PET-CT Guided Adipose Tissue Indices as Prognostic Factors in Multiple Myeloma

Demircan OZBALCI[1], Mehmet ERDOGAN[2], Emine GUCHAN ALANOGLU[1], Sevim Sureyya SENGUL[2], Burcu BACAK[3], Hande Nur EROGLU[4], Ismail OZKOC[2]

[1] Suleyman Demirel University Faculty of Medicine, Department of Hematology
[2] Suleyman Demirel University Faculty of Medicine, Department of Nuclear Medicine
[3] State Hospital of Kumluca, Department of Internal Medicine
[4] Isparta Provincial Health Directorate, Department of Public Health

ABSTRACT

This study evaluated the prognostic impact of obesity in multiple myeloma with 18F-FDG PET/CT guided measurement of total abdominal adipose tissue (TAAT) radiodensity, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) glucose uptake. Three hundred and eight patients who have been diagnosed with multiple myeloma and received chemotherapy in our hospital from 2011 to 2021 were retrospectively evaluated. 18F-FDG PET/CT scans at diagnosis were used to calculate TAAT, VAT and SAT maximum standardized uptake value (SUVmax) and these values were evaluated for their effect on adverse prognostic factors, progression free (PFS) and overall survival (OS). After being evaluated for exclusion criteria, 94 patients were included for the study. Adipose tissue volume greater than 6658 cc, TAAT radiodensity less than -97 Hounsfield units (HU), and SAT SUVmax of 0.3 or lower were associated with significantly increased the OS (p= 0.040, p< 0.001 and p< 0.001, respectively). Each step of worsening of response to treatment, no transplantation, SAT SUVmax more than 0.3 were associated with reduced PFS in patients with myeloma (p= 0.004, p= 0.001 and p= 0.005 respectively). Similarly, each step of worsening response to treatment, total protein greater than 6.6 mg/dl, each increase in stage, no transplantation, TAAT radiodensity more than -97 HU were associated with significantly reduced OS (p= 0.003, p= 0.009, p< 0.001, p= 0.028 and p< 0.001 respectively). SAT SUVmax and TAAT radiodensity are two independent prognostic marker that influences PFS and OS respectively.

Keywords: Multiple myeloma, Subcutaneous adipose tissue, Total abdominal adipose tissue, Radiodensity, 18F-FDG PET/CT

INTRODUCTION

Multiple myeloma (MM) is plasma cell malignancy that has an incidence of 6/100000 in western countries.[1] Its median age is 65 years old and usually represents with osteolytic bone disease due to increased osteoclastic activity and suppressed osteoblastic activity, renal failure and hyperviscosity related to monoclonal "M" protein secreted by clonal plasma cells. Therapy is directed to suppress plasma cells and restore bone architecture both directly by bisphosphanates and indirectly by chemotherapy. To date, there is no cure for MM; Bortezomib and lenalidomide based therapies are chosen for frontline therapy of disease and eligible patients are referred to autologous stem cell transplantation as a consolidation therapy. Newly introduced drugs such as carfilzomib, ixazomid, pomalidomide and recently daratumumab and their combinations challenges the need for transplantation, but autologous transplantation is still the first option for eligible patients for consolidation therapy.[2] Despite newly introduced therapies, MM is still an incurable disease and efforts to individualize therapy to each patient still continuing. Several prognostic indices have been developed to define the prognosis of patients.

Revised international staging system assessed not only beta-2 microglobulin and albumin but also cytogenetic abnormalities such as del 17p, t (4;14) and t (14;16) to reach conclusive results for prognosis.[3] Age, lactate dehydrogenase levels, platelet counts, and extramedullary disease are also important factors for prognosis.[4] Gene expression profile reveals important clues about prognosis but is not routinely available in many centres. Widely available and easily accessible prognostic markers are needed in multiple myeloma.

Obesity is defined as excessive or abnormal accumulation of health and linked to several health issues. This definition should not be simply relied to body mass index; rather it was found that the distribution of adipose tissue (subcutaneous versus visceral) also affects the nature and pathogenesis of several diseases.[5] Obesity was also associated with malignancies; several studies have clearly shown undeniable links to cancer development in obese patients.[6,7] Adipocytes were the most prevalent cell type of bone marrow, and these cells were shown to regulate the inflammatory cascade and alter immune mechanisms to initiate tumorigenesis and proliferation of cancer cells.[8] It was also shown that adipocytes from overweight and obese individuals had altered secretion of inflammatory cytokines compared to normal ones.[9] In case of MM, previous studies showed that obesity was clearly associated with monoclonal gammopathy of undetermined significance (MGUS) and MM.[10,11] Obesity had also negatively affected the prognosis of patients.[12] Therefore, obesity could be associated with adverse prognosis in Multiple Myeloma but there were few studies evaluating the subject so, the purpose of this study was to evaluate the prognostic impact of obesity in Multiple Myeloma with 18F-FDG PET/CT guided measurement of total abdominal adipose tissue (TAAT) radiodensity, subcutaneous tissue (SAT) and visceral adipose tissue (VAT) glucose uptake.

PATIENTS and METHODS

Three hundred and eight patients who have been diagnosed with multiple myeloma and received chemotherapy in our hospital from 2011 to 2021 were retrospectively evaluated. Those who were diagnosed as MM but lost on follow-up or did not have an 18F- FDG PET/CT scan on diagnosis were excluded. Patients who had not adequate information about follow-up, treatment response, PET/CT scan were excluded from the study. After evaluation for excluding criteria, ninety-four patients with MM were included in the study. Two patients were also excluded from the analysis at treatment analysis stage, as they did not receive treatment in our hospital and the treatment response was unknown. Age, gender, Durie-Salmon stage, total blood count, lactate dehydrogenase, creatinine, calcium, albumin values, bone marrow plasma cell percentages, genetic mutations, the number of course of treatment and the treatment protocol, their response to treatment, progression free survival (PFS) and overall survival (OS) of the patients were recorded. In the second phase of the study, the effects of clinicopathology, treatment characteristics and calculated adipose tissue indices on PFS and OS were examined. Treatment protocols were classified as Bortezomib based, lenalidomide-thalidomide based, Vincristine-Adriamycin-Dexamethasone (VAD) and other. Overall survival was calculated as the period from the date of diagnosis to death in months, and for surviving patients, the time elapsed to the date of analysis (11.11.2021) was taken as a basis. Progression-free survival, on the other hand, was calculated as months between the end of treatment and relapse. Remission and relapse were determined according to criteria in the international myeloma study group as minimal response (MR), partial response (PR), very good partial response (VGPR), complete response (CR), and stringent complete response (SCR).

Body mass index (BMI) was calculated before first line treatment and 18F FDG PET/CT at diagnosis for staging were used for the study. 18F FDG PET/CT images were acquired with a Philips GEMINI TF PET/CT scanner (Philips Medical Systems, Cleveland, Ohio, USA) with the time-of-flight imaging and 64-slice Computed Tomography (CT) scanner. In each patient, L1-L5 vertebral level was drawn manually as the area of interest in the craniocaudal plane, and the scans were evaluated and interpreted by two Nuclear Medicine Specialists. In order to determine the amount TAAT in this area, in the Workstation Extended Brilliance TM

Workspace V4.0.3.5, the Hounsfield Units (HU) reference range was set to be centre: -110 (-190, -30), width: 160 in accordance with the oil density. Subcutaneous and visceral adipose tissue volume in the selected range and HU reference range was calculated. The mean HU value was recorded. In addition, standardized uptake value (SUVmax) was calculated automatically in subcutaneous adipose tissue and visceral adipose tissue around the kidney at the level of L1-L5 vertebrae in the craniocaudal plane. The computer program gave the amount of fat in this selected area quantitatively in cubic centimetres (cm^3).

The research protocol was reviewed and approved by Suleyman Demirel University Medical Faculty Clinical Research Ethics Committee (December 23, 2021/379), informed consent was obtained from all patients and the study was carried out according to the Declaration of Helsinki.

Statistical Analysis

The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/ Shapiro-Wilk tests). Descriptive analyzes were given using the mean and standard deviations. Variation of adipose tissue indices calculated in myeloma patients according to clinicopathological and treatment characteristics; Kruskal Wallis test was used to compare more than two independent groups that did not fit normally, Student's t-test was used to compare two independent groups of normally distributed variables, and Mann Whitney-U test was used for two independent group variables that did not have normal distribution. The relationship between adipose tissue indices was determined by Pearman correlation analysis.

The effect of predisposing factors on survival in myeloma patients was calculated using log rank test and survival rates using Kaplan-Meier survival analysis. In multivariate analysis, possible factors determined in previous analyzes (variables associated with univariate analyses and close to the type 1 error level [cut-off value p= 0.25]) were used, and independent factors in predicting survival were examined by using backward LR selection method and Cox regression analysis. Among the parameters with a similar effect on survival and with high correlation rates, those that were clinically significant with the model were selected. SPSS for Windows version 25.0 package program was used for statistical analysis and $p< 0.05$ was considered statistically significant.

RESULTS

The mean age of the patients at diagnosis was calculated as 65.3±10.5(min:41 - max:86). The mean height of the patients was 162.9±9.3 (min:126-max:182), the mean weight was 72.5±14.2 (min:39-max:113), and the mean BMI was 27.2±4.4 (min:18-max:39). The changes in fat tissue indices and BMI averages of the patients according to their clinicopathological differences were calculated. Patients over 65 years of age and male patients were found to have significantly lower adipose tissue indices. Patients with creatinine > 0.95 mg/dl, corrected calcium levels > 10.6 mg/dl, white blood cell count between 4000 and 10000, total protein 6.6 g/dl ≤, hemoglobin < 10 g/dl and albumin < 3.5 g/dl had significantly increased TAAT radiodensity. SAT and VAT SUVmax was significantly higher in patients with total protein below 6,6 g/dl and albumin below 3.5 g/dl respectively.

The changes in BMI and adipose tissue indices were analyzed according to the treatment status of the patients (Table 1). According to the treatments, patients were analyzed in four subgroups; bortezomib based treatment (bortezomib and/or cyclophosphamide and/or dexamethasone and/or doxorubicin); lenalidomide or thalidomide-based therapy, VAD and other treatment protocols (cyclophosphamide-vincristine-methyl prednisolone or cyclophosphamide-dexamethasone or interferon). SAT SUVmax and TAAT radiodensity of patients with bone marrow transplantation were significantly lower compared to patients without transplantation. In terms of treatment response; TAAT radiodensity of patients that showed partial response to treatment were found to be significantly lower than the group that showed progression and whose treatment outcome was unknown (p= 0.040, p= 0.035; respectively, Table 1).

Table 1. BMI and adipose tissue indices according to the treatment characteristics of the patients

Characteristics		BMI VE ABDOMINAL ADIPOSE TISSUE INDICES (Median ± SD)					
		Number	BMI	Volume (cc)	Hounsfield Units	SAT suvmax	VAT suvmax
Treatment††	Bortezomib	68	27.0±4.6	6742.8±2859.9	-94.1±13.7	0.39±0.2	0.62±0.3
	Lena& Thali	2	24.7±2.3	4715.1±226.3	-97.8±1.6	0.35±0.1	0.55±0.1
	VAD	13	29.2±4.9	7613.8±3118.2	-99.2±9.7	0.31±0.1	0.61±0.3
	Other	9	27.2±2.5	5964.1±1654.2	-96.5±8.9	0.33±0.1	0.71±0.2
		92	*p= 0.414*	*p= 0.317*	*p= 0.805*	*p= 0.851*	*p= 0.623*
Transplantation**	Negative	71	26.9±4.1	6455.0±2800.5	-93.3±13.1	0.41±0.3	0.64±0.3
	Positive	23	28.4±5.2	7287.8±2936.1	-99.9±10.0	0.30±0.1	0.63±0.3
		94	*p= 0.210*	*p= 0.322*	*p= 0.033*	*p= 0.038*	*p= 0.975*
Treatment	CR	13	27.6±3.9	6620.8±2211.1	-96.2±11.2	0.37±0.2	0.63±0.3
response††	VGPR	27	27.0±5.1	7043.1±3501.4	-97.2±12.6	0.37±0.2	0.60±0.3
	PR	15	27.4±3.4	7691.5±2367.5	-102.8±8.8	0.26±0.1	0.55±0.2
	MR	3	24.7±4.4	4042.2±1735.5	-82.6±8.2	0.77±0.6	0.90±0.1
	Stable	5	27.2±7.2	6968.9±3275.2	-91.6±18.9	0.42±0.2	0.58±0.2
	Progressive	7	27.2±1.9	5337.4±1177.8	-89.0±5.7	0.41±0.1	0.60±0.1
	Unknown	24	27.5±4.8	6249.4±2799.7	-90.7±13.5	0.41±0.2	0.71±0.3
		94	*p= 0.942*	*p= 0.204*	*p= 0.005^*	*p= 0.035^^*	*p= 0.185*
Survival*	Alive	47	27.9±4.4	7446.1±2704.6	-101.1±10.6	0.31±0.1	0.59±0.2
	Deceased	47	26.5±4.4	5871.4±2781.7	-88.7±11.6	0.46±0.3	0.68±0.3
		94	*p= 0.133*	*p= 0.007*	*p< 0.001*	*p= 0.001*	*p= 0.108*

In the analysis of variables; *= independent groups T-test; †= Mann Whitney-U test; ††= Kruskal Wallis test were performed.
^= In post hock tests, the difference is between the group with partial response and the group that progresses, and the treatment result is unknown.
VAD= Vincristine-adriamycin-dexamethasone, CR= Complete response, VGPR= Very good partial response, MR= minimal response,
PR= Partial response

Overall survival was found to be significantly increased for being under the age of 65 (p< 0.001), female gender (p= 0.048), creatinine values lower than 0.95 mg/dl and hemoglobin >10 gr/dl (p= 0.027). When stages 2a and 2b were combined and evaluated due to insufficient number of patients in each Durie-Salmon stage, each stage increase of the patients significantly decreased the overall survival time (linear p= 0.011). In addition, being under 65 years of age (p< 0.001) and creatinine values lower than 0.95 mg/dl (p= 0.033) significantly increased the progression-free survival.

When the effects of the treatments on both PFS and OS were examined; autologous transplantation was associated with significantly increased PFS and OS. Due to low number of patients in subgroups of response, CR-VGPR, PR-MR and stable-progressive disease were merged and analysis showed that each step worsening of the treatment response significantly decreased both progression free and overall survival (linear p= 0.011).

When the effects of adipose tissue indices of the patients on PFS and OS were examined by determining the cut-off values over the averages; volume greater than 6658 cc, TAAT radiodensity less than -97 HU, and SAT SUVmax of 0.3 or lower were associated with significantly increased the OS (p= 0.040, p< 0.001 and p< 0.001, respectively; Table 2).

When the correlations of the adipose tissue index values of patients with myeloma were examined, it was found that the indices were weakly, moderately and strongly correlated with each other respectively.

Finally, all factors affecting the survival of patients with myeloma were evaluated with the cox regression model. Each step of worsening of response to treatment (complete and good partial response/ partial and minimal response/stable and progressive / unknown) (linear HR= 1.327; p= 0.004), no transplantation (HR= 2.954; p= 0.001), SAT SUV

Table 2. Median survival of patients with myeloma and adipose tissue values

Characteristic		Progression Free Survival				Overall Survival			
		n	Median survival	SE	p	n	Median survival	SE	p
BMI	27 ≤	46	19.7	3.9	*0.756*	47	39.3	12.5	*0.212*
	27 >	46	25.2	1.6		47	69.4	9.0	
Volume (cc)	6658 ≤	46	17.9	5.2	*0.781*	48	39.2	13.2	*0.040*
	6658 >	46	25.2	2.3		46	92.6	31.2	
HU	-97 ≤	46	26.2	1.2	*0.644*	46	172.6	28.3	*< 0.001*
	-97 >	46	17.3	3.7		48	49.6	8.9	
SAT suvmax	0.3 ≤	53	25.5	1.4	*0.143*	53	92.6	21.9	*< 0.001*
	0.3 >	39	13.1	1.7		41	26.9	7.9	
VAT suvmax	0.5 ≤	41	23.1	2.7	*0.445*	41	67.9	27.0	*726*
	0.5 >	51	24.6	6.1		53	69.4	20.9	

Long Rank (p), HU= Hounsfield Units, VAT= visceral adipose tissue, SE= Standard error, SAT= subcutaneous adipose tissue

more than 0,3 (HR= 2.163; p= 0.005), bortezomib treatment (HR= 4.965; p< 0.001) were associated with reduced PFS in patients with myeloma. Similarly, each step of worsening response to treatment (complete and good partial response/ partial and minimal response/stable and progressive / unknowns) (linear HR= 1.804; p= 0.003), total protein greater than 6.6 mg/dl (HR= 2.442; p= 0.009) , each increase in stage (linear HR= 1.714; p< 0.001), no transplantation (HR= 2.681; p= 0.028), TAAT radiodensity more than -97 HU (HR= 4.403; p< 0.001) were associated with significantly reduced OS.

DISCUSSION

The association between obesity and cancer was the point of interest in many studies. Obesity was directly linked to 13 different and unrelated types of cancer in one study.[13] Obesity was not only related to tendency for cancer formation but also associated with worse prognosis in cancer patients; Calle et al highlighted the increased risk of death in several different malignancies in both genders.[14] The increase in body mass index was directly related to a change in inflammatory cytokine profile.[15] Bullwinkle et al, showed that adipocyte derived stem cells from overweight, obese and super obese patients secreted increased amounts inflammatory cytokines and leptin; also, adipocyte conditioned media from obese and super obese had increased MM cell adhesion compared to normal and overweight media.[8]

The effect of abdominal adipose tissue on malignancies was evaluated in previous studies. Based on the results; body mass index could not only define obesity alone; rather the type, volume and distribution of adipose tissue must also be considered.[16,17] The localization of adipose tissue (subcutaneous or visceral) seemed to directly affect the prognosis of cancer. Central obesity which is related to visceral adipose tissue storage was shown to be related to cancer progression.[18] GroΔ et al found that, lower area of visceral adipose tissue has been associated with better treatment response in patients with newly diagnosed MM.[12] In one study, newly diagnosed patients with MM had more TAAT and SAT volume and higher VAT metabolic activity com-

pared to patients who were diagnosed as MGUS. No correlation was found between BMI and prognosis.[19] A Korean study evaluated the relationship between BMI and MM and showed that patients with low BMI had shorter mean OS compared to patients with BMI higher than 25. Those patients had also lower haemoglobin, higher creatinine levels and lower performance status.[20] In correlation with these findings, TAAT radiodensity and SAT-VAT SUVmax were higher in patients with creatinine levels more than 0.95 mg/dl, total protein, albumin and haemoglobin lower than 6.6, 3.5 and 10 gr/dl respectively in our study. Also, patients who were still alive had significantly more adipose tissue, had high TAAT radiodensity and low SAT SUVmax compared to others. Each step of worsening of response to treatment, no transplantation and SAT SUVmax more than 0.3 were associated with reduced PFS in patients with myeloma; similarly, each step of worsening response to treatment, total protein greater than 6.6 mg/dl, each increase in stage, no transplantation and TAAT radiodensity more than -97 HU were associated with significantly reduced OS in regression analysis.

Low radiodensity (mean -101.1±10.6) was associated with white adipose tissue, as brown adipose tissue represents with HU of -10 to -87.[21] White adipose tissue is responsible for deposition and release of lipid as an energy source when needed and brown adipose is thermogenic.[22] Brown and white adipose tissues have different physiological roles; the conversion of white adipose tissue to brown was shown to be related to cachexia.[23] Cancer related lipolysis was found to be responsible for this conversion; wasting of white adipose tissue and increase in brown adipose tissue were seen in malignancies as a result.[24] Also, lipolysis was shown to reflect the aggressiveness of cancer.[25]

Patients with high 18F-FDG uptake and high brown tissue seemed to link with adverse prognosis in MM. High 18F- FDG uptake might be associated with ongoing inflammation in adipose tissue; in fact, several studies showed macrophage and leukocyte mediated inflammation in adipose tissue took an important part in oncogenesis.[22,26] Pro-inflammatory cytokine production (tumour necrosis factor-α, interleukin-6, interferon-γ, interleukin-1β), chronic inflammation, activated leukocyte induce oxidative stress, increased DNA damage and reduced DNA repair seemed to influence on prognosis of patients in MM as well as other cancer types.[27-29] Indeed, we found that, TAAT radiodensity lower than -97 HU, SAT SUVmax lower than 0.3 and total adipose tissue volume higher than 6658 cc were significantly associated with increased PFS and OS. Similarly, negative correlation was found between SAT SUVmax, TAAT radiodensity values and PFS-OS respectively. Each step of change in TAAT radiodensity and SAT SUVmax significantly affected PFS and OS. High SAT and VAT SUVmax were also significantly associated with adverse prognostic markers such as higher age, high creatinine and stage, low total protein and albumin values. Two recently published studies concluded similar results.[30,31] Patients with higher SAT radiodensity had significantly short event-free and OS. Adipose tissue uptake was also higher in these patients as in our study.[30] In the other study, although SAT SUVmax was found to be an adverse prognostic factor in univariate analysis, only high VAT 18F-FDG was found to be related to significantly reduced OS.[31] SAT or VAT area were not found to be associated with survival in these studies though; we found significantly longer PFS and OS in patients with larger adipose tissue volume in correlation with previous literature.[12,32]

Transplantation was related to significantly longer PFS and OS in our study. Previous studies also showed that autologous transplantation was safe and significantly increased OS in newly diagnosed MM after induction therapy.[33] Vogl et al found that obese and severe obese patient who received melphalan and total body irradiation conditioning had superior PFS and OS.[34] The authors noted that, this significance was not associated with dose modifications of Melphalan or total body irradiation. Similarly, Shultes et al pointed out that, Melphalan dose adjustment were not associated with adverse prognosis.[35] We also found that, patients who received autologous transplantation had more TAAT volume, and less SAT SUVmax levels and autologous transplantation had significant positive impact on PFS and OS.

Retrospective design was the main limitation for our study. The study did not include hormone and cytokine evaluations; leptin and pro-inflammatory

cytokine measurements certainly would add useful information as previous studies.[30,31] Also, bortezomid treatment was found to be associated with shorter PFS. This could be attributable to large part of study patients (about 74%) received bortezomib as a first line therapy. This could also be the main strength of the study; 76% of patients received new treatment schedules such as bortezomid and lenalidomide-thalidomide based therapies, so our evaluation was on subjects with new generation therapies. Also, large number of patients evaluated in our study compared to previous studies was also the other factor that could be mentioned as a main strength.

In conclusion, SAT SUVmax and TAAT radiodensity are two independent prognostic markers that influence PFS and OS respectively. 18F-FDG PET/CT can be used not only as a staging instrument but also a prognostic tool to determine the prognosis of patients with multiple myeloma.

Acknowledgement:

The authors appreciate the efforts of Ali Ozdamar for the study.

REFERENCES

1. Diaz-delCastillo M, Chantry AD, Lawson MA, Heegaard AM. Multiple myeloma- A painful disease of the bone marrow. Semin Cell Dev Biol 112: 49-58, 2021.
2. Devarakonda S, Efebera Y, Sharma N. Role of stem cell transplantation in multiple myeloma. Cancers (Basel) 13: 863, 2021.
3. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report from International Myeloma Working Group. J Clin Oncol 33: 2863-2869, 2015.
4. van de Donk NWCJ, Pawlyn C, Yong KL. Multiple myeloma. Lancet 397: 410-427, 2021.
5. Neeland IJ, Ayers CR, Rohatgi AK, et al. Associations of visceral and abdominal subcutaneous adipose tissue with markers of cardiac and metabolic risk in obese adults. Obesity (Silver Spring) 21: E439-447, 2013.
6. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 348: 1625-38, 2003.
7. Ligibel JA, Alfano CM, Courneya KS, et al. American Society of Clinical Oncology position statement on obesity and cancer. J Clin Oncol 32: 3568-3574, 2014.
8. Bullwinkle EM, Parker MD, Bonan NF, et al. Adipocytes contribute to the growth and progression of multiple myeloma: Unraveling obesity related differences in adipocyte signalling. Cancer Lett 380: 114-121, 2016.
9. Booth A, Magnuson A, Fouts J, Foster M. Adipose tissue, obesity and adipokines: role in cancer promotion. Horm Mol Biol Clin Investig 21: 57-74, 2015.
10. Landgren O, Rajkumar SV, Pfeiffer RM, et al. Obesity is associated with an increased risk of monoclonal gammopathy of undetermined significance among black and white women. Blood 116: 1056-1059, 2010.
11. Carson KR, Bates ML, Tomasson MH. The skinny on obesity and plasma cell myeloma: a review of the literature. Bone Marrow Transplant 49: 1009-1015, 2014.
12. GroΔ JP, Nattenmüller J, Hemmer S, et al. Body fat composition as predictive factor for treatment response in patients with newly diagnosed multiple myeloma - subgroup analysis of the prospective GMMG MM5 trial. Oncotarget 8: 68460-68471, 2017.
13. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body Fatness and Cancer--Viewpoint of the IARC Working Group. N Engl J Med 375: 794-798, 2016.
14. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 348: 1625-38, 2003.
15. Rajala MW, Scherer PE. Minireview: The adipocyte--at the crossroads of energy homeostasis, inflammation, and atherosclerosis. Endocrinology 144: 3765-3773, 2003.
16. Rosen ED, Spiegelman BM. What we talk about when we talk about fat. Cell 156: 20-44, 2014.
17. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev 21: 697-738, 2000.
18. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. Eur Urol 63: 800-809, 2013.
19. Veld J, O'Donnell EK, Reagan MR, et al. Abdominal adipose tissue in MGUS and multiple myeloma. Skeletal Radiol 45: 1277-1283, 2016.
20. Jung SH, Yang DH, Ahn JS, et al. Decreased body mass index is associated with poor prognosis in patients with multiple myeloma. Ann Hematol 93: 835-840, 2014.
21. Aust S, Knogler T, Pils D, et al. Skeletal muscle depletion and markers for cancer cachexia are strong prognostic factors in epithelial ovarian cancer. PLoS One 10: e0140403, 2015.
22. Lengyel E, Makowski L, DiGiovanni J, Kolonin MG. Cancer as a Matter of Fat: The Crosstalk between Adipose Tissue and Tumors. Trends Cancer 4: 374-384, 2018.