Original Study

Prognostic Effect of Low Subcutaneous Adipose Tissue on Survival Outcome in Patients With Multiple Myeloma

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Abstract

We retrospectively analyzed the volume of skeletal muscle and adipose tissue in 56 patients with newly diagnosed symptomatic multiple myeloma (MM) at a single institute. Low volume of subcutaneous adipose tissue was associated with poor overall survival (hazard ratio, 4.05; $P = .02$). Results of this study might indicate that a low volume of subcutaneous adipose tissue at baseline is an independent prognostic factor in patients with MM.

Background: Increasing evidence suggests that decreased skeletal muscle mass (sarcopenia) or adipose tissue assessed using computed tomography (CT) predicts negative outcomes in patients with solid tumors. However, the prognostic value of such an assessment in multiple myeloma (MM) remains unknown. **Patients and Methods:** Consecutive patients with newly diagnosed symptomatic MM were retrospectively analyzed. The cross-sectional area of skeletal muscles and subcutaneous or visceral adipose tissue was measured using CT. Body composition indexes (skeletal muscle index, subcutaneous adipose tissue index [SAI], and visceral adipose tissue index) were calculated. The association between these indexes and overall survival (OS) was examined. **Results:** Of 56 evaluable patients, 37 (66%) had sarcopenia. The 2-year OS in patients with SAI $<$ median was 58% compared with 91% in those with SAI $\geq$ median ($P = .006$). In multivariate analyses, SAI $<$ median was significantly associated with poor OS (hazard ratio, 4.05; $P = .02$). Sarcopenia was not associated with OS. The maximum value of the standardized uptake value was significantly higher in patients with SAI $<$ median ($P = .02$). **Conclusion:** The findings of this study suggest that low subcutaneous adipose tissue at baseline predicts poor survival outcome in patients with MM.

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Introduction

Multiple myeloma (MM) prognosis is influenced by several factors including disease status, treatment options, and host factors. The revised (R-) International Staging System (ISS) is used to determine MM stage on the basis of elevated or abnormal lactate dehydrogenase (LDH), albumin (Alb), or β-2 microglobulin (B2M) levels, and cytogenetic abnormalities.[1] MM treatment has significantly improved in recent years, introducing new treatment agents such as bortezomib (Bor) and immunomodulatory drugs (IMiDs).[2,3] The use of Bor- or IMiD-based chemotherapy regimens have been recommended for primary and salvage therapy.[4] Patients' age, performance status, and comorbidity index also affect clinical prognosis.[5,6]

Studies on solid tumors have shown that a low mass of skeletal muscle (sarcopenia) or adipose tissue at baseline is associated with clinical outcomes.[7-13] Only a few studies on non-Hodgkin lymphoma have examined body composition parameters in patients with hematological malignancies.[14-16] Computed tomography (CT) scan images have been commonly used to evaluate body composition parameters. The cross-sectional area of skeletal

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muscle and adipose tissue at the third lumbar vertebra correlates highly with the total body skeletal muscle and adipose tissue volume.[17,18] A CT scan is routinely used to diagnose and assess treatment options for solid tumors and lymphoma. Until recently, skeletal x-rays had been the standard modality used to evaluate bone lesions in MM. A recent prospective study showed that high fluorine-18 (18F) fluorodeoxyglucose (FDG) uptake or high tumor burden assessed using positron emission tomography (PET) integrated with CT (PET/CT) is a strong prognostic factor for MM.[19] After the 2014 update of the International Myeloma Working Group (IMWG) criteria for the diagnosis of MM, CT or PET/CT were finally accepted as standard modalities for MM diagnosis.[20]

Because diagnostic imaging for MM has been under development, the relationship between body composition factors and clinical outcome in patients with MM has not been well studied and remains unclear. In this study, we performed a retrospective analysis of MM patients to investigate this relationship.

Patients and Methods

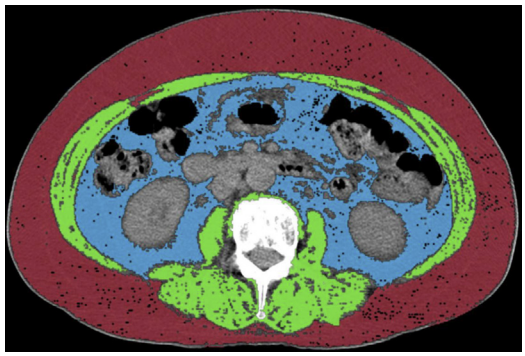
Patient Selection Criteria

This study included patients who were consecutively diagnosed with symptomatic MM between May 2009 and January 2015 in Saiseikai Nakatsu Hospital, Japan. The inclusion criteria were as follows: patients who underwent CT or 18F-FDG PET/CT examination before initial treatment with image quality adequate for evaluating body composition. 18F-FDG PET/CT examination in patients with newly diagnosed MM has been covered by the National Health Insurance in Japan since 2010. We have performed CT or 18F-FDG PET/CT examination as a part of a practical workup for MM regardless of clinical symptoms or characteristics. Patients who did not receive anticancer chemotherapy and those lost to follow-up before the completion of the first chemotherapy regimen were excluded. This study was approved by our institutional ethics committee and was conducted in accordance with the Declaration of Helsinki.

Body Composition Evaluation

The measurements of body composition were conducted using images from CT or PET/CT scans performed as part of a practical workup for MM before any treatment. The third lumbar vertebra region was used for evaluating body composition. Images were analyzed using the free image viewer Osirix Lite version 6.5.2 (Osirix Foundation). The cross-sectional area of skeletal muscles and subcutaneous or visceral adipose tissue were measured in units of squared centimeters. The CT Hounsfield unit thresholds were −29 to 150 for skeletal muscles, −190 to −30 for subcutaneous adipose tissue, and −150 to −50 for visceral adipose tissue. Skeletal muscles assessed included the psoas, abdominal, rectus abdominus, and paraspinal muscles. These values were normalized to height in squared meters to calculate the skeletal muscle index (SMI), subcutaneous adipose tissue index (SAI), and visceral adipose tissue index (VAI) in units of centimeters squared/meters squared (Figure 1).[16,17] The cutoff values for sarcopenia were defined as SMI of <43 for men with body mass index (BMI) of <25, SMI of <53 for men with BMI of ≥25, and SMI of <41 for women, as previously reported.[8] As in preceding studies, the cutoff values for low subcutaneous or visceral adipose tissue were adopted if SAI or VAI were lower than the median for men and women. These measurements were conducted by 2 physicians (Y.T. and K.S.), who were blinded to patient name and clinical outcome.

Figure 1 Adipose Tissue and Skeletal Muscle Assessment Using Computed Tomography Imaging. Red Area Indicates Subcutaneous Adipose Tissue, Green Area, Skeletal Muscle, and Blue Area, Visceral Adipose Tissue



Previously Known Prognostic Factors and Other Clinical Parameters

The following information was collected using the database at our institution: type of M protein; levels of serum LDH, Alb, and B2M; presence of high-risk cytogenetic abnormalities t(4;14), t(14;16), or del 17p in interphase fluorescence in situ hybridization (FISH) analyses; estimated glomerular filtration rate (eGFR); Eastern Cooperative Oncology Group performance status (ECOG PS); Charlson comorbidity index (CCI); ISS; BMI; Bor- or IMiD-based induction chemotherapy; whether autologous peripheral blood stem cell transplantation (aPBSCT) was performed; Grade ≥3 nonhematologic adverse events at the time of induction chemotherapies; and cause of death. They received salvage therapy in case of disease progression. The choice of induction chemotherapy or salvage therapy was left to physicians. The chemotherapy regimens during this period were recorded. In patients who underwent 18F-FDG PET/CT scan, the maximum value of the standardized uptake value (SUV_{max}) of MM lesions was recorded. The degree of FDG uptake was indicated by SUV_{max} in the hottest lesion. The evaluation of PET/CT scans for MM lesions was performed by 2 radiologists (H.S. and T.O.), who have substantial experience in MM image assessment.

Statistical Analysis

The primary end point was overall survival (OS), which was calculated from the date of diagnosis to the date of death from any cause or the date of last follow-up. Body composition indexes at baseline (sarcopenia, median SMI, SAI, and VAI) and BMI of ≥ 25 (ie, obese or overweight) were considered. The following previously known prognostic factors or other clinical parameters were considered: Alb < 3.5 g/dL, B2M ≥ 5.5 mg/L, LDH > upper limit of