Original Article

Prognostic significance of ¹⁸F-sodium fluoride in newly diagnosed multiple myeloma patients

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Abstract: Focal bone lesions and fractures due to weakened bone are associated with higher morbidity and mortality of multiple myeloma (MM) patients. 18F-sodium fluoride (18F-NaF) is a sensitive PET radiotracer for detection of abnormal bone metabolism and, therefore, is particularly suited to assess the degree of bone involvement in MM patients. We aimed to investigate the prognostic significance of metabolic active volume (MAV) of ¹⁸F-NaF-avid lesions in MM patients. In addition to MAV, conventional methods of PET quantification, namely SUVmean and SUVmax, were measured in each patient for the purpose of comparison. Thirty-seven newly diagnosed MM patients were included. PET imaging was performed after intravenous administration of 200 MBq NaF. Active bone lesions and fractures on whole-body 18F-NaF-PET/CT scans were identified. An adaptive thresholding algorithm automatically calculated the total MAV, SUVmean and SUVmax for each patient (ROVER, ABX, Radeberg, Germany). The patients were followed for a median of 39.8 months after treatment (range: 17.8-55.4). The overall survival (OS) of patients with 18F-NaF-MAV value > 38.65 (36.36% [N of Events/Total N: 4/11]) was significantly shorter than that of patients with ¹⁸F-NaF-MAV value < 38.65 (3.85% [1/26]; P = 0.002). In multivariate forward stepwise (conditional LR) Cox regression analysis of prognostic factors of OS (including 18F-NaF-MAV (> 38.65 or < 38.65), age, gender, beta-2 microglobulin, and revised international staging system), ¹⁸F-NaF-MAV remained the only significant factor (HR: 14.39, P = 0.02). The results for PFS were not significant. Moreover, Kaplan-Meier analyses of conventional methods of PET quantification did not reveal any statistically significant log-rank p-values. MM patients with high ¹⁸F-NaF-MAV had shorter overall survival, compared to those with low ¹⁸F-NaF-MAV levels (NCT02187731).

Keywords: ¹⁸F-sodium fluoride, multiple myeloma, PET/CT, survival, metabolic active volume, myeloma bone disease, osteolytic lesion, fracture

Introduction

The majority of multiple myeloma (MM) patients will have bone lesions and/or fracture due to weakened bone over the course of the disease [1]. Lytic bone lesions are the hallmark of myeloma bone disease that are marked by local areas of increased osteolysis in areas adjacent to MM cells [2]. In addition to lytic lesions, pathological fractures can occur in patients, which result not only from the malignant plasma infiltration of the bone, but also from overexpression of signaling factors such

as the receptor activator of nuclear factor-kappa B ligand [RANK ligand (RANK-L)] that constitutively activate osteoclasts and stimulate bone resorption [3]. The combination of enhanced weakened bone due to bone lesions and fractures is associated with higher morbidity and mortality of the patients, an as a result increase the cost of the management [2].

According to the International Myeloma Working Group, due to the low sensitivity and specificity of X-ray, which was the standard modality for detecting lesions in MM patients, there is a dire

need for usage of more sophisticated imaging modalities such as positron emission tomography (PET) in assessment of the patients [4]. Among PET radiotracers, fluorodeoxyglucose (FDG) has previously demonstrated high sensitivity and specificity in evaluation of MM lesions [5]. In addition to FDG, in recent years, the potential role of a bone-seeking PET radiopharmaceutical, ¹⁸F-sodium fluoride (¹⁸F-NaF), for detecting and characterizing bone changes in MM has been investigated [5]. 18F-NaF is a highly sensitive and specific radiotracer biomarker of bone remodeling [6-8]. The fluoride atom of 18F-NaF is transferred to hydroxyapatite, generating fluorapatite [8, 9]. The tracer accumulates in nearly all sites of increased new bone formation, reflecting regional blood flow and bone turnover [6, 10, 11]. It was shown previously that the accumulation of 18F-NaF in MM patients represents both osteoblastic and osteolytic activities [12, 13]. Therefore, the combined use of FDG-PET/CT and 18F-NaF-PET/CT provides different molecular information regarding the biological processes that take place in MM osseous lesions [14]. Compared to FDG, which portrays primarily osteolytic activity [15], ¹⁸F-NaF is a better indicator of osteoblastic activity, such healing of osteolytic lesions. In addition, it was shown that NaF is able to detect more fractures in comparison to FDG [14]. Considering that bone lesions and fractures can cause high rates of morbidity and mortality in MM, and since both can be accurately detected by ¹⁸F-NaF-PET/CT with high sensitivity and specificity [16], 18F-NaF-PET/CT may play an important role in prognostication of the patients. Further, because 18F-NaF-PET/ CT is highly sensitive to bone remodeling, it represents a powerful method of detecting and assessing malignant bone disorders [16]. Thus, this study aimed to determine whether metabolic active volume (MAV) of 18F-NaF-avid lesions (both focal bone lesions and fractures) in MM patients can predict survival and outcome.

Methods and material

Study design

The FULIMA (Functional Imaging in Multiple Myeloma-PET/CT and Diffusion Weighted Imaging in Multiple Myeloma) trial was conducted between June 2013 and March 2016 at the Department of Hematology, Odense University

Hospital and Department of Hematology, Vejle Hospital. Inclusion criteria encompassed: age > 50 years and suspicion of treatment-demanding MM in concordance with Danish cancer society criteria [17]. Exclusion criteria encompassed: history of treated MM, current or recent radiotherapy or surgery less than two weeks prior to screening, history of prior malignancy (except for treated basal cell carcinoma), in situ cervical, breast, or prostate cancer with a disease-free period of at least three years, known inflammatory disease or serious medical or psychiatric conditions, pregnant or breast feeding female subjects, POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein (M-protein) and skin changes) [17]. All subjects provided informed consent and the trial was registered at ClinicalTrials.gov (NCT0218-7731). Forty-two newly diagnosed MM patients were eligible for this study. Three patients were excluded due to lack of 18F-NaF-PET/CT imaging at baseline, one patient was excluded due to technical issues of NaF scanning. In addition, in order to harmonize the follow-up time for the patients, one patient that had a follow-up time less than 6 months was excluded, leaving a total of 37 MM patients for analysis (median age 67 years, ranging 50-87) (Table 1). Baseline ¹⁸F-NaF-PET/CT scans were conducted prior to any anti-myeloma treatment including bisphosphonates. In addition, bone imaging data based on conventional skeletal survey (x-ray) is included in Appendix 1.

The patients received standard first-line treatment, including bortezomib-based induction therapy followed by stem cell harvest and highdose melphalan with autologous stem cell transplantation for high-dose therapy. 18F-NaF-PET/CT scans were acquired in accordance with the European Association of Nuclear Medicine (EANM) guidelines, which include quality control, calibration and harmonization of the scanner, and SUV calculations [18, 19]. 18F-NaF-PET/CT was performed using the hybrid PET/CT scanners Philips Gemini TF (Philips, Amsterdam, Netherlands) and GE STE/VCT/ Rx/690/710 PET/CT (GE, Milwaukee, WI). NaF-PET imaging was performed 45 min after intravenous administration of 200 MBq NaF with an acquisition time of 2.5 min/bed. A low-dose CT (LDCT) scan was used for attenuation correction, which followed by a 3-D PET scan.

Table 1. Patient characteristics

Characteristic	MM (n = 37)
Gender, n (%)	(- /
Male	27 (73)
Female	10 (27)
Age (y)	
Median	67
Range	50-87
B2M (mg/L)	
Median	222
Range	152-581
Hgb (g/dl)	
Median	7.6
Range	3.8-9.4
Albumin (g/L)	
Median	38
Range	22-49
R-ISS, n (%)	
R-ISS 1	10 (27)
R-ISS 2	26 (70.3)
Unknown	1 (2.7)

Abbreviations: B2M: beta-2 microglobulin; Hgb: hemoglobin; R-ISS: revised international staging system.

Image analysis

Using ROVER software (ROVER, ABX, Radeberg, Germany), active lesions were localized on ¹⁸F-NaF-PET/CT scans [20]. To quantify metabolic and volumetric characteristics of lesions, a semiautomatic approach was used. First, for each ¹⁸F-NaF-avid lesion, a qualified physician defined a sub-volume that contained the lesion and adjacent background uptake. The lesion boundary was delineated using an iterative algorithm that combines background correction and adaptive thresholding to create a 3dimensional region of interest (ROI) [21]. With the same software, a spill-out region was identified as uptake immediately outside the ROI boundary greater than corrected background activity, thereby facilitating automatic modelfree partial volume correction [22]. The software output included total MAV, SUVmean and SUVmax for each patient (Figure 1).

Statistics

The optimal cut-off values for Kaplan-Meier curves was derived from receiver operating characteristic (ROC) analysis. Univariate and multivariate Cox regression analysis of prognostic factors was performed for overall survival (OS) and progression-free survival (PFS).

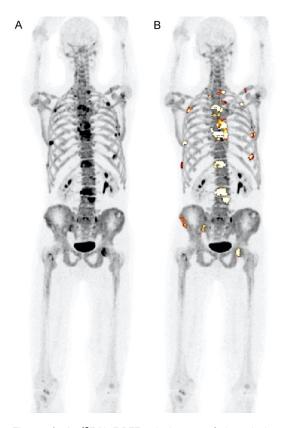


Figure 1. A. ¹⁸F-NaF-PET-only image of the whole-body without ROIs. B. ROVER software was used to localize active lesions on whole body ¹⁸F-NaF-PET/CT scans (ROVER, ABX, Radeberg, Germany).

Level of significance was set to 5%. Statistical analysis was performed using SPSS Statistics version 26 (IBM Corp, NY, USA).

Results

The patients were followed for a median of 39.8 months (range: 17.8-55.4). ROC curves used to determine the optimal cut-offs for OS and PFS. Area under curve (AUC) was 0.838, 95% CI: 0.624-1 for OS and was 0.641, 95% CI: 0.459-0.823 for PFS (Figure 2A and 2B). Cut off of 38.65 was determined for OS analysis (sensitivity: 0.80, specificity: 0.78). In Kaplan-Meier analysis for OS, ¹⁸F-NaF-MAV higher than 38.65 (36.36% [N of Events/Total N: 4/11], median: 50.7 months) was associated with inferior survival in comparison to ¹⁸F-NaF-MAV lower than this cut-off (3.85% [1/26], not reached; logrank P = 0.002) (Figure 2C). In Kaplan-Meier analysis for PFS, ¹⁸F-NaF-MAV higher than 26.52 was not associated with a statistically significant inferior survival in comparison to ¹⁸F-NaF-MAV lower than this cut-off (64% [14/22], median: 36.3 months vs 40% [6/15],

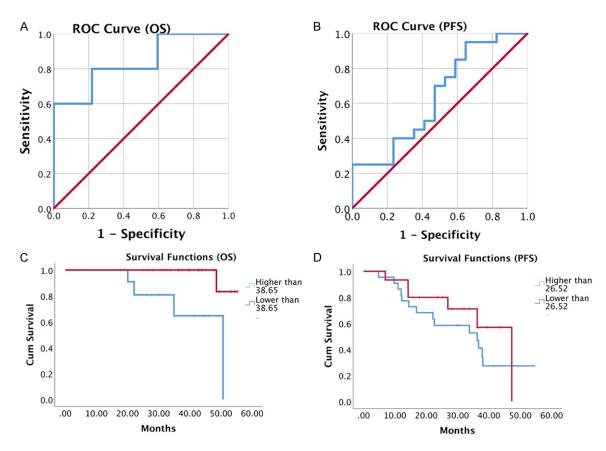


Figure 2. ROC curves (A and B) determined the optimal cut-off for OS and PFS Kaplan-Meier analyses. Kaplan-Meier graphs (C and D) for OS (log-rank p: 0.002) and PFS (log-rank p: 0.397, Breslow (Generalized Wilcoxon) p: 0.313).

Table 2. Univariate and multivariate (forward stepwise (conditional LR)) Cox regression analysis of prognostic factors of OS

Variable	Univariate		Multivariate			
	HR	95% CI	р	HR	95% CI	р
NaF-MAV	14.74	1.62-134.5	0.02	14.39	1.57-131.58	0.02
Age	1.11	0.98-1.26	0.10	-	-	-
Gender						
Male vs. Female	0.705	0.078-6.34	0.76	-	-	-
B2M	1.006	1.00-1.01	0.088	-	-	-
R-ISS	31.72	0.01-178681.1	0.43	-	-	-

Abbreviations: B2M: beta-2 microglobulin, CI: confidence interval, HR: hazard ratio, MAV: metabolic active volume, OS: overall survival, R-ISS: revised international staging system.

47.3 months; (log-rank p: 0.397, Breslow (Generalized Wilcoxon) p: 0.313) (**Figure 2D**). In univariate Cox regression analysis for OS, 18 F-NaF-MAV was a significant prognostic factor for OS (NaF-MAV HR for OS: 14.74, 95% CI: 1.62-134.5, P = 0.02) (**Table 2**). In a stepwise forward (conditional LR) multivariate Cox regression analysis for OS (including 18 F-NaF-MAV (> 38.65 or < 38.65), age, gender, beta-2 microglobulin and revised international staging sys-

tem), 18 F-NaF-MAV remained the only significant factor (HR: 14.39, 95% CI: 1.57-131.58, P = 0.02) (**Table 2**). The results for PFS were not significant (not shown). Kaplan-Meier analyses of conventional methods of PET quantification (SUVmax and SUVmean) did not reveal any statistically significant log-rank p-values (OS SUVmean: 0.54 OS SUVmax: 0.11, PFS SUVmean: 1.00, PFS SUVmax: 0.12) (**Figure 3**).

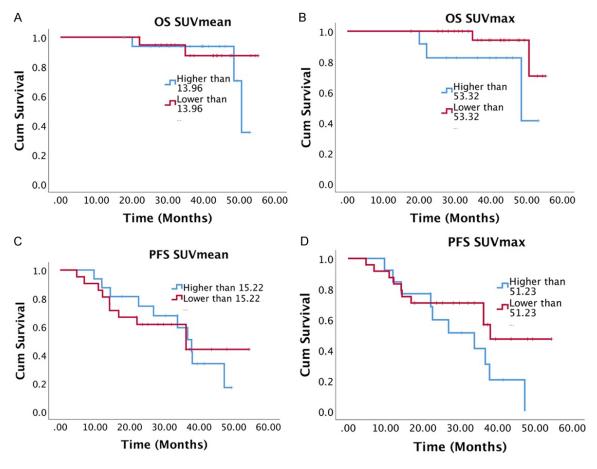


Figure 3. Kaplan-Meier graphs of conventional methods of PET quantification (SUVmean and SUVmax). All the log-rank p-values were statistically insignificant [(A) OS SUVmean: 0.54, (B) OS SUVmax: 0.11, (C) PFS SUVmean: 1.00, (D) PFS SUVmax: 0.12].

Discussion

The manifestations of bone involvement in patients with MM can have devastating clinical effects and cause increased mortality [23]. This is one of the few studies that evaluated the prognostic significance of a bone-seeking PET radiotracer, ¹⁸F-NaF, in MM patients. Recently and for the first time. Sachpekidis et al. evaluated the prognostic significance of ¹⁸F-NaF in 47 MM patients that underwent 18F-NaF PET/ CT before treatment [16]. They observed that patients with a pathological 18F-NaF-PET/CT have a shorter PFS in comparison to those with physiological scan (median = 55.6 months) (P = 0.02). However, none of the quantitative ¹⁸F-NaF parameter could be shown to adversely affect PFS [16]. In this study, we did not observe that our ¹⁸F-NaF-PET quantification parameter significantly affects PFS. We used a volumetric parameter, which showed that it is superior to the conventional methods for predicting survival [24]. Our result demonstrated that the higher MAV ¹⁸F-NaF is a significant prognostic factor for OS. We did not observe any significant log-rank *p*-values for conventional method of PET quantification (SUVmean and SUVmax) (**Figure 3**). In addition, in previous studies, another PET tracer, FDG, demonstrated prognostic utility in patients with newly diagnosed, refractory, and relapsed MM [25-27]. Specifically, the detection of 3 focal osteolytic lesions by FDG-PET/CT has been associated with the presence of high-risk genetic profiles, adverse serum biomarkers and decreased OS and PFS [28].

Current studies assessing the clinical utility of ¹⁸F-NaF-PET/CT in MM are limited. Some studies have shown promise for diagnostic utility of ¹⁸F-NaF-PET/CT in MM [29-31]. For instance, FDG- and ¹⁸F-NaF-PET/CT were compared in a study by Xu et al., who found intense ¹⁸F-NaF accumulation in a dorsal vertebra of a MM

patient but unimpressive uptake by FDG [30]. Other studies investigating the ability of ¹⁸F-NaF-PET/CT to determine response to treatment in addition to diagnosis of MM concluded there was limited utility of this radiotracer for either purpose [32]. For instance, ¹⁸F-NaF-PET/CT did not add significantly to FDG-PET/CT in treatment response evaluation of a group of 34 primary MM patients undergoing high-dose chemotherapy followed by autologous stem cell transplantation [32].

However, ¹⁸F-NaF uptake represents both osteolytic and osteoblastic activity and therefore can provide different molecular information regarding the biological processes that take place in a MM osseous lesion [12]. In the studies by Sachpekidis et al., it was shown that 18F-NaF may represent old myelomatous lesions that still accumulate ¹⁸F-NaF due to persistent increased osteoblastic activity [11, 12]. In other words, ¹⁸F-NaF uptake can represent lesions that are in the process of healing. In addition, it was shown that 18F-NaF is able to detect more fractures in comparison to FDG. For instance, in a study by Ak et al. [14], although 18F-NaF-PET/CT demonstrated fewer myeloma lesions than FDG-PET/CT, this modality detected an additional 135 bone lesions defined as fractures. Based on these results and the fact that a higher number of lesions and fractures that incurred over time can affect the outcome of the patients, it is worth investigating the role of ¹⁸F-NaF in prognostic stratification of MM patients. The results that we observed in this study is in accordance with this theory.

In this study we evaluated a global assessment methodology to assess the whole skeletal uptake of 18F-NaF. The newer methods of PET quantification such as MAV has proven to overcome some shortcomings that exist in the conventional methods of PET quantification such as SUVmax. SUVmax only represents the highest metabolic activity of a single voxel within the ROI and is negatively affected by noise [33, 34]. Therefore, increased variability of SUVmax hampers the true representation of the uptake in the structure or lesion of interest [33, 34]. It has been shown that metabolic tumor volume (MTV) has the potential to improve the value of this approach and enhance the prognostic value of disease burden measures [24, 35]. For instance, using the same methodology that we employed in this study but with FDG-PET/CT, Mcdonald et al. showed that MTV > 210 cm³ remained a significant factor of poor PFS and OS after adjusting for baseline myeloma variables in 192 patients underwent whole body PET/CT [35].

We used MAV for our measurements to predict the outcome of the patients, which has demonstrated prognostic utility and evaluation of treatment response [24, 35-37]. However, despite the promising research on MAV, there has not been a consensus regarding optimal segmentation of PET images, and therefore this technique has not been widely adopted clinically. We used ROVER software for this purpose. This software has shown to have the potential to allow for rapid, accurate, and precise quantification of whole-body malignant disease burden [38-40], which can be useful in evaluating the degree of bone involvement in MM patients.

This study has some limitations. A relatively small number of patients is one. Another potential limitation could be the harmonization of the results, since the FULIMA trial was a two-center study. However, because the protocol wasstrictlyfollowed and the scanners were calibrated and harmonized, we believe using different PET instruments minimally affected the final results. We suggest conducting further trial studies with a larger number of patients and longer follow-up.

Conclusion

This study is one of the few studies that evaluated the prognostic significance of MM patients using ¹⁸F-NaF-PET/CT. Our results showed that higher MAV is associated with inferior OS but not PFS. Further trials are warranted to investigate the role of ¹⁸F-NaF for survival assessment of MM patients.

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Informed consent was obtained from all individual participants included in the study.

Disclosure of conflict of interest

None.

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Appendix 1. Bone imaging data based on conventional skeletal survey (x-ray)

Number	Bone Disease	Bone Disease	Fracture	Location
1	2	multiple	1	several vertebrae
2	2	multiple	1	left humerus
3	0		0	
4	2	multiple	0	
5	2	multiple	1	os pubis
6	0		0	
7	1	os pubis	1	os pubis
8	2	multiple	1	th7
9	0		0	
10	2	multiple	1	th11
11	0		0	
12	1	osteolysis os ileum	0	
13	2	multiple	0	
14	0		0	
15	1	left ramus ileum	0	
16	1	os sacrum	0	
17	2	multiple	1	right humerus
18	0		0	
19	2	multiple	0	
20	0		1	L4
21	2	multiple	0	
22	2	multiple	1	right hip
23	2	multiple	0	
24	2	multiple	0	
25	2	multiple	0	
26	1	right clavicula	0	
27	2	multiple	0	
28	2	multiple	1	th4, th10, th12
29	2	multiple	0	
30	0		0	
31	1	osteolysis os ileum dx	0	
32	2	multiple	0	
33	0		0	
34	2	multiple	0	
35	0		0	
36	2	multiple	1	left femur
37	0		0	

Bone disease: 0 = No osteolysis; 1 = One or more osteolysis but limited to one region (e.g. crane or pelvis), comment with region; 2 = Several osteolysis distributed in more than more region or whole skeleton. Fracture: 0 = No fracture; 1 = Yes, comment with location.