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GENERAL RADIOLOGY

ORIGINAL ARTICLE

Prognostic value of low muscle mass at the 12th thoracic vertebral level in multiple myeloma treated with transplantation: CAREMM-2101 study

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PURPOSE

Autologous hematopoietic stem cell transplantation (ASCT) has been introduced as a standard treatment for newly diagnosed multiple myeloma (NDMM) following novel agent-based induction chemotherapy. This study investigated whether pre-ASCT low muscle mass evaluated using the paraspinal muscle index (PMI) at the 12th thoracic vertebra (T12) level is a reliable prognostic marker in NDMM after chemotherapy.

METHODS

A multi-center registry database was retrospectively analyzed. Between 2009 and 2020, 190 patients with chest computed tomography images underwent frontline ASCT following induction therapy. The PMI was defined as the value of the paraspinal muscle area at the T12 level divided by the square of the patient's height. The cut-off value indicating a low muscle mass was sex-specific, using the lowest quintiles.

RESULTS

Of the 190 patients, 38 (20%) were in the low muscle mass group. The low muscle mass group had a lower 4-year overall survival (OS) rate than the non-low muscle mass group (68.5% vs. 81.2%; $P = 0.074$). The median progression-free survival (PFS) in the low muscle mass group was significantly shorter compared with the non-low muscle mass group (23.3 months vs. 29.2 months; $P = 0.029$). The cumulative incidence of transplant-related mortality (TRM) was significantly higher in the low muscle mass group than in the non-low muscle mass group (4-year probability of TRM incidence, 10.6% vs. 0.7%; $P < 0.001$). In contrast, no significant difference in the cumulative incidence of disease progression was found between the two groups. Multivariate analysis revealed that low muscle mass was associated with significant negative outcomes for OS [(hazard ratio (HR): 2.14; $P = 0.047$], PFS (HR: 1.78; $P = 0.012$), and TRM (HR: 12.05; $P = 0.025$).

CONCLUSION

Paraspinal muscle mass may have a prognostic role in NDMM patients who undergo ASCT. Patients with low paraspinal muscle mass have lower survival outcomes compared to non-low muscle mass group.

KEYWORDS

Sarcopenia, myeloma, autologous, transplantation, computed tomography, thoracic

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of malignant plasma cells.[1] The outcomes of MM have improved dramatically in the past two decades owing to the introduction of novel agents, such as immunomodulatory drugs, proteasome inhibitors, and targeted monoclonal antibodies.[2,3] High-dose chemotherapy with autologous hematopoietic stem cell transplantation (ASCT) following upfront induction therapy using a novel agent is considered the standard of care for transplant-eligible and newly diagnosed MM (NDMM).[4] Patient-related prognostic factors, such as age or comorbidities, can limit the eligibility for ASCT.[5] Several prognostic tools based on multidisciplinary evaluation have been used to assess patient fitness for ASCT.[5-8] Howev-

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er, these tools rely on patients self-reporting their comorbidities and are prone to reporting bias. Therefore, tools that can facilitate the standardization of individualized risk factors for MM need to be developed.

Sarcopenia has recently been defined by the European Working Group on Sarcopenia in Older People 2 as the combination of low muscle mass and poor muscle function.[9] Furthermore, sarcopenia has been highlighted as an independent disorder based on individual cancer-related prognostic biomarkers in various malignancies.[10,11] However, published studies reporting patients with MM and sarcopenia and survival outcomes have been unsatisfactory to date due to their retrospective designs and small sample sizes. Williams et al.[12] measured psoas muscle mass at the third lumbar vertebra (L3) using computed tomography (CT) in 142 patients with MM treated with ASCT. They showed that low muscle mass was related to a higher incidence of post-ASCT cardiac complications but was not associated with survival outcomes. Takeoka et al.[13] demonstrated that a low muscle mass at the L3 level did not result in a significant survival difference between 56 patients with NDMM. Although muscle mass at L3, commonly used for CT measurements, was not related to survival outcomes in patients with MM, the prognostic role of muscle mass measured at other sites and sex-specific approaches is yet to be elucidated.[14] Previous studies have revealed that sarcopenia assessment using skeletal muscle measurements at the 12th thoracic vertebra (T12) level is a reliable biomarker for chest CT.[15,16] In addition, the cut-off for low muscle mass should be determined differently based on sex because it is directly related to the total muscle mass.[13,17,18] Therefore, further MM cohort studies are required to determine whether muscle mass is a useful prognostic indicator.

Main points

- Low muscle mass was defined based on a sex-specific cut-off using low-dose chest computed tomography before autologous hematopoietic stem cell transplantation (ASCT).
- Post-ASCT outcomes were significantly associated with low muscle mass in patients with multiple myeloma.
- NDMM patients undergoing ASCT with low paraspinal muscle mass have shorter progression-free survival, higher incidence of transplant-related mortality, and higher significant negative outcomes for overall survival.

This study measured the paraspinal muscle mass area (PSMA) at T12 (12th-PSMA, the area corresponding to the iliocostalis thoracis, longissimus thoracis, spinalis thoracis, rotator thoracis, multifidus, and semispinalis thoracis muscles) on chest CT scans. Low muscle mass was defined as a lower paraspinal muscle index (PMI) (12th-PSMA divided by the height^2) than the sex-specific cut-off. Further, the study explored the prognostic impact of low muscle mass on survival outcomes in patients with NDMM who underwent an ASCT.

Methods

Patient selection and data acquisition

The current study was a multi-center retrospective analysis of patient data from three centers. For patient with MM to be eligible for enrollment in the study, the following criteria had to be met: ND with symptomatic MM, treated with frontline ASCT after induction chemotherapy, aged 20 years or older, and having undergone chest CT within 60 days before the ASCT procedure. First, data from 1511 consecutive patients ND with plasma cell disorders between 2009 and 2020 were analyzed. Then, 264 patients diagnosed with plasma cell disorders other than symptomatic MM were excluded. Of the remaining 1,247 patients with symptomatic NDMM, 414 were transplant-eligible cases. The low-dose chest CT (LDCT) findings of selected patients with a history of pneumonia or airway disease were evaluated between 2009 and 2014. Since 2015, LDCT has been routinely performed to screen for malignancies involving the lungs and mediastinum, subclinical pneumonia, and airway diseases. Two hundred nine patients who lacked a LDCT image before ASCT and 15 patients who received ASCT as a salvage treatment following the failure of induction therapy were excluded. The final cohort included 190 patients with intention-to-treat NDMM who underwent frontline ASCT after induction chemotherapy (Figure 1). Since all centers participating in this study have used thalidomide- or bortezomib-based induction chemotherapy, alone or in combination, since 2009, all patients enrolled in the final cohort received novel agent-based induction therapy. Patient data were collected from August 2021 onward. This study was approved by the Institutional Review Board of Catholic Medical Center (IRB no. KC21RASI0352) and complied with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Computed tomography image acquisition

The CT examinations were performed using multidetector CT scanners with 64 or more channels, either a SOMATOM Definition AS+ (Siemens Healthineers, Erlangen, Germany) or a Discovery CT750 HD (GE Healthcare, Milwaukee, WI, USA). All scans were obtained during a single breath-hold from

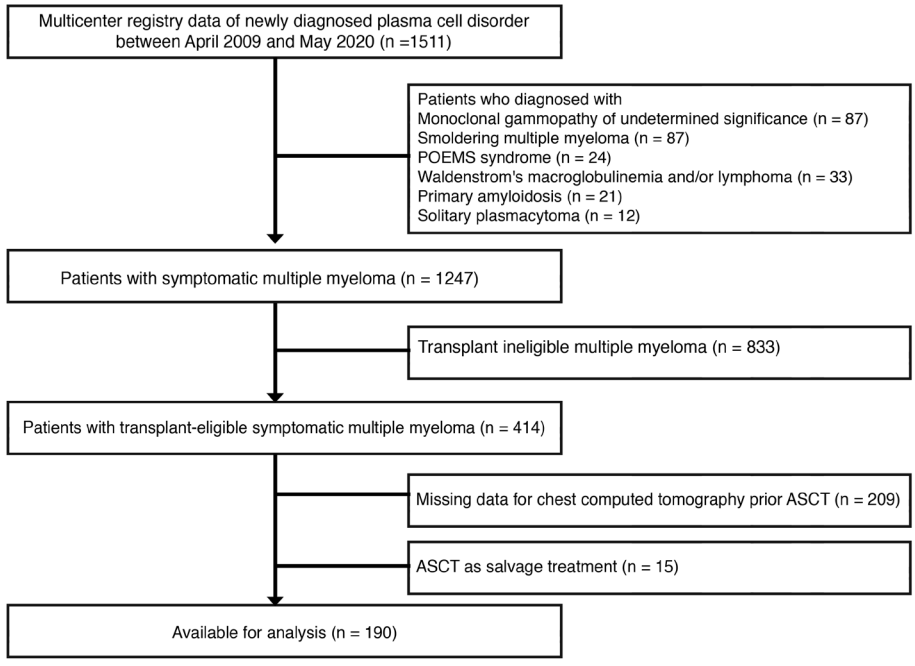

Figure 1. Flow diagram outlining the selection of the study cohort. The final cohort of this study included 190 cases of newly diagnosed multiple myeloma patients who received frontline autologous stem cell transplantation following induction chemotherapy.

the levels of the lower neck to the adrenal glands. The acquisition parameters were as follows: tube voltage 120 kV, tube current 35 mAs for the low-dose scan, automatic exposure control with 130 quality reference value mAs for the standard-dose scan (SOMATOM Definition AS+), a pitch of 1.1–1.2, rotation time of 0.5 s, detector collimation of 64 × 0.6 mm (SOMATOM Definition AS+), or 64 × 0.625 mm (Discovery CT750 HD).

Measurement of the paraspinal muscle at the 12th thoracic vertebra

The patients' 12th-PSMA was evaluated using LDCT within two months before the date of the ASCT according to the strategies used at the participating centers. The LDCT was primarily performed to confirm ASCT eligibility after completing the scheduled induction chemotherapy. A board-certified radiologist with nine years of experience, who was blinded to the clinical information, drew the region of interest using a semi-automated contouring tool available in a non-commercial prototype software (RADIOMICS, Siemens Healthineers, Erlangen, Germany) for all three centers' cases. An axial CT image at the level of T12 was obtained for each patient. The contours of the erector spinae muscles (iliocostalis thoracis, longissimus thoracis, and spinalis thoracis) and transversospinales muscles (rotator thoracis, multifidus, and semispinalis thoracis) were drawn. The 12th-PSMA (mm^2) was obtained from the contours (Figure 2). The mean densities (Hounsfield unit) of these muscles were also determined. Then, the patient's individual PMI was calculated by dividing the 12th-PSMA by the square of the patient's height (mm^2/m^2). The cut-off for low muscle mass was based on sex-specific PMI values using the lowest quintile in each subgroup of males and females.[12]

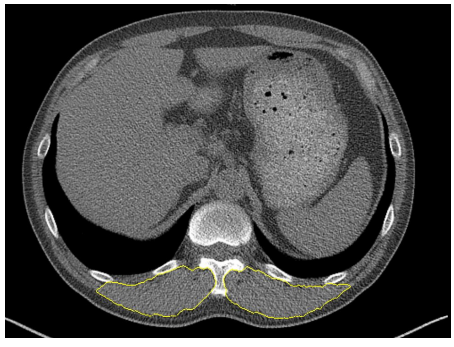

Figure 2. Measurement of paraspinal muscle area using axial computed tomography at the 12th thoracic vertebra level. An axial computed tomography image was selected at the level of the 12th thoracic vertebra's spinous process. The boundaries of the paraspinal muscles (iliocostalis thoracis, longissimus thoracis, spinalis thoracis, rotator thoracis, multifidus, and semispinalis thoracis) were drawn as the region of interest (yellow line). The area of these muscles was obtained to measure muscle mass.

Treatments and transplantation procedures

All patients received an induction treatment consisting of dexamethasone (or prednisolone) together with bortezomib or thalidomide, individually or a combination, in chronological order of approval by the National Health Insurance Service. After the induction chemotherapy, the collected stem cells were mobilized with subcutaneous granulocyte colony stimulation factor (10 μg/kg/day) for five days with or without prior cyclophosphamide therapy (1.5 g/m^2) for two days, etoposide (375 mg/m^2) for one day, or plerixafor (0.24 mg/kg) for one to two days. According to the conditioning strategies implemented by the three centers, a conditioning regimen consisting of high-dose melphalan (70 or 100 mg/m^2/day for two days) was commonly used. Occasionally, busulfan (3.2 mg/kg/day for three days), melphalan (70 mg/m^2/day for two days), busulfan (3.2 mg/kg/day for three days), melphalan (100 mg/day)-thiotepa (150 mg/m^2/day for one day), and busulfan (3.2 mg/kg/day for three days)-thiotepa (150 mg/m^2/day for one day) were used when melphalan was unavailable, as described in a previous report.[19] Some patients received an experimental regimen of bortezomib, busulfan, and melphalan in phase II clinical trials.[20] Other supportive care, including prophylactic antibiotics, prophylaxis for hepatic sinusoidal obstruction syndrome, granulocyte colony stimulation factor, and bisphosphonates, was administered concurrently across the three centers, as described in a previous report.[21,22] A maintenance therapy strategy was designed using thalidomide for 12 months;[23] however, a few individuals rejected this strategy due to insufficient insurance coverage.[19]

Definitions

The patient's MM stage was classified using the MM International Staging System,[1] and the response to treatment was assessed according to the International Myeloma Working Group response criteria.[24] High-risk cytogenetic abnormalities were defined as the presence of one or more of the following aberrations detected by fluorescent *in situ* hybridization: del(17p), t(4;14), or t(14;16).[25]

The PMI cut-off was based on sex-specific PMI values using the lowest quintile in each subgroup of males and females.[12] The low muscle mass group was defined as patients with a lower PMI than the sex-specific cut-off. The overall survival (OS) was defined as the time from transplantation to death from any cause or the date of the last follow-up, and events for progression-free survival (PFS) included disease progression or death from any cause. The transplant-related mortality (TRM) probability and the progression rate were computed by estimating the cumulative incidence based on competing risks, including progression and TRM.

Statistical analysis

Categorical variables were presented as frequencies and percentages, and comparisons used the chi-squared or Fisher's exact tests, as appropriate. Continuous variables were analyzed using the Kolmogorov–Smirnov test to evaluate the null hypothesis of a normal distribution. Normally distributed continuous variables were presented as the mean ± standard deviation and compared using the Student's t-test. Non-normally distributed continuous variables were expressed as medians with interquartile ranges and were compared using the Mann–Whitney U test. Pearson's correlation coefficients determined the statistical correlation between the continuous variables and the PMI. Multiple linear regression analyses were used to confirm the parameters related to the PMI. Regarding linear regression analysis, parameters with $P < 0.050$ on the Student's t-test or Pearson correlation test were included as covariants.

The reverse Kaplan–Meier estimator was used to assess the median duration of the interval. The Kaplan–Meier survival curves were determined, and log-rank tests were performed to analyze time-to-event endpoints, such as the OS and PFS. Univariate survival analyses were performed using Kaplan–Meier estimates and log-rank tests. Cumulative incidence estimates and the Gray's test were used to analyze the data, including competing risks. Variables with $P < 0.150$, according to the univariate analyses, were included in the multivariate models of OS, PFS, and TRM. The Cox proportional hazards model and the Fine–Gray regression model, both with backward stepwise selection, were generated with hazard ratios (HRs) and 95% confidence intervals (CIs) for multivariate analysis. All statistical analyses were performed using R software (ver. 3.6.1, Jul. 07, 2019; R Foundation for Statistical Computing, Vienna, Austria. https://cran.r-project.org/bin/windows/base/old/3.6.1/). A *P* value

of <0.050 was considered statistically significant.

Results

Patient characteristics and outcomes

The final study cohort included 190 of the initial 1,511 consecutive patients, 104 (55.3%) males and 86 (45.3%) females, with a mean age of 55.9 ± 7.0. The mean interval between the LDCD assessment date and the date of the ASCT was 28 ± 16.1 days. As expected, the 12th-PSMA (3206 ± 648 mm^2 for males vs. 2358.9 ± 538.8 mm^2 for females; P < 0.001) and the PMI (1117.3 ± 232.8 mm^2/m^2 for males vs. 973.7 ± 220.2 mm^2/m^2 for females; P < 0.001) were significantly higher in males than in females (Figure 3a). Among the variables considered in the decision-making for ASCT, non-extramedullary plasmacytoma and lower levels of albumin at diagnosis related to lower PMI values (Supplementary Table 1). Supplementary Table 2 shows the results of multiple regression analysis for the PMI, where the dependent parameter was sex. Accordingly, the cut-offs for the 12th-PSMA were defined as 916.9 mm^2/m^2 for males and 807.2 mm^2/m^2 for females. The mean PMI of the low muscle (n = 38) and non-low muscle (n = 152) mass groups were 760.9 ± 103.2 and 1125.1 ± 203.4, respectively. The comparative data of the two groups based on the definition of low muscle mass are presented in Table 1. These characteristics were relatively similar between the two groups.

The median follow-up of the total cohort was 40.7 months (95% CI; 38.1–44.9 months). Among the 36 deaths in the entire cohort, 86.1% (n = 31) were progression-dependent, and 13.9% (n = 5) died of TRM. The TRM-related causes of death included three cases of sepsis, one of hepatic sinusoidal obstruction syndrome, and one of sudden death following fatal arrhythmia.

Survival outcomes of the low and non-low muscle mass groups

The estimated OS rate was poor in the low muscle compared with the non-low muscle mass group [4-year OS rate, 68.5% (95% CI; 49.9%–81.3%) vs. 81.2% (95% CI; 71.7%–87.8%); P = 0.074] (Figure 4a). The median PFS in the low muscle mass group was significantly poorer than in the non-low muscle mass group (23.3 months (95% CI, 14.5–31.4 months) vs. 29.2 months (95% CI, 24.3–38.7 months); P = 0.029) (Figure 4b). The cumulative incidence of TRM was significantly higher in the low muscle than in the non-low muscle mass group [4-year probability of incidence of TRM, 10.6% (95% CI, 3.3%–22.9%) vs. 0.7% (95% CI, 0.1%–3.3%); P < 0.001] (Figure 4c). No statistically significant cumulative incidence of progression was found between the two groups (P = 0.301) (Figure 4d).

Analyses of the factors affecting overall and progression-free survival, and transplant-related mortality

In the univariate analysis (Supplementary Table 3), some variables were identified as potentially related to OS, PFS, and TRM. Eight variables were potentially associated with OS, including low muscle mass, age (≥60 years), lambda chain type MM, high β2-microglobulin at diagnosis (≥5.5 mg/L), low albumin at diagnosis (<3.5 g/dL), mobilization of peripheral blood mononuclear cells using cyclophosphamide, low glomerular filtration rate at baseline (<60 mL/min/1.73 m^2), and conditioning, except for melphalan plus busulfan. Seven variables were found to be potentially related to PFS, including low muscle mass and density, lambda chain type MM, high β2-microglobulin at diagnosis (≥5.5 mg/L), low albumin at diagnosis (<3.5 g/dL), poor response status at baseline, and low platelet at baseline (<150/mm^3). Six variables were found to be potentially related to TRM, including low muscle mass, lambda chain type MM, high β2-microglobulin at diagnosis (≥5.5 mg/L), low albumin at diagnosis (<3.5 g/dL), high lactate dehydrogenase (> upper limit of normal), and low glomerular filtration rate at baseline (<60 mL/min/1.73 m^2). The multivariate analysis (Table 2) showed that low muscle mass resulted in a significantly negative association with OS (HR of 2.14; 95% CI of 1.01–4.87; P = 0.047), PFS (HR of 1.78; 95% CI of 1.14–2.78; P = 0.012), and TRM (HR of 12.05; 95% CI of 1.36–104.93; P = 0.025), even after adjustment for other potential factors.

Discussion

This study evaluated the prognostic role of the PMI using the 12th-PSMA derived from LDCT images and height. Low muscle mass was defined as the sex-specific lowest quintile of the PMI. Low muscle mass was significantly associated with survival outcomes, even after adjusting for confounding factors; this suggests that the lower survival outcomes in the low muscle mass group resulted from a higher incidence of TRM.

Quantitative body composition measurements, including skeletal muscle and visceral and subcutaneous adipose tissue volumes, at various anatomical sites have been extensively performed to identify their role in predicting the outcomes and survival of cancer patients.[14] Studies exploring the association between body composition at the L3 level and clinical outcomes are the most common in cancer cohorts, including MM cohort studies. Previous studies[12,13,26] that applied low muscle mass at the L3 level in patients with MM showed that a low muscle index did not affect survival outcomes, contrary to the conclusion of this study. However, evidence associating low muscle mass at the L3 level with survival has been disputed in cohort studies of patients with MM. For example, Williams et al.[12] and Takeoka et al.[13] did not apply sex-specific cut-offs for the L3 low muscle index. Surov et al.[26] used the sex-specific cut-off values suggested by Prado et al.[27], which were derived for solid tumors of the respiratory or gastrointestinal tract rather than for MM. Although three previous studies on low muscle mass measured at the lumbar vertebral level were not linked to OS in a cohort

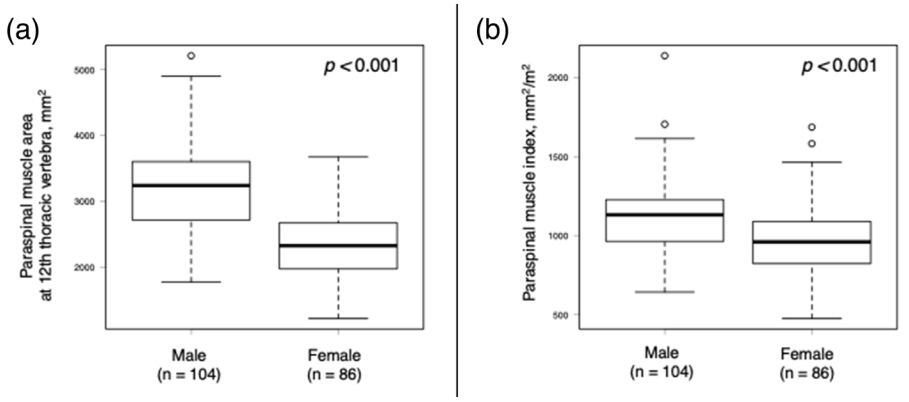

Figure 3. Comparison of **(a)** paraspinal muscle area at the 12th thoracic vertebra (mm^2) and **(b)** paraspinal muscle index (PMI, mm^2/m^2) based on sex using the Student's t-test. The mean of paraspinal muscle area at the 12th thoracic vertebra was 3206 ± 648 mm^2 for males vs. 2358.9 ± 538.8 mm^2 for females. The mean of the PMI was 1117.3 ± 232.8 mm^2/m^2 for males vs. 973.7 ± 220.2 mm^2/m^2 for females. Boxes, 5–95% percentiles; horizontal bars, median; vertical brackets, ranges. PMI, paraspinal muscle index.

Table 1. Comparisons of characteristics between the low and non-low muscle mass groups

Variables	Low muscle mass, (n = 38)	Non-low muscle mass, (n = 152)	*P* value
Paraspinal muscle index, mm^2/m^2, mean ± SD	760.9 ± 103.2	1125.1 ± 203.4	<0.001
Time to ASCT from the assessing date of LDCT scan, days, mean ± SD	27.9 ± 18.9	28.0 ± 15.4	0.975
Age at transplant, years, mean ± SD	54.1 ± 6.3	56.3 ± 7.1	0.071
Sex, number (%)			0.999
Male	21 (55.3)	83 (54.6)	
Female	17 (44.7)	69 (45.4)	
Type of myeloma, number (%)			0.851
IgG	23 (60.5)	80 (52.6)	
IgA	6 (15.8)	27 (17.8)	
IgM or IgD	3 (7.9)	15 (9.9)	
Light chain disease	6 (15.8)	30 (19.7)	
Presence of extramedullary disease at diagnosis, number (%)			0.160
None	34 (89.5)	118 (77.6)	
Present	4 (10.5)	34 (22.4)	
Lactate dehydrogenase at diagnosis, number (%) (missing n = 8)			0.475
> Upper limit of normal	26 (68.4)	116 (76.3)	
Normal	10 (26.3)	30 (19.7)	
β2-microglobulin at diagnosis, mg/L, median (Q1–Q3) (missing n = 5)	3.82 (2.52–6.89)	3.17 (2.32–4.97)	0.103
Albumin at diagnosis, g/dL, mean ± SD (missing n = 5)	3.5 ± 0.7	3.7 ± 0.7	0.267
Cytogenetic risk, number (%) (missing n = 60)			0.426
Standard	20 (52.6)	73 (48.0)	
High	5 (13.2)	32 (21.1)	
Time to ASCT from diagnosis, months, mean ± SD	6.2 ± 1.5	6.5 ± 1.3	0.203
Induction treatment, number (%)			0.182
Bortezomib-thalidomide-dexamethasone	32 (84.2)	141 (92.8)	
Others[a]	6 (15.8)	11 (7.2)	
Lactate dehydrogenase at time prior ASCT, number (%)			0.381
> Upper limit of normal	16 (42.1)	50 (32.9)	
Normal	22 (57.9)	102 (67.1)	
Response status at time prior ASCT, number (%)			0.384
Complete response	15 (39.5)	62 (40.8)	
Very good partial response	21 (55.3)	71 (46.7)	
Partial response or stable disease	2 (5.3)	19 (12.5)	
Mobilization of peripheral blood mononuclear cell			0.679
G-CSF only	9 (23.7)	27 (17.8)	
G-CSF plus cyclophosphamide	14 (36.8)	53 (34.9)	
G-CSF plus etoposide	14 (36.8)	70 (46.1)	
G-CSF plus plerixafor	1 (2.6)	2 (1.3)	
Absolute neutrophil count before ASCT, $/mm^3$, median (Q1–Q3)	2.81 (2.2–3.98)	2.93 (1.93–3.72)	0.364
Platelet count before ASCT, $/mm^3$	236 ± 81.6	226 ± 58.4	0.434
Glomerular filtration rate before ASCT, mL/min/1.73 m^2	87.4 ± 35.0	91.1 ± 25.9	0.468
Conditioning regimen, number (%)			0.278
High dose melphalan	30 (78.9)	92 (60.5)	
Melphalan plus busulfan	2 (5.3)	21 (13.8)	
Melphalan, busulfan, plus thiotepa	4 (10.5)	28 (18.4)	
Busulfan plus thiotepa	0 (0)	2 (1.3)	
Bortezomib, busulfan, plus melphalan	2 (5.3)	9 (5.9)	
Infused CD34+ × 10^6 cells/kg, median (Q1–Q3)	5.22 (4.04–8.56)	5.55 (4.36–6.79)	0.999
Maintenance therapy after ASCT			0.253
Yes	23 (60.5)	109 (71.7)	
No	15 (39.5)	43 (28.3)	

[a]Others included four of bortezomib-dexamethasone, four of bortezomib-melphalan-prednisolone, nine of thalidomide-dexamethasone; ASCT, autologous hematopoietic stem cell transplantation; Ig, immunoglobulin; LDCT, low-dose chest computed tomography; G-CSF, granulocyte-colony stimulation factor; SD, standard deviation; Q, quantile.

of patients with MM,[12,13,26] Umit et al.[28] reported that low femoral muscle mass was significantly associated with poor OS, whereas measuring muscle mass in the lumbar area was not. Therefore, this study hypothesized that muscle volume measurements at different sites from the L3 level and the modality of abdominal CT were worthwhile to explore the prognostic impact in patients with MM.

First, pilot investigations were performed to identify which single muscle area could correspond to the entire muscle volume shown in the cross-sectional image at the T12 level. It was determined that measurements at one site of the paraspinal muscle could be a surrogate marker for the entire muscle volume shown at the T12 level (Supplementary Figure 1). In line with this study's results, pectoralis muscle attenuation and low muscle mass evaluated at the T12 level were negatively associated with clinical outcomes, such as severe airflow obstruction in patients with chronic obstructive pulmonary disease and survival in patients who underwent lung transplantation.[29,30] Furthermore, in several studies, LDCT image muscle mass measurements at the T12 level showed a prognostic role in clinical outcomes.[31,32] Although understanding the pathogenic mechanism of sarcopenia according to the measured site on the clinical outcomes is still lacking, it is suggested that low muscle mass measured at sites other than L3 are valuable prognostic markers, even in patients with MM.

To the researchers' knowledge, the current study is the first to investigate the association between low muscle mass at the T12 level and the survival of patients with MM. As LDCT is routinely performed before ASCT, an additional abdominal CT for muscle mass assessment at the lumbar level may be limited. Although it has been suggested that measuring one muscle area could assess the patient's generalized muscle mass status,[33] such an approach is inevitably linked to increased laboriousness, particularly when measuring larger areas in clinical practice. Furthermore, T12 level evaluation via LDCT is associated with the significant benefit of contrast-free assessment and minimization of radiation exposure compared with conventional abdominal CT of the lumbar region.[34,35]

Although the definition of low muscle mass is yet to be established,[36] it is generally indicated by different cut-off levels based on sex and is closely related to body size. Furthermore, the revised European Working Group on Sarcopenia in Older People 2 guidelines state that sex-specific threshold values for sarcopenia diagnosis improve the prediction of outcomes.[9] It is well known that the body composition index measured

Table 2. Multivariable analysis of overall survival, progression-free survival, and treatment-related mortality

	Overall survival			Progression-free survival			Cumulative incidence of TRM		
Variables	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Paraspinal muscle index, $mm^2/m^{2*\dagger\ddagger}$			0.047			0.012			0.025
Low muscle mass vs. non-low muscle mass	2.14	1.01–4.54		1.78	1.14–2.78		12.05	1.36–104.93	
Muscle density, Hounsfield density			NA			0.011			NA
Low density vs. high density	NA	NA		1.73	1.13–2.65		NA	NA	
Age at transplant			0.014			NA			NA
≥60 vs. <60	2.42	1.2–4.89		NA	NA		NA	NA	
Light chain type*†‡			0.139			0.084			0.500
Kappa vs. Lambda	1.66	0.85–3.27		1.39	0.96–2.01		2.35	0.2–27.81	
β2-microglobulin at diagnosis, mg/L*†‡			0.011			0.003			0.430
<5.5 vs. ≥5.5	2.44	1.23–4.83		1.89	1.25–2.85		2.02	0.36–11.29	
Albumin at diagnosis, g/dL*†‡			0.273			0.185			<0.001
≥3.5 vs. <3.5	0.68	0.34–1.36		1.28	0.88–1.86		13.7	3.42–54.9	
Lactate dehydrogenase at time prior ASCT‡			NA			NA			0.790
> Upper limit of normal vs. normal	NA	NA		NA	NA		1.57	0.06–41.63	
Mobilization of peripheral blood mononuclear cell*			0.019			NA			NA
G-CSF plus cyclophosphamide vs. others	2.31	1.15–4.65		NA	NA		NA	NA	
Response status at time prior ASCT†			NA			0.043			NA
SD, PR, vs. VGPR vs. CR or better	NA	NA		1.35	1.01–1.81		NA	NA	
Conditioning regimen			0.170			NA			NA
High dose melphalan vs. melphalan plus busulfan vs. others[1]*	1.33	0.89–1.98		NA	NA		NA	NA	
Platelet count at time prior ASCT, $/mm^{3\dagger}$			NA			0.167			NA
≥150 vs. <150	NA	NA		1.57	0.83–2.97		NA	NA	
Glomerular filtration rate at time prior ASCT, $mL/min/1.73m^{2*\ddagger}$			0.605			NA			0.002
≥60 vs. <60	1.36	0.42–4.39		NA	NA		18.4	3.04–111.7	

*Eight variables were selected by univariate analysis for overall survival with *P* values less than 0.15; †seven variables were selected by univariate analysis for progression-free survival with *P* values less than 0.15; ‡six variables were selected by univariate analysis for cumulative incidence of TRM with *P* values less than 0.15; [1]others include 32 of melphalan, busulfan plus thiotepa, 2 of busulfan plus thiotepa, and 11 of bortezomib, busulfan plus melphalan. ASCT, autologous hematopoietic stem cell transplantation; CI, confidence interval; CR, complete response; G-CSF, granulocyte-colony stimulation factor; NA, not available; PR, partial response; TRM, transplantation-related mortality; SD, stable disease; VGPR, very good partial response.

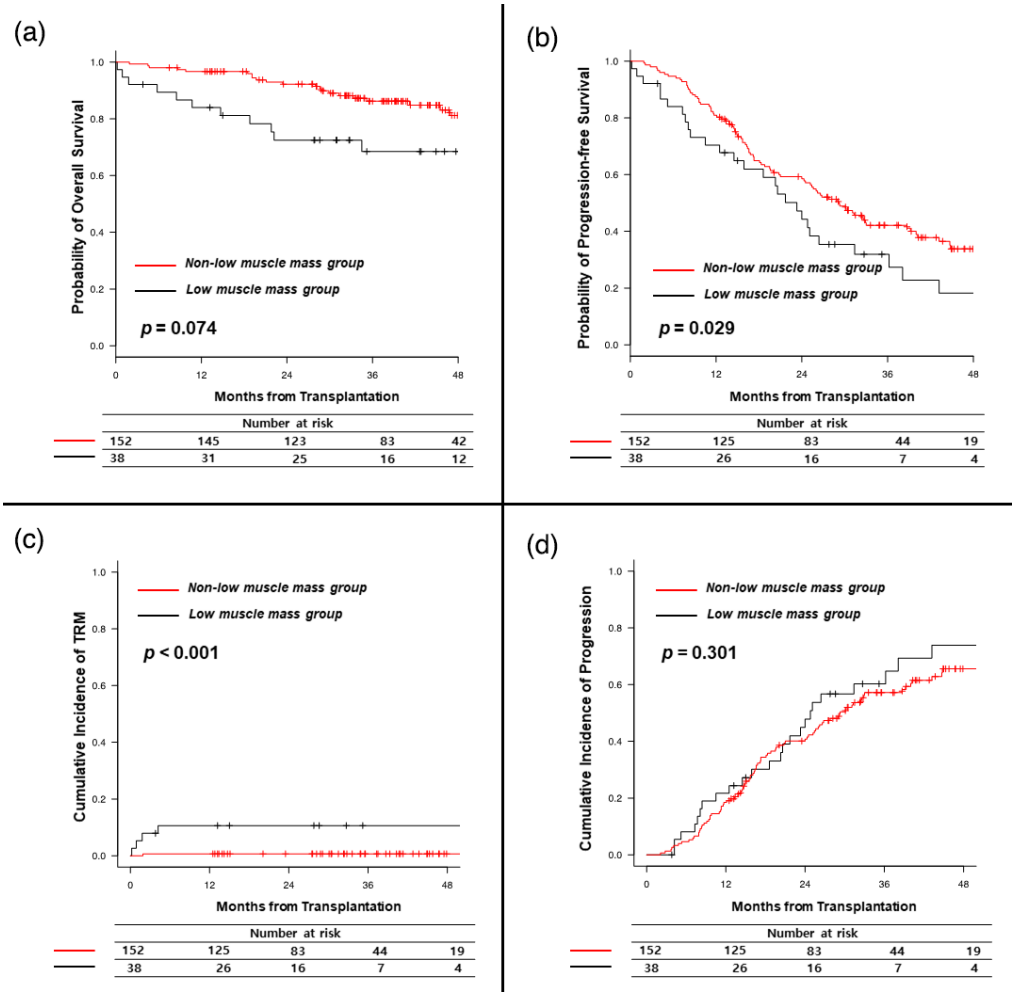

Figure 4. Comparison of survival outcomes between the low (black line) and non-low (red line) muscle mass groups. **(a)** Overall survival. **(b)** Progression-free survival. **(c)** Cumulative incidence of transplant-related mortality (TRM). **(d)** Cumulative incidence of disease progression. The estimated overall survival rate and median progression-free survival were poor in the low muscle mass group compared with the non-low muscle mass group ($P = 0.074$ and 0.029 for the overall survival rate and median progression-free survival, respectively). The cumulative incidence of TRM in the low muscle mass group was significantly higher than in the non-low muscle mass group ($P < 0.001$). No statistical significance in the cumulative incidence of disease progression was found between the two groups ($P = 0.301$).

at the L3 level varies significantly depending on sex.[17] Accordingly, most previous studies defined sex-specific cut-offs to investigate the associations between low muscle mass at the L3 level and the clinical outcomes of several cancers.[37] However, most previous MM cohort studies defined low muscle mass with sex-specific cut-off values.[12,13] Based on previous studies' findings, the researchers believe this methodology is a decisive factor related to the lack of significant association with survival outcomes in this study's MM cohort. Unfortunately, because of the lack of correlation between low muscle mass and survival of patients with MM in previous studies, CT muscle mass measurements have not received substantial attention in MM cohort studies.

No clinical impact of sex-non-specific muscle mass on clinical outcomes was observed in this MM cohort (data not shown). However, this study's results showed that low muscle mass at the T12 level, defined by a sex-specific methodology, was negatively associated with comprehensive survival outcomes, including OS, PFS, and TRM, in patients with MM who received ASCT. The results of this study highlight the need for future studies to establish a reliable sex-specific approach for lowering the muscle mass in patients with MM undergoing ASCT.

Prognostic marker-based treatments are essential to improve the survival of patients with MM. Relevant prognostic parameters for each patient were divided into the patient-, disease-, and treatment-related factors.[38] Patient-related factors, such as age, performance status, MM-specific comorbidity index of the revised myeloma comorbidity index,[8] or the International Myeloma Working Group frailty scale,[5] can predict individual tolerance to anti-MM treatment. It was hypothesized that the PMI using the 12th-PSMA in this study might be a patient-related parameter facilitating pretreatment decisions including its regimen and intensity. Further, the current study demonstrated that low muscle mass significantly contributed to high TRM and poor PFS and OS. The study cohort consisted of intention-to-treat patients with MM with frontline ASCT following the achievement of an overall response to induction chemotherapy. It is critical to avoid TRM after ASCT. Since no optimal conditioning regimen has been developed for ASCT in patients with MM, clinicians should adopt a weak conditioning regimen for individuals with low muscle mass. Evidence from cancer cohorts supports this study's finding that muscle mass status is directly related to critical chemotherapeutic toxicity.[12,37] Above all, MM appears to be strongly linked to low muscle mass because of multidimensional factors, such as epidemiologically old-age onset;[39,40] therefore, patients with MM may face disability related to devastating bone

destruction, including vertebral compression fractures[41] or heavy exposure to high-dose steroids as part of anti-MM treatment.[42] It is known that comprehensive rehabilitation with nutritional support and exercise programs treats and prevents low muscle mass.[43] Moreover, nutritional therapy, including protein of approximately 1.2–1.5 g/kg/day and fat within 20%–30% of total energy content, and exercise therapy, such as resistance training, are recommended for patients with MM.[43,44] Therefore, further studies are needed to investigate the potential clinical benefits of intensive rehabilitation programs for preventing or treating sarcopenia following the diagnosis of MM or before the initiation of induction treatment; this may provide a more comprehensive understanding of the effectiveness of such interventions in managing sarcopenia and enhancing patient outcomes.

This study was limited by its retrospective design and lack of prospective validation using another cohort. Potential selection bias exists as some patients without LDCT images before the ASCT were excluded from the initial cohort. The study's population was also limited by confounding factors, such as heterogeneous induction treatment and the ASCT's conditioning regimen. Further, as some data associated with cytogenetic risk were missing, statistical bias could exist in the association between the cytogenetic risk and clinical outcomes. Although the study's results indicated a prognostic impact of low muscle mass at the T12 level, the optimal sites for computing muscle mass were not confirmed. Therefore, further studies are needed to identify the optimal site among the candidate muscle sites, such as the pectoralis or paraspinal muscles, at other thoracic levels. Nevertheless, the researchers believe the T12 level approach is preferable because it is simpler to measure muscle mass than at other sites. Further studies are warranted to validate the role of the PMI using the 12th-PSMA on outcomes in a larger cohort of transplant-eligible patients with NDMM based on the results of this study.

In conclusion, sex-specific low muscle mass evaluated at the T12 level could be related to the prognosis of patients with MM receiving ASCT. For patients with NDMM preparing for ASCT, an inspection of muscle mass using LDCT may contribute to developing individualized management, including conditioning intensity, rehabilitation, and nutrition.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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Supplementary Table 1. Analysis to identify factors associated with paraspinal muscle index

Characteristics	Paraspinal muscle index, mm^2/m^2		
	Correlation coefficient (95% CI)	Mean ± SD (or median with interquartile)	*P* value
Muscle density (Hounsfield unit)	0.045 (-0.099 ~ 0.188)	NA	0.541
Age years at transplant	-0.029 (-0.171 ~ 0.114)	NA	0.692[a]
Sex			<0.001[b]
Male	-	1117.2 ± 232.8	
Female	-	973.7 ± 220.2	
Type of myeloma			0.121[c]
IgG	-	1036.5 ± 248.7	
IgA	-	1034.7 ± 203.9	
IgM or IgD	-	1179.5 ± 289.8	
Light chain disease	-	1049.8 ± 191.0	
Light chain type			0.084[b]
Kappa	-	1024.3 ± 233.6	
Lambda	-	1084.0 ± 239.5	
Presence of extramedullary plasmacytoma			0.009[b]
None	-	1029.8 ± 225.8	
Present	-	1142.1 ± 264.9	
Lactate dehydrogenase at diagnosis			0.699[b]
> Upper limit of normal	-	1039.3 ± 255.3	
β2-microglobulin at diagnosis	-0.033 (-0.112 ~ 0.177)	-	0.654[a]
Albumin at diagnosis, g/dL	0.15 (0.007 ~ 0.288)	-	0.04[a]
ISS stage at diagnosis			0.355[c]
I, n (%)	-	1089.5 ± 206.2	
II, n (%)	-	1045.4 ± 258.0	
III, n (%)	-	1024.9 ± 241.7	
Cytogenetic status at diagnosis			0.23[b]
Standard risk	-	1030.5 ± 246.5	
High risk	-	1085.8 ± 206.9	
Time to transplantation from diagnosis	0.063 (-0.08 ~ 0.204)	NA	0.387[a]
Induction treatment			0.115[c]
Bortezomib-thalidomide-dexamethasone	-	1062.7 ± 239.4	
Bortezomib-dexamethasone	-	831.9 ± 236	
Thalidomide-dexamethasone	-	1078.4 ± 249.3	
Bortezomib-melphalan-prednisolone	-	937.8 ± 126.9	
Lactate dehydrogenase at time prior ASCT			0.323[b]
> Upper limit of normal	-	1028.9 ± 229.4	
Normal	-	1064.7 ± 242.9	
Response status at time prior ASCT			0.246[c]
Complete response	-	1081.0 ± 248.7	
Very good partial response	-	1022.5 ± 213.5	
Partial response or stable disease	-	1077.6 ± 288.5	
Mobilization			0.341[c]
G-CSF	-	996.1 ± 241.8	
G-CSF plus cyclophosphamide	-	1058.4 ± 210.9	
G-CSF plus etoposide	-	1075.0 ± 256.6	
G-CSF plus plerixafor	-	951.7 ± 136.3	
Absolute neutrophil count at time prior ASCT	-0.117 (-0.255 ~ 0.025)	-	0.107[a]
Platelet count at time prior ASCT	0.054 (-0.195 ~ 0.089)	-	0.457[a]
Glomerular filtration rate at time prior ASCT	-0.025 (-0.167 ~ 0.118)	-	0.734[a]
Collected CD34+ cells	-0.02 (-0.162 ~ 0.123)	-	0.786[a]

[a]Correlations between paraspinal muscle index and continuous variables were evaluated using Pearson correlation coefficients; [b]paraspinal muscle index by numerical variable were compared by the Student's t-test; [c]paraspinal muscle index by 3 or more multiple numerical variables were compared by the One-Way ANOVA test. CI, confidence interval; SD, standard deviation; ISS, International Staging System; ASCT, autologous hematopoietic stem cell transplantation; G-CSF, granulocyte-colony stimulation factor; Ig, immunoglobulin.

Supplementary Table 2. The multilinear regression analysis with paraspinal muscle index to independent parameter

Parameters	Paraspinal muscle index, mm^2/m^2	
	Regression coefficient ± SD	*P* value
Sex; male, female	-143.6 ± 53.4	<0.001
Type of myeloma; IgG, IgA, IgM or D, and light chain disease	12.1 ± 17.4	0.489
Light chain type; kappa, lambda	47.9 ± 34.3	0.165
Presence of extramedullary plasmacytoma; none, present	-80.3 ± 43.0	0.063
Albumin at diagnosis, g/dL	-36.9 ± 23.0	0.11
Induction treatment; bortezomib-thalidomide-dexamethasone, bortezomib-dexamethasone, thalidomide-dexamethasone, and bortezomib-melphalan-prednisolone	-44.5 ± 26.3	0.093
Absolute neutrophil count at time prior ASCT	-0.17 ± 0.1	0.089

ASCT, autologous hematopoietic stem cell transplantation; Ig, immunoglobulin; SD, standard deviation.

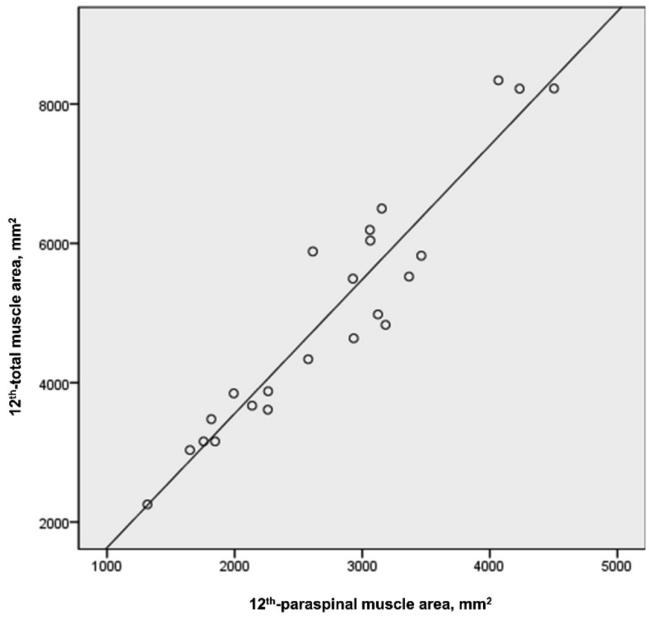
Supplementary Table 3. Univariable analysis to identify factors associated with survival outcomes

		Overall survival			Progression-free survival			Cumulative incidences of TRM		
Variables	Number	Median	95% CI	*P* value	Median	95% CI	*P* value	% at 4 years	95% CI	*P* value
Paraspinal muscle index, mm^2/m^2				0.074			0.029			<0.001
Low muscle mass	38	NA	34.5–NA		23.3	14.5–31.4		10.6	3.3–22.9	
Non-low muscle mass	152	NA	NA–NA		29.2	24.3–38.7		0.7	0.1–3.3	
Muscle density, Hounsfield unit[1]				0.19			0.01			0.276
Low muscle density	38	NA	45.5–NA		27.2	22.6–38.0		5.3	0.9–15.7	
High muscle density	152	NA	NA–NA		35.8	32.2–49.0		2.0	0.6–5.4	
Time to ASCT from the assessing date of LDCT scan, days				0.984			0.487			0.534
≥ Mean value (28 days)	88	NA	58.2–NA		27.8	20.0–33.0		3.4	0.9–8.8	
< Mean value (28 days)	102	NA	NA–NA		26.4	20.3–38.1		2.0	0.4–6.3	
Age at transplant, years				0.101			0.215			0.483
≥60	66	58.2	52.4–NA		25.2	16.1–32.4		1.5	0.1–7.2	
<60	124	NA	NA–NA		29	21.7–36.2		3.2	1.1–7.5	
Sex				0.217			0.324			0.502
Male	104	NA	54.9–NA		25.4	18.8–31.1		1.9	0.4–6.2	
Female	86	NA	NA–NA		29.3	21.7–43.2		3.5	0.9–9.0	
Type of myeloma				0.192			0.309			0.596
IgG	103	NA	NA–NA		25.4	19.5–30.1		1.9	0.4–6.2	
IgA	33	NA	52.4–NA		43.2	14.5–NA		3.0	0.2–13.6	
IgM or IgD	18	48.5	33.3–NA		18.6	9.6–36.2		0.0	0.0	
Light chain disease	36	NA	NA–NA		32.4	15.7–52.1		5.6	1.0–16.5	
Light chain type				0.086			0.112			0.13
Kappa	101	NA	NA–NA		31.1	24.5–43.2		1.0	0.1–4.9	
Lambda	89	NA	54.9–NA		24.3	17.3–30.2		4.5	1.5–10.3	
Presence of extramedullary disease at diagnosis				0.421			0.946			0.258
None	152	NA	NA–NA		24.8	21.7–32.6		3.3	1.2–7.1	
Present	38	NA	52.4–NA		26.6	15.7–44.8		0.0	0.0	
Lactate dehydrogenase at diagnosis (missing n = 8)				0.883			0.543			0.885
> Upper limit of normal	40	NA	58.2–NA		26.2	21.7–38.7		2.6	0.2–11.7	
Normal	142	NA	NA–NA		29.3	13.9–36.2		2.1	0.6–5.6	
β2-microglobulin at diagnosis, mg/L (missing n = 5)				0.002			<0.001			0.123
≥5.5	99	NA	NA–NA		39.2	30.1–52.1		1.0	0.1–5.0	
<5.5 and ≥3.5	44	NA	54.9–NA		17.3	14.5–30.2		2.3	0.2–10.5	
<3.5	42	NA	31.3–NA		16.4	11.2–24.0		7.1	1.8–17.6	

Supplementary Table 3. Continued

		Overall survival			Progression-free survival			Cumulative incidences of TRM		
Variables	Number	Median	95% CI	*P* value	Median	95% CI	*P* value	% at 4 years	95% CI	*P* value
Albumin at diagnosis, g/dL				0.047			0.122			0.06
≥3.5	113	NA	NA–NA		30.2	24.5–36.2		0.9	0.1–4.4	
<3.5	74	NA	58.2–NA		24	16.4–29.0		5.4	1.7–12.2	
Cytogenetic risk (missing n = 60)				0.732			0.394			0.371
Standard	93	NA	NA–NA		30.2	21.7–40.0		2.2	0.4–6.8	
High	37	NA	58.2–NA		29.2	16.6–38.7		0.0	0.0	
Time to ASCT from diagnosis, months							0.419			0.681
≥ Median (6.4 months)	96	NA	52.4–NA		27.8	18.6–36.2		3.1	0.8–8.1	
< Median (6.4 months)	94	NA	NA–NA		26	21.0–38.1		2.1	0.4–6.8	
Induction treatment				0.475			0.636			0.478
Bortezomib-thalidomide-dexamethasone	173	NA	NA–NA		26.6	12.5–76.5		2.9	1.1–6.2	
Others[2]	17	NA	54.9–NA		25.6	23.3–32.4		0.0	0.0	
Lactate dehydrogenase at time prior ASCT				0.241			0.206			0.033
> Upper limit of normal	66	NA	48.5–NA		24	16.8–32.9		6.1	1.9–13.6	
Normal	124	NA	NA–NA		29	24.3–40.0		0.8	0.1–4.0	
Response status at time prior ASCT				0.898			0.148			0.174
Complete response	77	NA	54.9–NA		30.1	21–51.8		0.0	0.0	
Very good partial response	92	NA	58.2–NA		26.6	18.8–32.6		4.4	1.4–10.0	
Partial response or stable disease	21	NA	NA–NA		17.3	11.7–NA		4.8	0.3–20.2	
Mobilization of peripheral blood mononuclear cell				0.055			0.794			0.469
G-CSF plus cyclophosphamide	67	NA	58.2–NA		26.8	21.0–38.1		1.5	0.1–7.1	
Others[3]	123	NA	NA–NA		25.6	17.3–32.6		3.3	1.1–7.6	
Absolute neutrophil count at time prior ASCT, /mm³				0.973			0.16			0.438
≥1.5	170	NA	NA–NA		26.2	21.0–31.4		2.9	1.1–6.3	
<1.5	20	NA	33.3–NA		52.1	12.1–NA		0.0	0.0	
Platelet count at time prior ASCT, /mm³				0.332			0.149			0.508
≥150	175	79.6	71.2–85.8		29	24–32.9		2.9	1.1–6.2	
<150	15	72.2	41.7–88.6		14.5	7.3–26.4		0.0	0.0	
Glomerular filtration rate at time prior ASCT, mL/min/1.73m²				0.119			0.191			<0.001
≥60	167	NA	NA–NA		29	24.0–32.9		1.2	0.2–3.9	
<60	23	NA	48.5–NA		18.6	14.5–33.0		13.0	3.1–30.2	
Conditioning regimen				0.145			0.336			0.653
High dose melphalan	122	77.6	65.3–86.0		24	18.6–29.2		3.3	1.1–7.6	
Melphalan plus busulfan	23	95.2	70.7–99.3		32.7	25.4–NA		0.0	0.0	
Others[4]	45	72.8	56.9–83.6		29	17.3–39.2		2.2	0.2–10.3	
Infused CD34+ cell, x10⁶/kg				0.697			0.541			0.174
≥ Median (5.45)	95	NA	58.2–NA		29.2	20.3–43.2		1.1	0.1–5.2	
< Median (5.45)	95	NA	NA–NA		25.6	18.8–32.6		4.2	1.4–9.7	
Maintenance therapy after ASCT				0.4			0.224			0.601
Yes	58	NA	58.2–NA		31.1	18.8–31.4		1.8	0.1–8.3	
No	132	NA	NA–NA		25.6	24.0–51.8		3.0	1.0–7.1	

[1]Cut-off for low muscle density was defined by sex-specific lowest quantile: 31.8 HU in male and 18.4 HU in female, respectively; [2]others include four of bortezomib-dexamethasone, four of thalidomide-dexamethasone, and nine of bortezomib-melphalan-prednisolone; [3]others include 36 of G-CSF only, 84 of G-CSF plus etoposide, and 3 of G-CSF plus plerixafor; [4]others include 32 of melphalan, busulfan plus thiotepa, 2 of busulfan plus thiotepa, and 11 of bortezomib, busulfan plus melphalan; NA, not available due to not-reached median survival outcome; CI, confidence interval; ASCT, autologous hematopoietic stem cell transplantation; Ig, immunoglobulin; LDCT, low-dose chest CT; G-CSF; granulocyte-colony stimulation factor; TRM, transplant-related mortality; HU, Hounsfield unit.



Supplementary Figure 1. A strong correlation between 12th-paraspinal muscle area and 12th-total muscle area. In pilot investigation (n = 23), paraspinal muscle area (PSMA) and total muscle area (TMA) including latissimus dorsi, intercostal, rectus abdominis, external oblique, internal oblique, and paraspinal muscles were measured from axial computed tomography image at the level of 12th thoracic vertebra. Pearson correlation analysis showed that 12th-PSMA had a strong correlation with 12th-TMA (Pearson's correlation coefficient, 0.949). Since measuring 12th-PSMA instead of 12th-TMA is a simpler and more convenient method, 12th-PSMA was finally selected as the criterion in current study.