Int J Clin Exp Pathol 2019;12(2):619-627
www.ijcep.com /ISSN:1936-2625/IJCEP0088219

Original Article

Clinical relevance of PET/CT in patients with newly diagnosed multiple myeloma

Chaoyu Wang, Ling Wu, Chengtao Sun, Yizhuo Zhang

Department of Hematology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin 300060, China

Received November 10, 2018; Accepted December 21, 2018; Epub February 1, 2019; Published February 15, 2019

Abstract: Objective: Currently, the prognosis of standardized uptake value still has no consensus. We evaluated the role of the maximum standardized uptake value (SUV_{max}) of the MM lesions and the extramedullary disease (EMD) with the highest metabolic activity on PET/CT in predicting survival of newly diagnosed multiple myeloma (MM) patients. Methods: A total of 123 previously untreated, newly diagnosed patients were enrolled in this study, who were diagnosed at the Tianjin Medical University Cancer Institute and Hospital between September 2008 and February 2018. All patients with available PET/CT information at diagnosis were analyzed. Results: We found that no clinical characteristics were significantly different between the pathological fracture groups. However, laboratory findings including elevated creatinine and anemia at diagnosis corresponded to osteolytic lesions at baseline PET/CT (elevated creatinine, P = 0.024; anemia, P = 0.025). Compared to $SUV_{max} < 5.7$ group, the proportion of patients with EMD was significantly high in the $SUV_{max} \geq 5.7$ group (P = 0.046). Multivariate analysis using a Cox proportional hazards model showed that age > 65, poor treatment response and EMD positive were independent poor prognostic factors for newly diagnosed MM patients. Conclusion: We confirm the prognostic value of EMD, as detected by PET/CT, in newly diagnosed multiple myeloma patients. Therefore, the presence of EMD in newly diagnosed MM tends to be more important than the SUV_{max}.

Keywords: Multiple myeloma, PET/CT, extramedullary disease, prognosis

Introduction

Multiple myeloma (MM) is a hematologic neoplasm characterized by monoclonal proliferation of malignant plasma cells derived from B cells in the bone marrow and production of monoclonal immunoglobulins, and accounts for more than 10% of all hematologic malignancies [1, 2]. Over the past few decades, clinical outcomes of MM have significantly improved with the introduction of novel therapeutic agents such as thalidomide and bortezomib into autologous stem cell transplantation (ASCT). With the use of these newer therapeutic strategies, progression free survival (PFS) and overall survival (OS) have improved [3-5].

Positron emission tomography (PET) uses ^{18}Fluorine-fluoro-deoxy- glucose (^{18}F-FDG) as a radiotracer to detect glucose metabolism throughout the body. Compared with normal cells, tumor cells have a higher metabolic rate. Uptake can be estimated by calculating the standardized uptake value (SUV), which is the uptake of ^{18}F-FDG corrected for administered dose and patient weight. PET imaging has limited spatial resolution but combining it with computed tomography (CT) imaging addresses this issue and enables areas of active disease to be identified with exact anatomical localization [6-8].

Bone disease is one of the major clinical features of MM, and plain radiography has been the conventional method for skeletal survey in MM patients [9]. Whole-body X-ray can detect the presence of osteolytic or osteopenic lesions and is classified as a 'morphological' imaging technique. However, it is now being challenged by advanced radiological modalities [10]. In contrast to simple X-ray, novel imaging methods such as magnetic resonance imaging (MRI) and PET/CT provide 'functional' information regarding lesions, as well as morphologic and

anatomic details [11-13]. Several studies have shown that PET/CT identifies more lesions than X-rays in 40-60% of cases and can also detect lesions in patients with negative skeletal surveys [14]. PET/CT is useful for investigating equivocal cases when skeletal survey has not detected clear evidence of lytic bone damage, but patients remain symptomatic.

Recently, PET/CT has also been used in MM imaging. Preliminary reports have shown that high uptake of ^{18}F-FDG by tumor cells is associated with the metabolic activity of the tumor in MM [15].

The aim of this study was to investigate the role of the SUV_{max} of the MM lesions and the extramedullary disease (EMD) with the highest metabolic activity on PET/CT in predicting survival of newly diagnosed myeloma patients.

Methods

Patient samples

Patients diagnosed with MM were retrospectively reviewed at Tianjin Medical University Cancer Institute and Hospital from September 2008 to February 2018. These patients were diagnosed as MM on the basis of the criteria defined by the International Myeloma Working Group (IMWG). Patients who lost follow-up or lack indispensable medical documents were excluded. All patients had symptomatic myeloma requiring anti-myeloma chemotherapy. The patients with available PET/CT information at diagnosis were analyzed. One hundred and twenty-three patients were finally enrolled.

Treatment response was defined according to the IMWG criteria. MM results in bone destruction and extramedullary lesions, which is defined as EMD. EMD is a type of MM defined by the presence of extra-skeletal clonal plasma cell infiltration. EMD can be present at the time of either diagnosis (primary EMD) or relapse (secondary EMD) [16, 17].

^{18}F-FDG PET/CT

All ^{18}F-FDG PET/CT imaging was done according to the standard protocol. Patients fasted for at least 6 h prior to PET/CT. Blood glucose levels were measured before the injection of FDG and were below 160 mg/dl. Sixty minutes after the injection of ^{18}F-FDG (dose 0.14 mCi/kg) imaging was started on a Discovery LS PET/CT scanner (General Electric Medical Systems, Milwaukee, WI, USA). A real whole-body emission PET scanning in 3-D mode (at 3 min/bed position) was done following a dose (120 keV, 10-100 mAs) whole-body CT that was principally used for attenuation correction purposes.

Criteria to define PET/CT positivity included the following: either presence of focal areas of detectable increased tracer uptake within bones (e.g., more intense than background BM uptake) excluding articular processes, with or without any underlying lesion identified by CT, or a standardized uptake value (SUV) maximum (max) based on body weight according to standard formula ≥ 2.5 within osteolytic CT areas exceeding 1 cm in size or > 1.5 within osteolytic CT areas ranging between 0.5 and 1 cm in size.

All ^{18}F-FDG PET/CT images were visually evaluated and quantified by a single nuclear medicine physician. In patients with more than one lesion with positive FDG uptake, the lesion with the highest SUV_{max} was included in the analysis. SUV_{max} was calculated using the following formula: tissue concentration (MBq/g)/injected dose (MBq)/body weight (g). SUV_{max} was defined as the maximum SUV of the hypermetabolic lesion showing the highest ^{18}F-FDG uptake.

Follow-up

The median follow-up was 18 months (range 1-75 months) starting from the date of diagnosis up to February 2018 or when death occurred. OS was measured from the date of diagnosis until the date of death from any cause or until the date of final follow-up. PFS was determined from the time of diagnosis until relapse or death from any cause.

Definitions

For a description of clinical characteristics, various laboratory findings were evaluated and defined as follows: hypoalbuminemia (albumin < 3.5 g/dl), elevated β2-microglobulin (β2-MG $\geq$ 5.5 mg/l), anemia (hemoglobin < 10 g/dl), azotemia (creatinine > 2 mg/dl), hypercalcemia (calcium > 10 mg/dl) and elevated lactate dehydrogenase (LDH, more than the upper limit of normal for LDH).

Statistical analysis

The statistical evaluation of the data was performed using SPSS statistical package version 24.0 (IBM, IL, USA). Differences in clinical char-

Table 1. Clinical characteristics of patients

Baseline characteristics	N (%)
Gender	
Male	77 (62.6)
Female	46 (37.4)
Age	
≤ 65	82 (66.7)
> 65	41 (33.3)
Histologic subtype	
IgG	64 (52.9)
IgA	23 (19.0)
IgD	5 (4.1)
Light chain	25 (20.3)
Non-secretory	4 (3.3)
Baseline laboratory findings	
Anemia	83 (67.5)
Hypoalbuminemia	78 (63.4)
Azotemia	41 (33.3)
Elevated LDH	29 (23.6)
Elevated β2-MG	93 (75.6)
Hypercalcemia	41 (33.3)
Elevated CRP	28/67 (41.8)
EMD	43 (35.0)
Osteolytic lesions	67 (54.5)
Pathological fracture	41 (33.3)
ISS stage	
I	31 (25.2)
II	35 (28.5)
III	57 (46.3)
R-ISS stage	
I	22 (17.9)
II	64 (52.0)
III	37 (30.1)
D-S stage	
I	10 (8.1)
II	27 (22.0)
III	86 (69.9)
Therapeutic strategy	
Chemotherapy based on thalidomide	42 (34.1)
Chemotherapy based on bortezomib	67 (54.5)
Chemotherapy plus ASCT	22 (17.9)
Treatment response	
CR	42 (34.2)
PR	40 (32.5)
SD	17 (13.8)
PD	24 (19.5)

acteristics were examined using the χ^2 test or Fisher's exact test. Relationships between variables were evaluated with Pearson's or Spearman's correlation tests. Survival analysis was carried out by using Kaplan-Meier and log-rank tests. Survivors were censored at the time of last contact. Univariate and multivariate analyses of prognostic factors were carried out using Cox regression. The variables found to be independently predictive of survival in univariate analysis were entered into the multiple regression method. p values < 0.05 were considered significant.

Results

Baseline characteristics

A total of 123 patients were retrospectively reviewed, which consisted of 77 men and 46 women with a median age of 60 years (range 37-81 years). At diagnosis, the distribution of patients according to the Durie-Salmon stage (DS) at presentation was I (n = 10, 8.1%), II (n = 27, 22.0%) and III (n = 86, 69.9%), respectively. Based on the International Staging System (ISS), 31 (25.2%), 35 (28.5%) and 57 (46.3%) patients fell into stage I, II and III. All 123 patients in the study received anti-myeloma chemotherapy, including thalidomide (T) containing regimen, bortezomib (B) containing regimen and chemotherapy plus ASCT. Sixty seven (54.5%) patients were treated with bortezomib containing regimen for first-line therapy, forty two patients (34.1%) received thalidomide combined with chemotherapy such as adriamycin and cyclophosphamide, twenty two (17.9%) patients were treated with the above chemotherapy plus ASCT. **Table 1** shows patient baseline characteristics.

Baseline PET Findings

The median value of SUV_{max} was 5.7 (range 1.2-32.9), and 65 patients (52.8%) showed a SUV_{max} > 5.7. From PET/CT at diagnosis, 43 patients (35.0%) had EMD, which varied in origin, including soft tissue, lymph nodes, lung, liver, gall bladder, urinary bladder, muscle, subglottis, thyroid cartilage and tonsils.

Correlations between osteolytic lesions, pathological fracture, SUV_{max} and laboratory findings

Tables 2 and **3** show the correlations between osteolytic lesions, pathological fracture, SUV_{max} and laboratory findings. According to **Table 2**,

Table 2. Correlations between osteolytic lesions, pathological fracture, and laboratory findings

Laboratory findings		Osteolytic lesions		*p*-value	Pathological fracture		*p*-value
		No	Yes		No	Yes	
Hemoglobin	Normal	24	16	0.025	26	14	0.785
	Low	32	51		56	27	
Albumin	Normal	22	21	0.640	24	19	0.122
	Low	34	46		58	22	
β2-MG	Normal	13	17	0.781	19	11	0.656
	High	43	50		63	30	
LDH	Normal	43	51	0.945	61	33	0.453
	High	13	16		21	8	
Creatinine	Normal	44	38	0.024	54	28	0.902
	High	12	29		28	13	
Calcium	Normal	40	42	0.398	57	25	0.402
	High	15	26		25	16	
CRP	Normal	15	24	0.220	28	11	0.213
	High	15	13		16	12	
Cytogenetic abnormality	No	14	14	0.249	19	9	0.872
	Yes	23	39		41	21	
EMD	No	31	49	0.059	57	23	0.141
	Yes	25	18		25	18	

Table 3. Correlations between SUV_{max} and laboratory findings

Laboratory findings		SUV_{max}		*p*-value
		5.7	5.7	
Hemoglobin	Normal	16	24	0.270
	Low	42	41	
Albumin	Normal	21	24	0.992
	Low	37	41	
Globulin	Normal	28	26	0.352
	High	30	39	
β2-MG	Normal	21	9	0.030
	High	44	49	
LDH	Normal	48	46	0.118
	High	10	19	
Creatinine	Normal	37	44	0.829
	High	21	20	
Calcium	Normal	38	33	0.474
	High	18	23	
CRP	Normal	17	22	0.725
	High	11	17	
Cytogenetic abnormality	No	17	11	0.172
	Yes	28	34	
EMD	No	43	37	0.046
	Yes	15	28	

no clinical characteristics were significantly different between the pathological fracture groups. However, when comparing laboratory findings based on osteolytic lesions, which is found by PET/CT, there were substantial significant differences. Laboratory findings including elevated creatinine and anemia at diagnosis corresponded to osteolytic lesions at baseline PET/CT (elevated creatinine, P = 0.024; anemia, P = 0.025). The other clinical characteristics did not differ between the osteolytic lesion groups. The median value of SUV_{max} in these patients was 5.7, so we chose SUV_{max} 5.7 as the cutoff value. According to **Table 2**, high β2-MG at diagnosis is correlation to SUV_{max} > 5.7 at baseline PET/CT (P = 0.030). Interestingly, compared to $SUV_{max} \leq 5.7$ group, the proportion of patients with EMD was significantly high in the SUV_{max} > 5.7 group (P = 0.046).

Prognostic analysis of EMD and SUV_{max}

With a median follow-up of 18 months (range 1-75 months), patients with EMD and without EMD had prognostic significance on both OS and PFS. The OS (P = 0.017) and PFS (P = 0.004) of patients with EMD positive is significantly shorter than EMD negative (**Figure 1**). The OS of patients with SUV_{max} < 5.7 is significantly longer than SUV_{max} > 5.7 (P = 0.032). However, there were no statistically significant differences in PFS between the two groups (P = 0.088) (**Figure 2**).

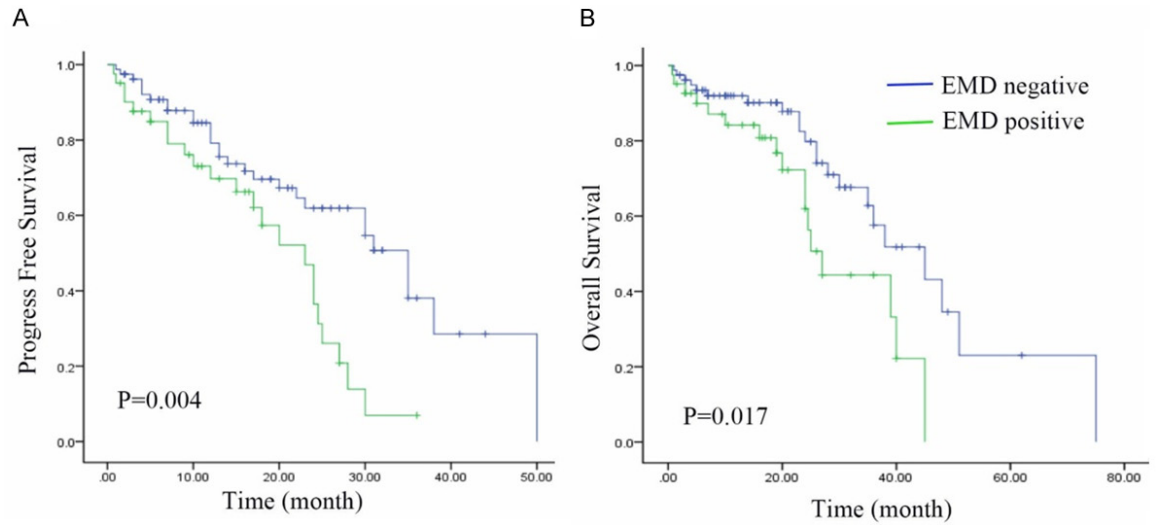

Figure 1. Kaplan-Meier curve of PFS (A) and OS (B) analysis. EMD negative patients had better PFS (P = 0.004) and OS (P = 0.017) than positive group.

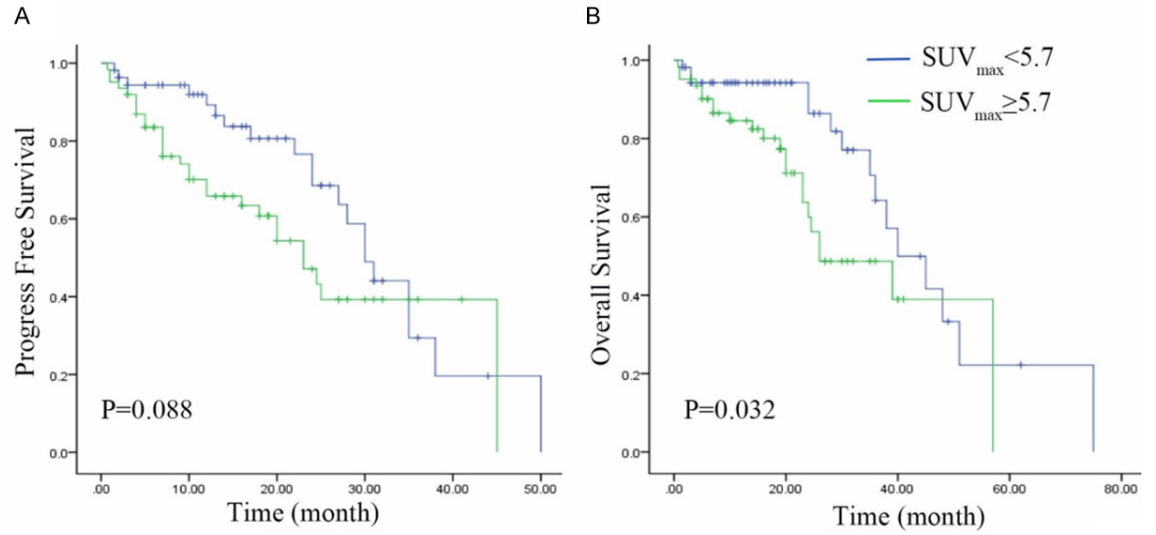

Figure 2. Kaplan-Meier curve of PFS (A) and OS (B) analysis. The OS (P = 0.032) of patients with SUV_{max} < 5.7 is significantly longer than SUV_{max} ≥ 5.7. There were no statistically significant differences in PFS (P = 0.088) between the two groups.

Univariate and multivariate analysis

In univariate analysis of the patients, age > 65 (P = 0.015), low albumin (P = 0.035), high LDH (P = 0.031), poor treatment response (P = 0.001), EMD positive (P = 0.049) and SUV_{max} > 5.7 (P = 0.032) were adverse prognostic factors for OS. While the unfavorable prognostic factors for PFS were age > 65 (P = 0.034), high β2-MG level (P = 0.038), poor treatment response (P = 0.001) and EMD positive (P = 0.043) (**Table 4**).

Multivariate analysis using a Cox proportional hazards model showed that age > 65 (P = 0.025), poor treatment response (P = 0.011), and EMD positive (P = 0.043) were independent poor prognostic factors for OS, and age > 65 (P = 0.02), high β2-MG level (P = 0.024), poor treatment response (P = 0.038), and EMD

Table 4. Univariate survival analysis of the patients

Variable	PFS *p*-value	OS *p*-value
Age	0.034	0.015
Hemoglobin	0.125	0.33
Albumin	0.223	0.035
Creatinine	0.346	0.225
LDH	0.06	0.031
β2-MG	0.038	0.051
Treatment response	0.001	0.001
EMD	0.043	0.049
SUV_{max}	0.088	0.032

positive (P = 0.001) were independent poor prognostic factors for PFS (**Table 5**).

Discussion

MM is a hematological neoplasm characterized by the clonal proliferation of malignant plasma cells in the bone marrow. MM results in diffuse or focal bone infiltration and extramedullary lesions. Over the past two decades, advances have been made with regard to the diagnosis, staging, treatment, and imaging of MM. Up to now, few studies focused on the correlation between osteolytic lesions and clinical characteristics. In this study, we confirmed that elevated creatinine and anemia correspond to osteolytic lesions at baseline PET/CT. However, no laboratory findings were significantly different between the pathological fracture groups.

CT and MRI are currently recommended as the most effective imaging modalities at diagnosis. However, recent data from the literature suggest that PET/CT is a promising technique for initial staging and therapeutic monitoring in this pathology. PET/CT permits a whole-body investigation with an overall sensitivity of 90% and specificity of 75% for the detection of myeloma lesions. It has the ability to show diffuse involvement or mixed bone diseases with variable glucose uptake, resulting in heterogeneous SUV_{max}. However, the PET/CT parameter SUV_{max} has rarely been connected to baseline clinical characteristics. In our study, we evaluated the correlation between SUV_{max} at diagnosis and baseline laboratory findings and observed that the SUV_{max} is associated with EMD.

Recently, the use of PET/CT has increased in patients with solid tumors [18, 19]. Among the hematologic diseases, PET/CT is widely used in the staging of most lymphomas and is an accepted tool for assessing treatment response [20]. The association between SUV_{max} and tumor aggressiveness has been reported in previous studies [21, 22]. In fact, many studies of lymphoma emphasized the importance of SUV_{max} in predicting disease aggressiveness and prognosis. However, we are skeptical of the clinical utility of SUV_{max} in MM. The value of SUV_{max} at MM diagnosis is not as high as in other cancers. Park's' study found that the median value of SUV_{max} at DLBCL (diffuse large B-cell lymphoma) diagnosis was 18.9 (range 2-57), compared to 5.3 (range 0-24) in MM patients [23]. In our study, the median value of SUV_{max} was 5.7 (range 0-32.9), which is similar to Park's' study.

The prognostic value of PET/CT at diagnosis has also been studied in a smaller series of 55 MM patients [24]. The bone marrow SUV_{max} was correlated with the ISS score (P = 0.013). The 44 patients with positive PET/CT had a shorter five-year survival than the 11 patients with negative PET/CT patients, all of whom were alive after five years (P = 0.01). In multivariate analysis, only the EMD with the highest SUV_{max} had a prognostic value on OS (P = 0.03). Zamagni's study also found that PET/CT imaging technique is a reliable predictor of prognosis [9]. They found that presence at baseline of at least 3 focal lesions, SUV > 4.2 and EMD adversely affected 4-year estimates of PFS. SUV > 4.2 and EMD were also correlated with shorter OS. In this study, the OS of patients with SUV_{max} < 5.7 is significantly longer than SUV_{max} > 5.7 (P = 0.032). However, there were no statistically significant differences in PFS between the two groups (P = 0.088)

EMD has been reported to predict a relatively shorter PFS and OS, both in newly diagnosed patients and in relapsed patients [25-28]. But, in the new drug era with bortezomib, EMD is still a huge problem in clinical treatment [29-33]. Our impression from this study is that in MM, the presence of EMD tends to be more important than the SUV_{max}.

Previous reports found that age, DS stage, ISS stage, hemoglobin (Hb), platelets (PLT), plasma

Table 5. Multivariate survival analysis of the patients

	PFS		OS	
Variable	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	10.735 (1.468-71.025)	0.02	3.720 (1.203-11.521)	0.025
β2-MG	3.173 (1.257-8.035)	0.024	--	--
Treatment response	3.807 (1.092-14.220)	0.038	3.505 (1.308-9.143)	0.011
EMD	0.267 (1.445-4.571)	0.001	0.308 (0.099-0.989)	0.043

cell number in BM, β2-MG, albumin, and lactate dehydrogenase (LDH) were prognostic factors for MM survival [33]. Multivariate Cox regression analysis showed that age, ISS stage, and β2-MG were independent prognostic factors for MM survival [34-36]. Our results showed that age, LDH, β2-MG, Albumin, and SUV_{max} were prognostic factors for survival in patients with newly diagnosed multiple myeloma patients. Age and EMD were independent prognostic factor after Cox regression analysis.

Conclusion

In conclusion, we confirm the prognostic value of EMD, as detected by PET/CT, in newly diagnosed multiple myeloma patients. Age and EMD were independent prognostic factors. Our cohort of patients is limited, and it is a retrospective study. We cannot be sure whether our conclusions are applicable in other or larger cohorts. More studies are warranted to confirm our findings.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (81600163, 81570201).

Disclosure of conflict of interest

None.

Address correspondence to: Yizhuo Zhang, Department of Hematology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin 300060, China. E-mail: yizhuozhang111@126.com

References

[1] Andrew C, Majid K, Sally B, Goh V, Mulholland N, Streetly M, Lai M, Pratt G; British Society for Haematology Guidelines. Guidelines for the use of imaging in the management of patients with myeloma. Br J Haematol 2017; 178: 380-393.

[2] Röllig C, Knop S, Bornhäuser M. Multiple myeloma. Lancet 2015; 385: 2197-2208.

[3] Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O, Paiva B, Dispenzieri A, Weiss B, LeLeu X, Zweegman S, Lonial S, Rosinol L, Zamagni E, Jagannath S, Sezer O, Kristinsson SY, Caers J, Usmani SZ, Lahuerta JJ, Johnsen HE, Beksac M, Cavo M, Goldschmidt H, Terpos E, Kyle RA, Anderson KC, Durie BG, Miguel JF. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014; 15: e538-e548.

[4] Dimopoulos MA, Hillengass J, Usmani S, Zamagni E, Lentzsch S, Davies FE, Raje N, Sezer O, Zweegman S, Shah J, Badros A, Shimizu K, Moreau P, Chim CS, Lahuerta JJ, Hou J, Jurczyszyn A, Goldschmidt H, Sonneveld P, Palumbo A, Ludwig H, Cavo M, Barlogie B, Anderson K, Roodman GD, Rajkumar SV, Durie BG, Terpos E. Role of magnetic resonance imaging in the management of patients with multiple myeloma: a consensus statement. J Clin Oncol 2015; 33: 657-664.

[5] Dimopoulos M, Kyle R, Fermand JP, Rajkumar SV, San Miguel J, Chanan-Khan A, Ludwig H, Joshua D, Mehta J, Gertz M, Avet-Loiseau H, Beksaç M, Anderson KC, Moreau P, Singhal S, Goldschmidt H, Boccadoro M, Kumar S, Giralt S, Munshi NC, Jagannath S; International Myeloma Workshop Consensus Panel 3. International myeloma workshop consensus panel 3 consensus recommendations for standard investigative workup: report of the international myeloma workshop consensus panel 3. Blood 2011; 117: 4701-4705.

[6] Agarwal A, Chirindel A, Shah BA, Subramaniam RM. Evolving role of FDG PET/ CT in multiple myeloma imaging and management. AJR Am J Roentgenol 2013; 200: 884-890.

[7] Bartel TB, Haessler J, Brown TL, Shaughnessy JD Jr, van Rhee F, Anaissie E, Alpe T, Angtuaco E, Walker R, Epstein J, Crowley J, Barlogie B.

F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. Blood 2009; 114: 2068-2076.

[8] Nanni C, Zamagni E, Farsad M, Castellucci P, Tosi P, Cangini D, Salizzoni E, Canini R, Cavo M, Fanti S. Role of (18)F-FDG PET/CT in the assessment of bone involvement in newly diagnosed multiple myeloma: preliminary results. Eur J Nucl Med Mol Imaging 2006; 33: 525-531.

[9] Zamagni E, Patriarca F, Nanni C, Zannetti B, Englaro E, Pezzi A, Tacchetti P, Buttignol S, Perrone G, Brioli A, Pantani L, Terragna C, Carobolante F, Baccarani M, Fanin R, Fanti S, Cavo M. Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. Blood 2011; 118: 5989-5995.

[10] Bailly C, Leforestier R, Jamet B, Carlier T, Bourgeois M, Guérard F, Touzeau C, Moreau P, Chérel M, Kraeber-Bodéré F, Bodet-Milin C. PET imaging for initial staging and therapy assessment in multiple myeloma patients. Int J Mol Sci 2017; 18: 445.

[11] Bannas P, Hentschel HB, Bley TA, Treszl A, Eulenburg C, Derlin T, Yamamura J, Adam G, Stübig T, Kröger N, Weber C. Diagnostic performance of whole-body MRI for the detection of persistent or relapsing disease in multiple myeloma after stem cell transplantation. Eur Radiol 2012; 22: 2007-2012.

[12] Bier G, Mustafa D, Kloth C, Weisel K, Ditt H, Nikolaou K, Horger M. Improved follow- up and response monitoring of thoracic cage involvement of multiple myeloma using a novel CT post-processing software: the lessions we learned. AJR Am J Roentgenol 2016; 206: 57-63.

[13] Bird JM, Owen RG, D'Sa S, Snowden JA, Pratt G, Ashcroft J, Yong K, Cook G, Feyler S, Davies F, Morgan G, Cavenagh J, Low E, Behrens J; Haemato-oncology Task Force of British Committee for Standards in Haematology (BCSH) and UK Myeloma Forum. Guidelines for the diagnosis and management of multiple myeloma. Br J Haematol 2011; 154: 32-75.

[14] Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, Verzijlbergen FJ, Barrington SF, Pike LC, Weber WA, Stroobants S, Delbeke D, Donohoe KJ, Holbrook S, Graham MM, Testanera G, Hoekstra OS, Zijlstra J, Visser E, Hoekstra CJ, Pruim J, Willemsen A, Arends B, Kotzerke J, Bockisch A, Beyer T, Chiti A, Krause BJ; European Association of Nuclear Medicine (EANM). FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015; 42: 328-354.

[15] Brooks FM, Ghatahora A, Brooks MC, Warren H, Price L, Brahmabhatt P, De Vauvert S, John C, Farnworth E, Sulaiman E, Ahuja S. Management of metastatic spinal cord compression. Eur J Orthop Surg Traumatol 2014; 24: S255-S259.

[16] Lee SE, Kim JH, Jeon YW, Yoon JH, Shin SH, Eom KS, Kim YJ, Kim HJ, Lee S, Cho SG, Lee JW, Min WS, Park CW, Min CK. Impact of extramedullary plasmacytomas on outcomes according to treatment approach in newly diagnosed symptomatic multiple myeloma. Ann Hematol 2015; 94: 445-452.

[17] Blade J, Fernandez DE, Larrea C, Rosiñol L. Extramedullary disease in multiple myeloma in the era of novel agents. Br J Haematol 2015; 169: 763-765.

[18] Cook Gary JR, Yip C, Siddique M, Goh V, Chicklore S, Roy A, Marsden P, Ahmad S, Landau D. Are pretreatment 18F-FDG PET tumor textural features in non-small cell lung cancer associated with response and survival after chemoradiotherapy? J Nucl Med 2013; 54: 19-26.

[19] Antoch G, Saoudi N, Kuehl H, Dahmen G, Mueller SP, Beyer T, Bockisch A, Debatin JF, Freudenberg LS. Accuracy of whole-body dual-modality fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: comparison with CT and PET. J Clin Oncol 2004; 22: 4357-68.

[20] Itti E, Meignan M, Berriolo-Riedinger A, Biggi A, Cashen AF, Véra P, Tilly H, Siegel BA, Gallamini A, Casasnovas RO, Haioun C. An international confirmatory study of the prognostic value of early PET/CT in diffuse large B-cell lymphoma: comparison between Deauville criteria and ΔSUVmax. Eur J Nucl Med Mol Imaging 2013; 40: 1312-20.

[21] Ceriani L, Martelli M, Zinzani PL, Ferreri AJ, Botto B, Stelitano C, Gotti M, Cabras MG, Rigacci L, Gargantini L, Merli F, Pinotti G, Mannina D, Luminari S, Stathis A, Russo E, Cavalli F, Giovanella L, Johnson PW, Zucca E. Utility of baseline 18FDG-PET/CT functional parameters in defining prognosis of primary mediastinal (thymic) large B-cell lymphoma. Blood 2015; 126: 950-6.

[22] Fuertes S, Setoain X, Lopez-Guillermo A, Carrasco JL, Rodríguez S, Rovira J, Pons F. Interim FDG PET/CT as a prognostic factor in diffuse large B-cell lymphoma. Eur J Nucl Med Mol Imaging 2013; 40: 496-504.

[23] Park S, Lee SJ, Chang WJ, Maeng CH, Hong JY, Choi MK, Kim YS, Jung CW, Jang JH, Kim SJ, Kim WS, Choi JY, Kim K. Positive correlation between baseline pet or PET/CT findings and clinical parameters in multiple myeloma patients. Acta Haematol 2014; 131: 193-199.

[24] Haznedar R, Aki SZ, Akdemir OU, Özkurt ZN, Çeneli Ö, Münci Yağcı, Sucak GT, Ünlü M. Value of 18F-fluorodeoxyglucose uptake in positron emission tomography/computed tomography in predicting survival in multiple myeloma. Eur J Nucl Med Mol Imaging 2011: 38: 1046-1053.

[25] Papanikolaou X, Repousis P, Tzenou T, Maltezas D, Kotsopoulou M, Megalakaki K, Angelopoulou M, Dimitrakoloulou E, Koulieris E, Bartzis V, Pangalis G, Panayotidis P, Kyrtsonis MC. Incidence, clinical features, laboratory findings and outcome of patients with multiple myeloma presenting with extramedullary relapse. Leuk Lymphoma 2013; 54: 1459-1464.

[26] Shin HJ, Kim K, Lee JW, Song MK, Lee JJ, Lee HS, Lee WS, Kim SJ, Chung JS. Comparison of outcomes after autologous stem cell transplantation between myeloma patients with skeletal and soft tissue plasmacytoma. Eur J Haematol 2014; 93: 414-421.

[27] Narita T, Inagaki A, Kobayashi T, Kuroda Y, Fukushima T, Nezu M, Fuchida S, Sakai H, Sekiguchi N, Sugiura I, Maeda Y, Takamatsu H, Tsukamoto N, Maruyama D, Kubota Y, Kojima M, Sunami K, Ono T, Ri M, Tobinai K, Iida S. t(14; 16)-positive multiple myeloma shows negativity for CD56 expression and unfavorable outcome even in the era of novel drugs. Blood Cancer J 2015; 5: e285.

[28] Cohen K, Ellis M, Shinderman E, Khoury S, Davis PJ, Hercbergs A, Ashur-Fabian O. Relevance of the thyroid hormones-alphavbeta3 pathway in primary myeloma bone marrow cells and to bortezomib action. Leuk Lymphoma 2015; 56: 1107-1114.

[29] Azab AK, Quang P, Azab F, Pitsillides C, Thompson B, Chonghaile T, Patton JT, Maiso P, Monrose V, Sacco A, Ngo HT, Flores LM, Lin CP, Magnani JL, Kung AL, Letai A, Carrasco R, Roccaro AM, Ghobrial IM. P-selectin glycoprotein ligand regulates the interaction of multiple myeloma cells with the bone marrow microenvironment. Blood 2012; 119: 1468-1478.

[30] Tian C, You MJ, Yu Y, Zhu L, Zheng G, Zhang Y. MicroRNA-9 promotes proliferation of leukemia cells in adult CD34-positive acute myeloid leukemia with normal karyotype by downregulation of Hes1. Tumour Biol 2016; 37: 7461-71.

[31] Moreau P, Cavo M, Sonneveld P, Rosinol L, Attal M, Pezzi A, Goldschmidt H, Lahuerta JJ, Marit G, Palumbo A, van der Holt B, Bladé J, Petrucci MT, Neben K, san Miguel J, Patriarca F, Lokhorst H, Zamagni E, Hulin C, Gutierrez N, Facon T, Caillot D, Benboubker L, Harousseau JL, Leleu X, Avet-Loiseau H, Mary JY. Combination of international scoring system 3, high lactate dehydrogenase, and t(4; 14) and/or del (17p) identifies patients with multiple myeloma (MM) treated with front-line autologous stem-cell transplantation at high risk of early MM progression-related death. J Clin Oncol 2014; 32: 2173-2180.

[32] Zhuang J, Da Y, Li H, Han B, Wan X, Zhu T, Chen M, Duan M, Xu Y, Zhao Y, Shen T, Wua Y, Zhou D. Cytogenetic and clinical risk factors for assessment of ultra high-risk multiple myeloma. Leuk Res 2014; 38: 188-193.

[33] Morgan GJ, Davies FE, Gregory WM, Cocks K, Bell SE, Szubert AJ, Navarro-Coy N, Drayson MT, Owen RG, Feyler S, Ashcroft AJ, Ross F, Byrne J, Roddie H, Rudin C, Cook G, Jackson GH, Child JA; National Cancer Research Institute Haematological Oncology Clinical Study Group. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. Lancet 2010; 376: 744-751.

[34] Sanfilippo K M, Gage B, Luo S, Weilbaecher K, Tomasson M, Vij R, Colditz G, Carson K. Comparative effectiveness on survival of zoledronic acid versus pamidronate in multiple myeloma. Leuk Lymphoma 2015; 56: 615-621.

[35] Chavan SS, He J, Tytarenko R, Deshpande S, Patel P, Bailey M, Stein CK, Stephens O, Weinhold N, Petty N, Steward D, Rasche L, Bauer M, Ashby C, Peterson E, Ali S, Ross J, Miller VA, Stephens P, Thanendrarajan S, Schinke C, Zangari M, van Rhee F, Barlogie B, Mughal TI, Davies FE, Morgan GJ, Walker BA. Bi-allelic inactivation is more prevalent at relapse in multiple myeloma, identifying RB1 as an independent prognostic marker. Blood Cancer J 2017; 7: e535.

[36] Shin SY, Eom HS, Sohn JY, Lee H, Park B, Joo J, Jang JH, Lee MN, Kim JK, Kong SY. Prognostic implications of monosomies in patients with multiple myeloma. Clin Lymphoma Myeloma Leuk 2016; 17: 159-164.