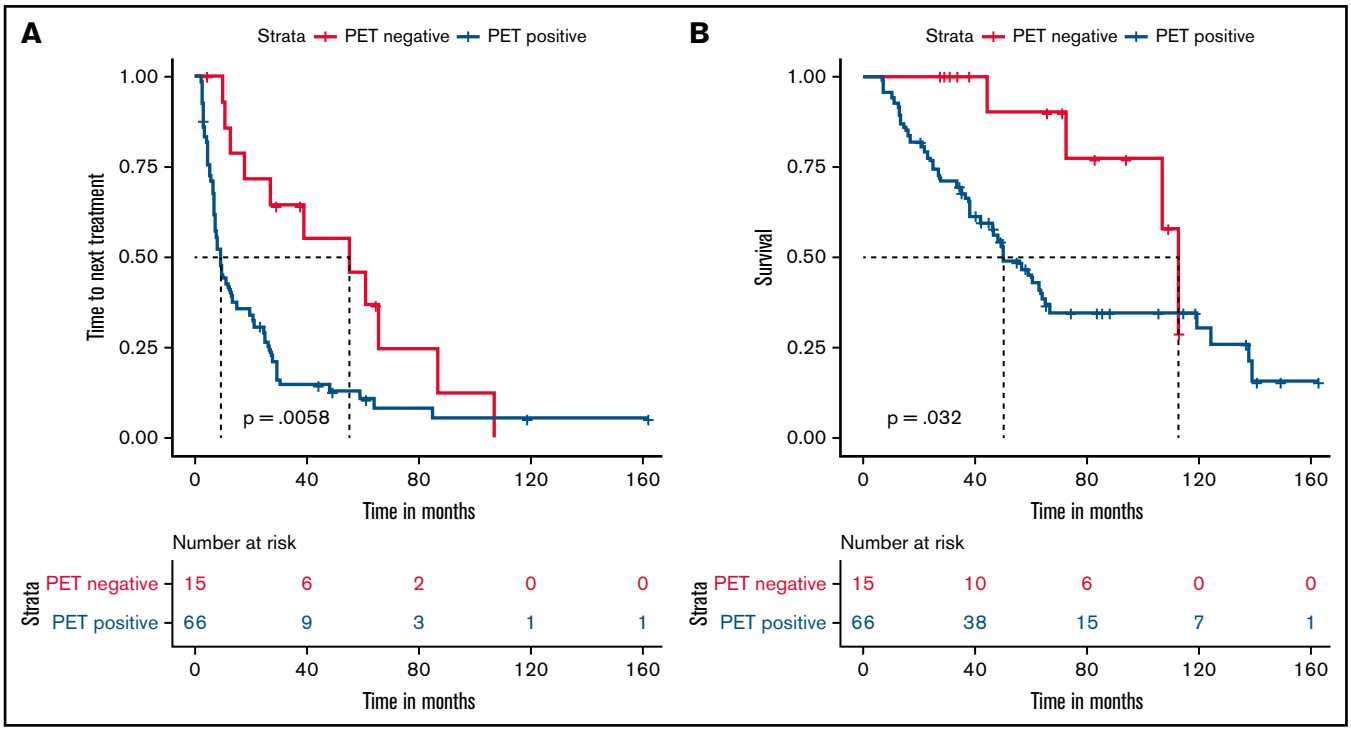


**Figure 3. Kaplan-Meier plots for TTNT and OS comparisons based on PET/CT scan findings for the less than VGPR group.** TTNT (A) and OS (B) for patients with less than a VGPR.

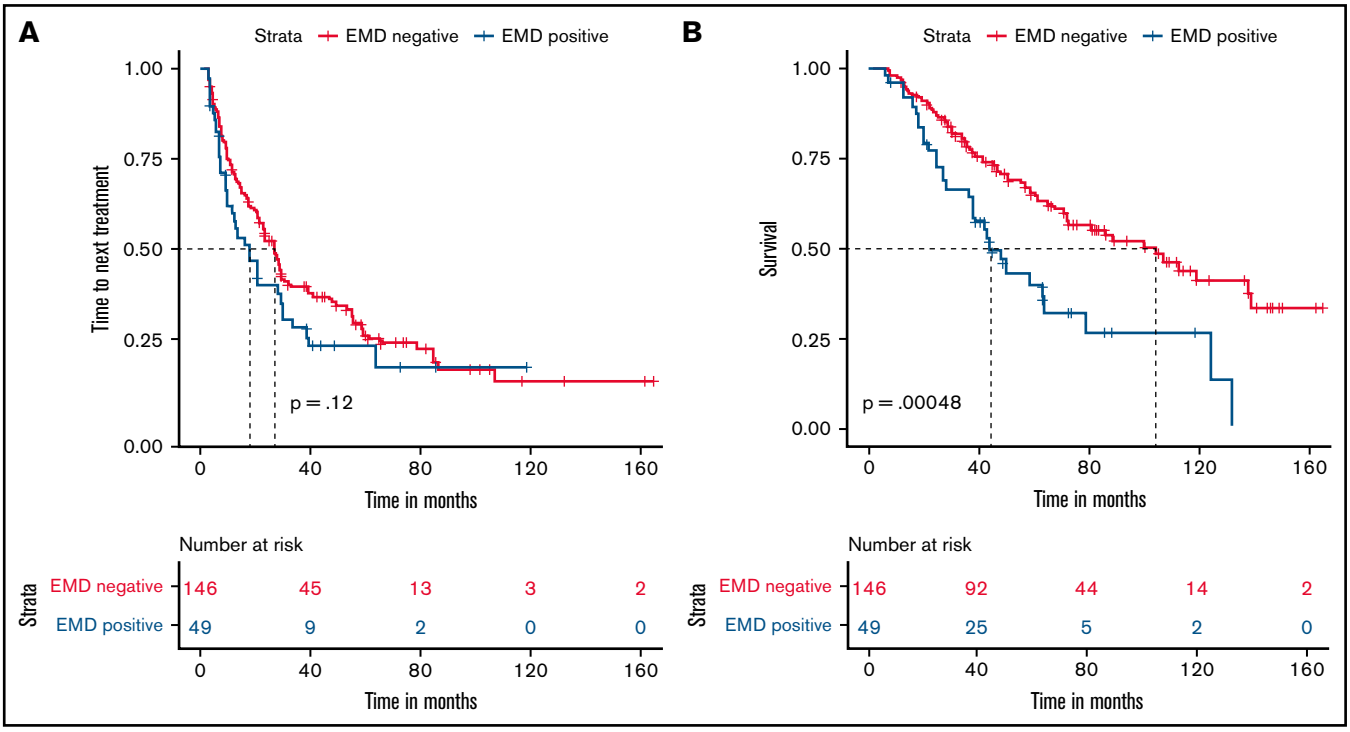


**Figure 4. Kaplan-Meier plots for TTNT and OS comparisons based on the presence of EMD at diagnosis.** TTNT (A) and OS (B) for patients with EMD at diagnosis.

PET/CT (−) at 6 months was associated with significantly prolonged median TTNT (55.2 months) compared with PET/CT (+) (25.1 months) and PET/CT with signs of progression (7 months) ($P < .0001$). Similarly, PET/CT (−) patients had unreached median OS compared to 72 and 27.7 months for PET/CT (+) and PET/CT progressive, respectively ($P < .0001$). When comparing PET/CT (−) and all PET/CT (+) patients (including those with progression), the same significant association was seen (55.2 vs 17.8 months for median TTNT, $P < .0001$; and unreached vs 60.8 months for median OS, $P < .0001$, respectively) (Figure 1).

Upon evaluation of the additive value of PET/CT (−) to the conventional biochemical criteria, we found that among the 54 (27.7%) patients who had attained a CR at the time of the second PET/CT, 24 were PET/CT (−) and 30 were PET/CT (+). Of note, the patients who experienced a CR and negative PET/CT had a prolonged TTNT and a significantly prolonged OS compared with those who only had a hematologic response (58.9 vs 39.2 months for TTNT, $P = .27$; unreached vs 72 months for OS, $P = .01$).

We then analyzed the patients who achieved a VGPR or better at the 6-month evaluation. Of these, 35 were PET/CT (−) and 79 were PET/CT (+). Significant results were seen for TTNT and OS. PET/CT (−) patients had a median TTNT of 46.9 months compared with 26.9 months for PET/CT (+) patients ($P = .02$). In terms of OS, PET/CT (−) patients did not reach median survival compared with 70.6 months for PET/CT (+) patients ($P = .00051$) (Figure 2).

The patients who did not achieve a VGPR or better were analyzed together for TTNT and OS. Notably, of the 81 (41.5%) patients who did not achieve a deep hematologic response, 15 (18.5%) had a negative PET/CT examination (4 had a negative PET/CT at diagnosis). These patients had a median TTNT of 55.2 months and a median OS of 112.7 months compared with 9.5 months and 50.4 months for the PET/CT (+) group ($P = .0058$ and $P = .032$, respectively) (Figure 3).

Upon evaluation of baseline characteristics that have an unfavorable effect on disease prognosis, a focused analysis on the presence of EMD showed significant difference in OS but not TTNT. More specifically, for the 49 (25.1%) patients with an extramedullary component on their initial PET/CT examination (definition included bone-related and unrelated lesions), the median TTNT was 17.9 months and 27 months for EMD-positive and EMD-negative patients, respectively ($P = .12$). In terms of OS, EMD-negative patients enjoyed a median difference of 60 months (104.2 vs 44.4 months for the negative and positive groups, respectively; $P = .00048$) (Figure 4).

Finally, we conducted a multivariable analysis adjusting for multiple risk factors associated with inferior outcomes in MM (presence of EMD, PET/CT response, ISS score, lack of CR, and high-risk FISH profile). In the model, we also included potential confounders: timing of the second PET/CT (a PET/CT at 8 months could be more predictive than a PET/CT at 3 months, because the latter may represent early posttreatment changes rather than true residual disease) and allogeneic stem cell transplantation before the second PET/CT. The results retained prognostic significance for PET/CT for TTNT and OS. More specifically, patients with a positive PET/CT at 6 months had a hazard ratio (HR) of 1.7 (95% CI, 1.02-2.9) for TTNT; an ISS score of 3 (HR, 1.99; 95% CI, 1.18-3.4), failure to achieve CR (HR, 2.41; 95% CI, 1.37-4.2), and a high-risk FISH abnormality (HR, 1.67; 95% CI, 1.05-2.7) also demonstrated prognostic significance. For OS, PET/CT (+) had an HR of 3.26 (95% CI, 1.35-7.9) and

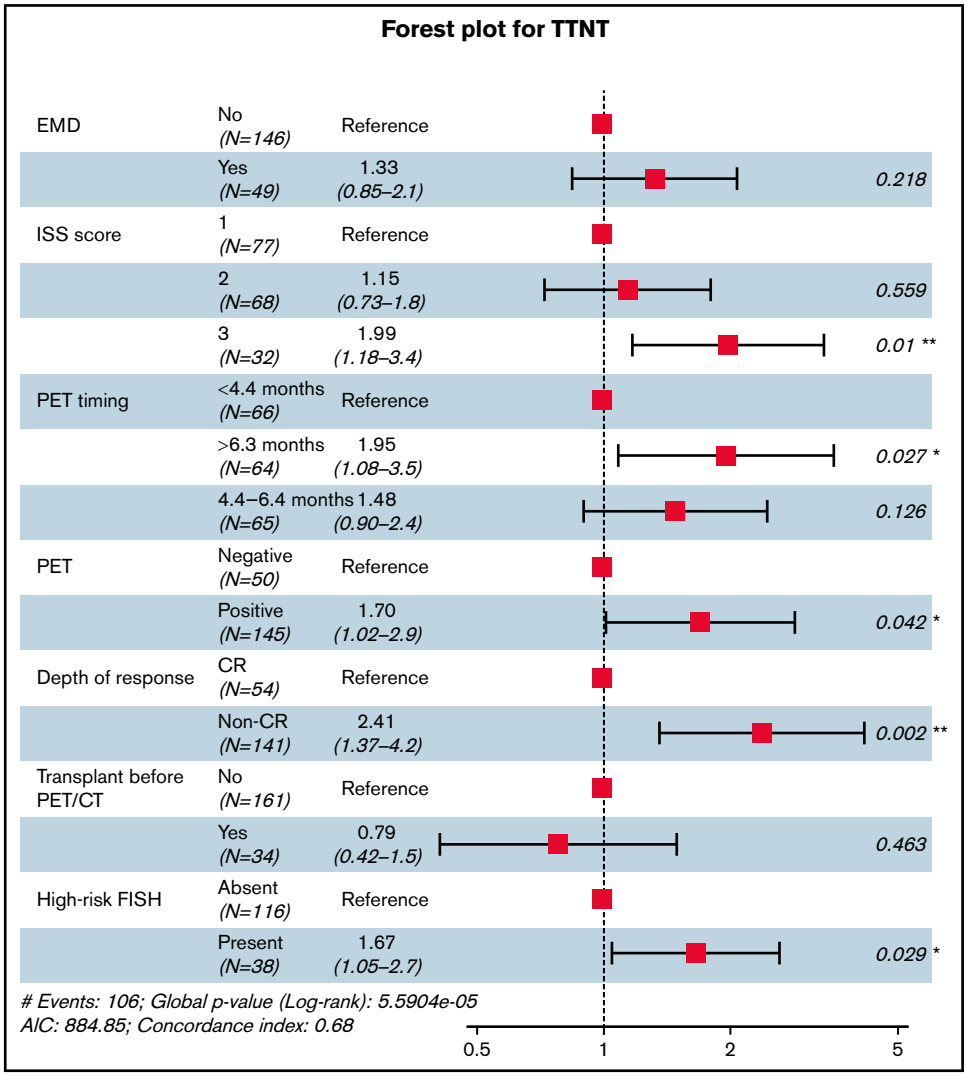


**Figure 5. Multivariable Cox regression analysis for TTNT.** * indicates significance in the 95% level. ** indicates significance in the 99% level. AIC, Akaike information criterion.

high-risk FISH abnormalities had an HR of 2.01 (95% CI, 1.18-2.4) (Figures 5 and 6).

## Discussion

The aim of this study was to assess the prognostic significance of PET/CT examinations at 6 months following induction therapy. In addition, we wanted to evaluate the additive value of PET/CT plus conventional IMWG criteria for hematologic response and raise the question of whether modification of treatment may be warranted based on imaging results. We hypothesized that patients with a complete metabolic response on PET/CT would have prolonged TTNT and OS compared with the patients who remained stable or had a moderately reduced uptake.

Indeed, we showed that PET/CT (−) was associated with significantly prolonged median TTNT and significantly prolonged median OS compared with patients who were PET/CT (+) and those who had PET/CT with evidence of progression. Comparison of PET/CT (−) and all PET/CT (+) patients (including those with progressive disease) yielded the same significant association between the 2 groups for TTNT and OS. We also assessed the prognostic impact in different subgroups, according to the hematologic response achieved at 6 months. Among the subset of patients with a VGPR or better response, we found significantly prolonged TTNT and OS for those who had a negative PET/CT compared with those with a positive PET/CT. The same results applied to the patients who had less than a VGPR; PET/CT (−) patients experienced significantly prolonged TTNT and OS. Importantly, these results identify true PET/CT improvement in the posttreatment setting, because only 8 (4.1%) patients in the entire cohort had a negative PET/CT at baseline. The prognostic significance of PET/CT for TTNT and OS was retained when multiple known risk factors for unfavorable outcomes were analyzed with the multivariable Cox regression model. For this analysis, we also adjusted for the time interval between diagnosis and the second PET/CT to eliminate the confounding effect of early posttreatment changes vs true residual disease. Herein, we demonstrate that the concurrent assessment of hematologic and

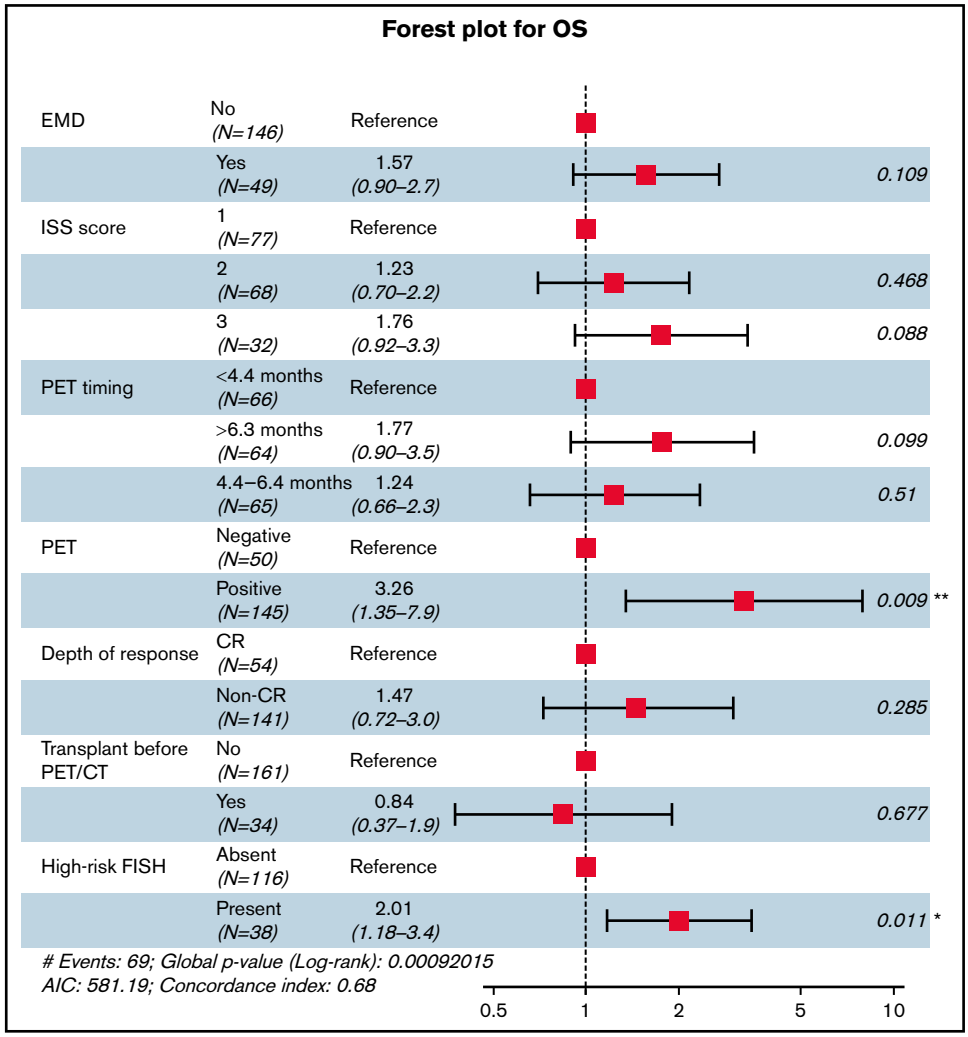


**Figure 6. Multivariable Cox regression analysis for OS.** * indicates significance in the 95% level. ** indicates significance in the 99% level. AIC, Akaike information criterion.

imaging response is relevant in the posttreatment setting for patients with MM, because biochemical information can be significantly improved.

Heterogeneity in the biological background and the clinical presentation of MM dictates a multidimensional approach in disease assessment at diagnosis and at subsequent follow-up. The comprehensive nature of the whole-body PET/CT evaluation can address multiple disease-monitoring lapses for patients with MM and justifies some discrepancies between hematologic and imaging responses. For instance, as also shown in previous studies,[12,18] differences in OS for patients with CR can be explained by the patchy pattern of malignant plasma cell infiltration into the BM.[19] As a result, blind BM biopsies often miss the niche with the highest plasma cell population, leading to falsely reassuring results and inferior outcomes. PET/CT identifies areas with the highest metabolic activity in the BM and also depicts EMD. Although the typical secretory nature of plasma cells adds an easy-to-measure systematic component for disease monitoring (M-protein and/or serum-free light chain measurement from blood samples), our results, along with those of other studies, suggest inconsistent outcomes with varying levels of concordance between imaging and biochemical responses.[16,20,21] These results highlight the diverse secretory behavior of plasma cells, which is especially relevant when early posttreatment changes preferentially alter the secretory kinetics of the malignant clone, when there may still be metabolically active disease detected by PET/CT.

Despite the clear implications of PET/CT for disease prognostication in MM, certain shortcomings need to be addressed. First, PET/CT has limited resolution for detecting FDG-avid lesions that are <5 mm, which may be important in the posttreatment setting.[22] Second, although PET/CT is very sensitive for monitoring focal lesions and detecting EMD, the sensitivity for diffuse marrow infiltration is lower compared with MRI, which may underestimate the disease burden for these patients. A particular limitation for MM is that a small subgroup of patients may not express the glucose transporters that are needed for radiotracer uptake and, thus, have a false-negative FDG PET/CT.[22] A misleading lack of uptake can also be seen in patients who express low levels of hexokinase-2, which catalyzes the first step in the glycolytic pathway.[23] Lastly, lack of standardization has been a major limitation for accurate disease quantification. Although standardized prognostic factors have been identified (eg, presence of >3

focal lesions at diagnosis, SUV >4.2), there is still little consistency in current reporting. A recent study validated the Deauville score, initially used for lymphoma, as an important prognostic indicator, and, hopefully, future studies incorporate more standardized approaches in PET/CT interpretation.[24,25]

Our study had several unique features that warrant further exploration. Because our cohort consisted of patients with an available PET/CT examination at diagnosis and at 6 months, we identified a high number of PET/CT (+) results at baseline (95.8%) and in the subsequent evaluation (74.3%). Most of these patients had a high burden of bone disease at baseline, a factor with known adverse implications for MM.[26] In addition, we found a higher proportion of patients with EMD (25.1%) compared with what is commonly reported in the literature, with OS being significantly reduced in this subset of patients.[27] Interestingly, when comparing the patients who were PET/CT (−), we found that the VGPR-or-better group and the less-than-VGPR group had comparable median TTNT: 46.9 vs 55.2 months, respectively ($P = .3$). The same results were true for median survival in PET/CT (−) patients; those with VGPR or better did not reach median survival vs 113 months in the less-than-VGPR group ($P = .5$). Although this finding again highlights the prognostic significance of a negative PET/CT, the small number of patients who were PET/CT (−) and had less than a VGPR might have had a considerable effect on the result.

Our study had several limitations. First, the retrospective nature of the study design has its inherent biases. For instance, there is possible selection bias for patients who received diagnostic and posttreatment PET/CT examinations, because this population may represent a high-risk subgroup with more aggressive biologic behavior and, thus, inferior outcomes. This is reflected in the shortened TTNT and OS observed in our study patients compared with all patients with myeloma who were treated at our institution from 2004 to 2018.[28] We tried to address this bias via our multivariable analysis, which included several risk factors. As mentioned above, because of the nonstandardized reporting of PET/CT results and the inconsistency of available SUVs, we could not precisely quantitate the metabolic activity of the PET/CT. As a result, we were not able to further delineate the recently validated Deauville criteria for MM or objectively compare SUVs between the 2 PET/CTs. There was a similar constraint in evaluating minimal residual disease in our cohort of patients who achieved CR, because the majority did not have BM biopsies assessed at that level of sensitivity. Lastly, there was significant variability in the treatment regimens that patients had been exposed to at the 6-month mark, which might have produced further heterogeneity in the outcomes.

Our study highlights the role of PET/CT in the evaluation of patients with MM in the posttreatment setting. We showed that PET/CT can consistently improve the definition of biochemical responses, as defined by the IMWG, especially for patients with skeletal involvement at diagnosis. Prognostic significance was also seen in multivariable analyses of TTNT and OS, with an independent association for both primary outcomes. In conclusion, we demonstrate that PET/CT could be incorporated into the posttreatment evaluation of patients with newly diagnosed MM, because it adds crucial prognostic information to the biochemical assessment.

## Acknowledgment

The authors thank the Mayo Clinic Hematological Malignancies Program.

## Authorship

Contribution: S.K.K. and C.C. designed the study, collected and analyzed data, and wrote the manuscript and U.G., S.M.B., D.D., P.K., M.A.G., M.Q.L., A.D., S.R.H., F.B., L.H., N.L., Y.L., W.I.G., T.V.K., R.W., A.F., M.H., M.B., R.A.K., S.V.R., and S.K.K. managed patients and revised and approved the final version of the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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