Evaluation of the Survival Outcomes of Multiple Myeloma Patients According to their Plasmacytoma Presentation at Diagnosis

Rafiye Ciftciler¹, Hakan Goker¹, Haluk Demiroglu¹, Salih Aksu¹, Nilgun Sayınalp¹, İbrahim C. Haznedaroğlu¹, Umit Yavuz Malkan², Yahya Buyukakşık¹, Osman Ozçebê¹

¹Hacettepe University Faculty of Medicine, Department of Hematology, Ankara, Turkey
²Diskapi Education and Research Hospital, Department of Hematology, Ankara, Turkey

Correspondence to: Rafiye Ciftciler, Departments of Hematology, Hacettepe University Faculty of Medicine, Ankara, Turkey.
E-mail: rafiyesarigul@gmail.com

14 February 2019
12 December 2019

Abstract
Objective: Multiple myeloma (MM) associated with extramedullary (EM) plasmacytoma has a poor therapeutic response and poor outcomes when treated with conventional chemotherapy. EM plasmacytoma is divided into two groups: the first group comprised tumors that are extending directly from osteolytic bone lesions (EM-B, bone-related), while the second results from plasmacytoma infiltration into soft tissues, with no relationship to the bone (EM-S, soft tissue-related). This study aimed to compare the general characteristics and survival outcomes of transplant eligible MM patients who had EM-S or EM-B and MM patients who did not have plasmacytoma at the time of diagnosis.

Materials and Methods: This study has been performed in a retrospective manner. The MM patients who were treated at our tertiary care center between January 2003 and January 2017 were evaluated retrospectively for the presence of a plasmacytoma at diagnosis.

Results: There were 141 (78.3%) MM patients who did not have plasmacytoma, 22 (12.2%) MM patients who had EM-B and 17 (9.4%) MM patients who had EM-S at the time of diagnosis in this study. The 5-year OS was 63% in patients who had bone EM-B, 63% in patients who had EM-S and 80% in patients who did not have plasmacytoma, respectively (p=0.02). The 5-year DFS was 47% in patients who had EM-B, 35% in patients who had EM-S and 54% in MM patients who did not have plasmacytoma, respectively (p=0.15).

Conclusion: In conclusion, these finding make us to suggest that MM patients who had EM plasmacytoma at the time of diagnosis had poor prognosis than patients without
plasmacytoma, even if ASCT was performed. The presence of EM involvement negatively affects survival outcomes.

**Keywords:** Multiple myeloma, bone related plasmacytoma, soft tissue related plasmacytoma

**Introduction**
Multiple myeloma (MM) is defined by the proliferation of neoplastic plasma cells in the bone marrow accompanied by various clinical manifestations including lytic bone lesions, anemia, hypercalcemia, renal function impairment and recurrent infections (1). EM plasmacytoma is divided into two groups: the first group comprised tumors that are extending directly from osteolytic bone lesions (EM-B, bone-related), while the second results from plasmacytoma infiltration into soft tissues, with no relationship to the bone (EM-S, soft tissue-related). EM plasmacytoma can develop in an association with MM or as an isolated form. EM plasmacytoma has been reported in 15–20% of MM patients at the time of diagnosis and develops in 15% of patients during the course of the disease (2). EM-S plasmacytoma and EM-B plasmacytoma are different in terms of their location, tumor progression and survival outcomes. EM plasmacytoma that accompanies MM differs from solitary EM plasmacytoma (3).

MM associated with EM plasmacytoma has a poor therapeutic response and poor outcomes when treated with conventional chemotherapy (4). This study aimed to compare the general characteristics and survival outcomes of MM patients who had EM-S plasmacytoma or EM-B plasmacytoma and MM patients who did not have plasmacytoma at the time of diagnosis.

**Materials and Methods**

**Study Design and Data Collection**
This study has been performed in a retrospective manner. Demographic data of the patients, diagnosis and treatment data of the patients were obtained from hospital database. As a result of application standards of the hospitals of Hacettepe Medical School, it has been recognized from the patient records that all of the studied patients had given informed consents at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standards of care.

**Patients and Disease Characteristics**
The MM patients who were treated at our tertiary care center between January 2003 and January 2017 were evaluated retrospectively for the presence of a plasmacytoma at diagnosis. In this study, 21.6% of the 180 patients who underwent autologous stem cell transplantation (ASCT) consisted of patients with plasmacytoma at the time of diagnosis and bone marrow involvement. The patients without plasmacytoma were patients only with bone marrow involvement but no plasmacytoma at the time of diagnosis. The presence of EM disease was diagnosed in most cases by magnetic resonance imaging (MRI), computed tomography (CT) scan or positron emission tomography (PET) which were carried out whenever an EM spread of disease was suspected on the basis of clinical or radiographic findings. Plasmacytoma was diagnosed by pathological examination in 30 (79.4%) out of 39 patients with plasmacytoma findings on CT, MRI or PET.

The patients who underwent ASCT were divided into three groups such as MM with EM-S plasmacytoma, MM with EM-B plasmacytoma and MM with no plasmacytoma at the time of diagnosis. All cases were included following EM plasmacytoma assessment at diagnosis and no relapse cases were not included. All patients underwent ASCT after receiving 6-8 courses of induction chemotherapy. Patients received VCD (bortezomib/cyclophosphamide/dexamethasone), VD (bortezomib/dexamethasone) or VAD (vincristine, doxorubicin and dexamethasone) as induction therapy. Patients who were not
eligible for transplantation and patients who received more than one ASCT were excluded from the study. Response was determined according to the current International Myeloma Working Group response criteria (5). Cytogenetic data were available only in a minority of patients and were not considered in this analysis.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 25. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorow-Simirnov/Shapiro-Wilk’s test) to determine whether they are normally distributed or not. One way ANOVA was used to compare parameters using means and standard deviations for normally distributed. Kruskal-Wallis test was used to compare parameters for non-normally distributed. Survival analyses were made using Kaplan-Meier test. Multivariate analysis of predictors of survival was performed using Cox regression test. Parameters with P values ≤0.15 in univariate tests were included in the multivariate analysis. P values <0.05 were considered to indicate statistical significance.

Results

Patient Characteristics

A total of 180 MM patients who underwent ASCT were included into the study between 2003 and 2017. Patient characteristics are summarized in Table 1. There were 141 (78.3%) patients who did not have plasmacytoma, 22 (12.2%) patients who had EM-B plasmacytoma and 17 (9.4%) patients who had EM-S plasmacytoma at the time of diagnosis. There were 113 (62.8%) males and 67 (37.2%) females with a median age of 57 (range, 35–72) years at the time of diagnosis. The number of patients classified with Eastern Cooperative Oncology Group performance status (ECOG PS) at diagnosis 0, 1, 2 and 3 were 27 (15.0%), 86 (47.8%), 55 (30.6%) and 12 (6.7%), respectively. There was no statistically significant difference between three groups in ECOG PS (p=0.13) (6). Ninety-five (52.8%) patients received VAD, 51 (28.3%) patients received VCD and 34 (18.9%) patients received VD as induction chemotherapy (p=0.29). No statistically significant difference was found between the three groups in terms of gender (p=0.36). The ISS staging (p=0.35) of all three groups were similar. Serum hemoglobin (Hb) (p=0.43), platelet (PLT) (p=0.25), calcium (p=0.72), LDH (p=0.32) and creatinine level (p=0.88) at diagnosis showed no statistically significant difference between three groups. Lytic bone lesions were higher with a statistical significance in patients who had EM-B or EM-S plasmacytoma (p=0.004) than in patients who did not have plasmacytoma. Radiotherapy was performed to more patients who had EM plasmacytoma than patients who did not have plasmacytoma (p=0.001). There was no statistically significant difference between the three groups in terms of MM types (p=0.64). Sites involved were soft tissues surrounding the axial skeleton in 76.4% (n=13 patients) of cases. Plasmacytomas of breast (n=1, 5.9%), spleen (n=1, 5.9%), oral cavity (n=1, 5.9%) and skin (n=1, 5.9%), accounted for 23.5% of cases. EM-B plasmacytomas were located in the vertebrae (n=14, 63.6%), ribs (n=1, 4.5%), sternum (n=2, 11.7%), clavicular (n=2, 11.7%), and pelvis (n=3, 13.6%). Median number of involved sites of plasmacytoma was 1 (1-5) for patients who had EM plasmacytoma.

Disease status after induction chemotherapy was similar between three groups (p=0.41). However, disease status after ASCT was better in patients without plasmacytoma than in patients with EM-B and EM-S plasmacytoma (p=0.002). Relapse rate (p=0.01) and mortality rate (p<0.001) were higher with a statistical significance in patients who had EM-B or EM-S plasmacytoma than in patients who did not have plasmacytoma.

Overall Outcomes

The median follow-up period was 39.3 months (range, 4.2-178.9 months) for the entire group. The 3-year OS was 85% in patients who had EM-B plasmacytoma, 74% in patients who had EM-S plasmacytoma and 95% in MM patients who did not have plasmacytoma, respectively.
The 5-year OS was 63% in patients who had EM-B plasmacytoma, 63% in patients who had EM-S plasmacytoma and 80% in patients who did not have plasmacytoma, respectively (p=0.02) (Figure 1).

The 3-year DFS was 81% in patients who had EM-B plasmacytoma, 56% in patients who had EM-S plasmacytoma and 81% in patients who did not have plasmacytoma, respectively. The 5-year DFS was 47% in patients who had EM-B plasmacytoma, 35% in patients who had EM-S plasmacytoma and 54% in patients who did not have plasmacytoma, respectively (p=0.15) (Figure 1).

The 3-year OS was 76% in patients with EM plasmacytoma at diagnosis who received VD, 80% in patients who received VCD and 83% in patients who received VAD as induction chemotherapy, respectively. The 5-year OS was 61% in patients with EM plasmacytoma at diagnosis who received VD, 80% in patients who received VCD and 59% in patients who received VAD as induction chemotherapy, respectively (p=0.89). (Figure 2).

The 3-year DFS was 76% in patients with EM plasmacytoma at diagnosis who received VD, 60% in patients who received VCD and 78% in patients who received VAD as induction chemotherapy, respectively. The 5-year OS was 29% in patients with EM plasmacytoma at diagnosis who received VD, 30% in patients who received VCD and 35% in patients who received VAD as induction chemotherapy, respectively (p=0.82). (Figure 2).

**Cox Regression Analysis**

In univariate analyses the factors that affected OS were age of the patients (≤57 years) (p=0.05) and absence of plasmacytoma at diagnosis (p=0.01) as shown in Table 2. Cox regression analysis revealed that the absence of plasmacytoma at diagnosis (p=0.01) as the only parameter to predict OS.

In univariate analyses the factors that affected DFS were age of the patients (≤57 years) (p=0.01), receiving RT (p=0.05) and ISS of the disease (p=0.12). Cox regression analysis revealed that age of the patients (≤57 years) (p=0.03) as the only parameter to predict DFS. Median age of 57 was used in the cox regression analysis because the median age of the whole group was 57 years.

**Discussion**

Focal infiltration by monoclonal plasma cells in the absence of systemic disease can be observed as solitary plasmacytoma. EM plasmacytoma can also develop with systemic disease (1). EM plasmacytoma has been defined to occur in up to 15–20% of MM patients at the time of diagnosis. Additionally it develops in 15% of patients during the course of the disease (7). In this study, the survival outcomes MM patients who underwent ASCT were evaluated according to the plasmacytoma presentation at diagnosis. Plasmacytoma was detected at the time of diagnosis in 21.6% of all patients. While 12.2% of the patients had EM-B plasmacytoma, 9.4% of them had EM-S plasmacytoma. This study showed that patients who did not have any plasmacytoma had better OS than patients who had EM-B or EM-S plasmacytoma. In multivariate analyzes, the only parameter predicting OS was the absence of plasmacytoma at diagnosis. Additionally, DFS was better in patients without plasmacytoma than patients with EM plasmacytoma. However, there was no statistically significant difference in DFS for all three groups.

In a time dependent analyses Varettoni et al. showed that the presence of EM involvement at any time during the course of disease is associated with shorter OS and DFS, even after adjusting for age, sex, and stage (8). MM with EM plasmacytoma showed significant differences from the rest of the MM population as regards age, sex, MM subtype, disease stage, and prior history of MGUS. In addition, patients who developed EM spread during follow-up showed significantly lower hemoglobin and M-protein and higher LDH levels compared with patients with EM disease at diagnosis (8). Another study reported that patients
with MM with EM-B and EM-S plasmacytoma, the disease had an aggressive course, with a median OS of 15 months (9). There are few studies focusing on treatment of MM patients with EM disease. Some clinical reports indicate a low efficacy of thalidomide on EM disease (10, 11), while bortezomib seems more promising in this setting (12, 13). Wu et al. evaluated the outcomes of newly diagnosed MM with and without EM plasmacytomas and reported that the presence of EM plasmacytomas at diagnosis was associated with poor prognosis in patients treated with conventional chemotherapy. However, patients treated with high-dose melphalan followed by ASCT had similar outcomes, regardless of the presence or absence of EM plasmacytomas (14). Lee et al. showed that the negative impact of EMPs was significant on OS (p=0.007) and nearly significant on DFS (p=0.054) among the patients who was not eligible for ASCT (15). On the other hand, some studies showed that there was no statistically significant difference in survival outcomes in patients with MM with or without EM plasmacytoma at diagnosis who received ASCT after chemotherapy. These studies reported that ASCT can succeed in dealing with the negative prognostic effect of EM plasmacytomas at time of diagnosis with MM (8, 16). In this study, although all patients underwent ASCT, survival outcomes of patients with EM were worse than patients without EM plasmacytoma at diagnosis. When we look only in patients with EM plasmacytoma, there was no significant difference in OS and DFS between VAD, VCD or VD as induction chemotherapy.

Our study had a few limitations. The lack of data regarding the cytogenetic features of the patients is the major limitation of this study. Additionally, all patients were not received the same chemotherapy before ASCT. In our study, as in other studies, it is clear that patients with EM plasmacytoma have a poor prognosis. In the era of highly active new anti-myeloma regimens, further trials are needed to determine the effect of MM presenting with EM plasmacytoma, preferably with higher patient numbers and longer follow up. In conclusion, these finding make us to suggest that MM patients who had EM plasmacytoma at the time of diagnosis had poor prognosis than patients without plasmacytoma, even if ASCT was performed. The presence of EM involvement negatively affects survival outcomes.

Conflict of Interests
The authors of this paper have no conflict of interests, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Role of the funding source
None.

Ethical approval: All of the ethical considerations had been strictly followed in accordance with the 1964 Helsinki declaration. As a standard care/action of the hospitals of the Hacettepe Medical School, it has been recognized from the patient records that all of the studied patients had given informed consents at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standard of care.

References


<table>
<thead>
<tr>
<th>Parameters</th>
<th>MM without plasmacytoma</th>
<th>MM with EM-B plasmacytoma</th>
<th>MM with EM-S plasmacytoma</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>141 (78.4%)</td>
<td>22 (12.2%)</td>
<td>17 (9.4%)</td>
<td></td>
</tr>
<tr>
<td>Age (range)</td>
<td>57 (37-72)</td>
<td>59 (36-67)</td>
<td>50 (35-67)</td>
<td>0.47</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------</td>
</tr>
<tr>
<td>Sex (male/female) (%)</td>
<td>85/56 (60.3%/39.7%)</td>
<td>15/7 (68.2%/31.8)</td>
<td>13/4 (76.5%/23.5%)</td>
<td>0.36</td>
</tr>
<tr>
<td>ISS</td>
<td></td>
<td></td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>ISS-I (%)</td>
<td>26 (18.4%)</td>
<td>3 (13.6%)</td>
<td>1 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>ISS-II (%)</td>
<td>43 (30.5%)</td>
<td>6 (27.3%)</td>
<td>3 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>ISS-III (%)</td>
<td>72 (51.1%)</td>
<td>13 (59.1%)</td>
<td>13 (76.5%)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS (0-3)</td>
<td></td>
<td></td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>0 (%)</td>
<td>21 (14.9%)</td>
<td>4 (18.2%)</td>
<td>2 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>1 (%)</td>
<td>75 (53.2%)</td>
<td>7 (31.8%)</td>
<td>4 (23.5%)</td>
<td></td>
</tr>
<tr>
<td>2 (%)</td>
<td>37 (26.2%)</td>
<td>9 (40.9%)</td>
<td>9 (52.9%)</td>
<td></td>
</tr>
<tr>
<td>3 (%)</td>
<td>8 (5.7%)</td>
<td>2 (9.1%)</td>
<td>2 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>Type of the MM</td>
<td></td>
<td></td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td>Ig G kappa (%)</td>
<td>50 (35.5%)</td>
<td>9 (40.9%)</td>
<td>5 (29.4%)</td>
<td></td>
</tr>
<tr>
<td>Ig G lambda (%)</td>
<td>29 (20.6%)</td>
<td>3 (13.6%)</td>
<td>2 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>Ig A kappa (%)</td>
<td>19 (13.5%)</td>
<td>4 (18.2%)</td>
<td>2 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>Ig A lambda (%)</td>
<td>10 (7.1%)</td>
<td>2 (9.1%)</td>
<td>1 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Ig D lambda (%)</td>
<td>1 (0.7%)</td>
<td>1 (4.5%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ig M kappa (%)</td>
<td>1 (0.7%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Kappa light chain (%)</td>
<td>15 (10.6%)</td>
<td>3 (13.6%)</td>
<td>5 (29.4%)</td>
<td></td>
</tr>
<tr>
<td>Lambda light chain (%)</td>
<td>16 (11.3%)</td>
<td>0</td>
<td>2 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>Serum Hb level at diagnosis (g/dl)</td>
<td>11.0±1.9</td>
<td>12.5±1.5</td>
<td>11.9±2.2</td>
<td>0.43</td>
</tr>
<tr>
<td>Serum PLT level at diagnosis (per/nl)</td>
<td>210±94.9</td>
<td>212±95</td>
<td>258±105</td>
<td>0.25</td>
</tr>
<tr>
<td>Serum creatinine level at diagnosis (mg/dl)</td>
<td>0.8±1.5</td>
<td>0.9±1.1</td>
<td>0.8±1.1</td>
<td>0.88</td>
</tr>
<tr>
<td>Serum calcium level at diagnosis (mmol/l)</td>
<td>9.1±1.1</td>
<td>9.0±0.8</td>
<td>9.5±1.0</td>
<td>0.72</td>
</tr>
<tr>
<td>LDH&gt;UNL at diagnosis (%)</td>
<td>93 (66.0%)</td>
<td>18 (81.8%)</td>
<td>12 (70.0%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Lytic bone lesion (%)</td>
<td>69 (48.9%)</td>
<td>15 (68.2%)</td>
<td>15 (88.2%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Induction chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>VD (%)</td>
<td>20 (14.2%)</td>
<td>9 (40.9%)</td>
<td>5 (29.4%)</td>
<td></td>
</tr>
<tr>
<td>VCD (%)</td>
<td>45 (31.9%)</td>
<td>1 (4.5%)</td>
<td>5 (29.4%)</td>
<td></td>
</tr>
<tr>
<td>VAD (%)</td>
<td>76 (53.9%)</td>
<td>12 (54.5%)</td>
<td>7 (41.2%)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy (%)</td>
<td>12 (8.5%)</td>
<td>10 (45.5%)</td>
<td>6 (35.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease status after induction chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>CR/VGPR (%)</td>
<td>23 (16.3%)</td>
<td>4 (18.2%)</td>
<td>5 (29.4%)</td>
<td></td>
</tr>
<tr>
<td>PR or less (%)</td>
<td>118 (83.7%)</td>
<td>18 (81.8%)</td>
<td>12 (70.6%)</td>
<td></td>
</tr>
<tr>
<td>Disease status after ASCT</td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>CR/VGPR (%)</td>
<td>131 (92.9%)</td>
<td>19 (86.4%)</td>
<td>12 (70.6%)</td>
<td></td>
</tr>
<tr>
<td>PR or less (%)</td>
<td>10 (7.1%)</td>
<td>3 (13.6%)</td>
<td>5 (29.4%)</td>
<td></td>
</tr>
<tr>
<td>Relapse rate (%)</td>
<td>37 (26.2%)</td>
<td>12 (54.5%)</td>
<td>7 (41.2%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total mortality rate (%)</td>
<td>19 (13.5%)</td>
<td>10 (45.5%)</td>
<td>7 (41.2%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Non-relapse mortality (%)

|   | 10 (7.1%) | 3 (13.6%) | 3 (17.6%) | 0.24 |

Abbreviations: ASCT: autologous stem cell transplantation; ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; UNL: upper normal limit

Table 2. Univariate and Multivariate Analyses (Cox model) of Overall Survival and Disease Free Survival for all patients

<table>
<thead>
<tr>
<th>Parameters for OS</th>
<th>Univariate analyses</th>
<th>Multivariate analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Plasmacytoma (without/EM-B/EM-S)</td>
<td>0.448</td>
<td>0.232-0.864</td>
</tr>
<tr>
<td>ISS staging</td>
<td>1.498</td>
<td>0.835-2.688</td>
</tr>
<tr>
<td>Age (≤57 years)</td>
<td>0.142</td>
<td>0.019-1.042</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>0.960</td>
<td>0.483-1.908</td>
</tr>
<tr>
<td>Type of MM</td>
<td>1.082</td>
<td>0.912-1.283</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>1.155</td>
<td>0.779-1.712</td>
</tr>
<tr>
<td>High LDH level</td>
<td>0.763</td>
<td>0.292-1.995</td>
</tr>
<tr>
<td>Lytic bone lesions</td>
<td>0.696</td>
<td>0.340-1.426</td>
</tr>
<tr>
<td>Induction chemotherapy</td>
<td>0.979</td>
<td>0.632-1.469</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>1.465</td>
<td>0.669-3.209</td>
</tr>
</tbody>
</table>

Parameters for DFS

<table>
<thead>
<tr>
<th>Parameters for DFS</th>
<th>Univariate analyses</th>
<th>Multivariate analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Plasmacytoma (without/EM-B/EM-S)</td>
<td>0.759</td>
<td>0.455-1.240</td>
</tr>
<tr>
<td>ISS staging</td>
<td>1.347</td>
<td>0.920-1.970</td>
</tr>
<tr>
<td>Age (≤57 years)</td>
<td>0.558</td>
<td>0.346-0.901</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>1.033</td>
<td>0.635-1.679</td>
</tr>
<tr>
<td>Type of MM</td>
<td>1.024</td>
<td>0.900-1.166</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>1.005</td>
<td>0.763-1.324</td>
</tr>
<tr>
<td>High LDH level</td>
<td>1.049</td>
<td>0.554-1.990</td>
</tr>
<tr>
<td>Lytic bone lesions</td>
<td>0.895</td>
<td>0.549-1.458</td>
</tr>
<tr>
<td>Induction chemotherapy</td>
<td>0.989</td>
<td>0.738-1.325</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>1.771</td>
<td>0.992-3.163</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; UNL: upper normal limit; ISS: International staging system

Note: Univariate comparisons with a P value <0.15 were included in multivariate analyses
**Figure 1.** Overall survival (p=0.02) and disease free survival (p=0.15) of patients according to their plasmacytoma presentation at diagnosis

**Figure 2.** Overall survival (p=0.89) and disease free survival (p=0.82) according to induction chemotherapy in patients who had EM plasmacytoma at diagnosis