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Comparison of $^{18}$F-sodium fluoride uptake in the whole bone, pelvis and femoral neck of multiple myeloma patients before and after high-dose therapy and conventional-dose chemotherapy

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Abstract

Aim To compare the effect of high-dose therapy (HDT consisting of high-dose chemotherapy followed by autologous stem cell transplantation) and conventional-dose chemotherapy (non-HDT) on the uptake of $^{18}$F-sodium fluoride (NaF) in the whole bone, pelvis and femoral neck of multiple myeloma (MM) patients.

Method The data of 19 MM patients who received HDT (61.5, SD (5.6) years) and 11 MM patients who received conventional-dose chemotherapy (70.9, SD (7.2) years) were collected in a prospective study. NaF PET/CT imaging was performed at baseline and eight weeks and two weeks after treatment for the HDT group and the non-HDT group, respectively. A CT-based algorithm was applied to segment the bones, and the global mean SUV (GSUVmean) of the whole bone and pelvis was calculated (OsiriX MD v.9.0, Pixmeo SARL; Bernex, Switzerland). In addition, regions of interest for the whole, medial, and lateral femoral neck were delineated bilaterally. Whole bone and pelvis measurements were replicated by two observers.

Results The average GSUVmean in the whole bone and pelvis of the patients who underwent HDT significantly decreased from before to after treatment (-16.27%, p= 0.02 and -16.54%, p= 0.01, respectively). A significant decrease in the whole and lateral femoral neck was also observed bilaterally in the HDT group. No significant decrease in average GSUVmean was observed in the non-HDT group. A high level of inter-observer reliability was found in intra-class correlation (ICC for pre-treatment whole bone: 0.983, post-treatment whole bone: 0.989, pre-treatment whole pelvis: 0.998, post-treatment whole pelvis: 0.996).

Conclusion NaF uptake significantly decreased after treatment in patients who received high dose therapy. A high level of agreement was observed between two operators for whole bone and pelvis measurements.
Keywords: Multiple Myeloma, Positron Emission Tomography, NaF, Bone Metabolism, PET/CT Quantification, High Dose Chemotherapy, Autologous Stem Cell Transplantation, conventional-dose chemotherapy
Introduction

High-dose therapy (HDT consisting of high-dose chemotherapy followed by autologous stem cell transplantation (HDC/ASCT)) has shown to prolong overall survival and disease-free survival in newly diagnosed multiple myeloma (MM) patients but is associated with some side effects. One of the areas that requires more exploration is the assessment of bone metabolism in patients after therapy, which is still not well understood. Prior to treatment, loss of bone density in MM patients is driven by a variety of osteoblast inhibitory and osteoclast-activating factors that are produced by malignant plasma cells [1]. For instance, Silvestris et al. found that osteoblastic cells initiate apoptosis in the presence of myeloma cells from patients with severe myeloma bone disease [2]. Thus, the decrease in the number of malignant plasma cells after treatment [3] could theoretically escalate the chance of increasing osteoblastic activity and bone formation. On the other hand, previous studies have shown that high-dose therapy may result in continuing bone loss, mainly because of dose-dependent toxicity of preparatory chemotherapeutic regimen given prior to ASCT. These preparatory regimes affect bone marrow osteoprogenitors and can explain the observed osteopenia after bone marrow transplantation [4-6].

Uptake of $^{18}$F-sodium fluoride (NaF) radiotracer indicates osteoblastic and calcium metabolic activity by identifying reactive changes in the underlying affected bone [7, 8]. The hydroxyapatite matrix interacts with the radiotracer so as to exchange OH$^-\ $with $^{18}$F$^-\ $[9]. Present clinical use of NaF PET is limited to the detection of metastasis to the skeletal structures; however, NaF has been proven to accurately detect bone turnover changes in previous studies [10-14]. The high sensitivity and specificity of NaF for assessment of bone metabolism can be particularly important in evaluating the side effects of high-dose...
therapy on bone in MM patients. Two recently published results regarding the performance of NaF PET/CT in MM [15, 16] showed that although the contribution of NaF PET/CT in this neoplastic plasma cell disorder is rather limited, this radiotracer provides valuable information regarding bone remodeling and the patient’s skeletal history.

Conventional methods of PET reporting typically use a lesion-based approach for assessment of NaF radiotracer, in which the maximum standardized uptake value or mean (SUVmax or SUVmean) of one or very few lesions are described. Such approaches would provide an inaccurate estimation of the true bone turnover for the whole skeleton. In addition, the high variability among different lesions and readers with lesion-based approaches increases the need for more reproducible methods of quantification [17]. We believe a whole-body approach may provide an understanding and add valuable information in the grading of the extent of bone disease and the effects of treatment on bone formation to the current routine methods of PET quantification.

The present study aimed to assess NaF uptake in the whole bone, pelvis and femoral neck in MM patients who received HDT before and after therapy and to compare the changes in uptake with that observed in patients who received conventional-dose chemotherapy (non-HDT group). Whole bone and pelvis measurements were performed using a semi-automated global quantitative technique by two independent observers to determine the inter-rater reliability.

**MATERIALS AND METHODS**

**Study Design**
This study is a part of the prospective FULIMA study that was conducted between June 2013 and March 2016 at the Department of Hematology, Odense University Hospital and Department of Hematology, Vejle Hospital. Inclusion criteria were age >50 years, suspicion of treatment-demanding MM in concordance with Danish cancer society criteria. Exclusion criteria were 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 poly-neuropathy, organomegaly, endocrinopathy, monoclonal protein (M-protein) and skin changes) [18]. All subjects provided informed consent, and the trial was registered at ClinicalTrials.com (NCT02187731). Forty-two MM patients were eligible for this study, from whom 12 were excluded due to lack of NaF-PET/CT imaging either at baseline or at end of treatment, leaving a total of 30 MM patients for analysis. Of these, 19 were scheduled for HDC/ASCT (15 men, 4 women; 61.5, SD (5.6) years) and 11 not suitable for high-dose therapy because of their age (8 men, 3 women; aged 70.9, SD (7.2) years) were scheduled for conventional-dose chemotherapy (non-HDT group) [Table 1 and Figure 1]. NaF PET/CT was performed at baseline and about eight weeks after treatment for the HDT group and two weeks after the treatment for the non-HDT group. MM patients received standard first-line treatment, including bortezomib-based induction therapy followed by stem cell harvest and high dose melphalan with autologous stem cell transplantation in the patients in the HDT group [Appendix 1].

**PET/CT acquisition**

NaF-PET/CT scans were acquired in accordance with EANM guidelines, which include quality control, calibration and harmonization of the scanner and SUV calculations [19,
The scanners underwent regular quality and calibration control that fully met all EARL requirements.

NaF PET/CT was performed using the hybrid PET/CT scanners Philips Gemini TF (Philips, Amsterdam, Netherlands) and GE STE/VCT/Rx/690PET/CT (GE, Milwaukee, WI). PET images were acquired 45 min after intravenous NaF administration with an acquisition time of 2.5 min/bed. A low-dose CT (LDCT) scan was used for attenuation correction and followed by a 3-D PET scan using a ‘whole-body’ (base of skull to mid-thigh) acquisition protocol.

**Image Analysis**

Attenuation-corrected PET data were normalized to injected NaF tracer dose and subject body weight to calculate the SUV. In each subject, uptake was measured in the whole bone and pelvis. Whole bone measurement included the axial skeleton and proximal appendicular skeleton, excluding the skull, jaw, and appendages more than 20 cm distal to the gleno-humeral joint and more than 10 cm inferior to the lowest portion of the ischium [Figure 2a]. After manual exclusions were made to define a ROI, a region growing algorithm with a lower threshold of 150 Hounsfield units (HU) followed by morphological closing was applied to the CT image, segmenting only the bony skeleton [Figure 2a]. Measurements of the pelvis included the whole pelvis inferiorly to L5, the iliac crests, and the sacrum [Figure 2b]. The global mean SUV (GSUVmean) was calculated as the average of the SUVs of all voxels within the ROI. In addition, GSUVmean was multiplied to the whole-volume of each patient and the percentage of change from pre-treatment to post-treatment for each patient for these measurements were calculated.

In addition, ROI series for the whole femoral neck, medial femoral neck, and lateral femoral neck were delineated bilaterally for each subject according to pre-determined
anatomical criteria [Figure 2c]. The epiphyseal line served as the medial boundary and the intertrochanteric line served as the lateral boundary of the whole femoral neck. A line parallel to the intertrochanteric line and equidistant from the medial and lateral boundaries bisected the whole femoral neck into medial and lateral portions. Following ROI delineation, SUVmean for uptake of NaF in the femoral neck was calculated.

OsiriX MD v.9.0 (DICOM viewer and image-analysis program, Pixmeo SARL; Bernex, Switzerland) was used for image analysis.

**Inter-Operator Agreement**

Whole bone and pelvis measurements were performed by two independent investigators. The validity of femoral neck approach has been already tested and confirmed [10, 21, 22].

**Statistical Analysis**

Descriptive statistics were done according to data type; continuous variables were described by mean and standard deviation or median and range, categorical variables by frequencies and respective percentages. Wilcoxon signed rank test was used to assess the change in response to therapy in HDT and non-HDT groups (non-parametric). Linear regression was used to assess the relationship between changes in NaF uptake for the global measurements of whole bone and pelvis. Intra-class correlation was used to assess inter-operator reliability. Statistical analysis was conducted using IBM SPSS Statistics version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp).
Results

The average percentage change in GSUVmean in the whole bone from before to after treatment in the HDT group was -16.27% (median: -12.45, IQR: 41.29, range -57.89 to 26.36%; p= 0.02) and -16.54 % in the pelvis (median: -17.20, IQR: 31.41, range -55.66 to 26.07; p= 0.01) [Table 2]. In this group, a statistically significant decrease was also observed in the lateral and whole femoral neck measurements in both sides (left and right) but the decrease in the medial sides was not significant [Table 2]. In the HDT group, 14 patients showed a decrease and 5 patients showed an increase following treatment in the NaF whole body and pelvis uptake [Figures 3a and 3c]. However, none of the differences in the non-HDT group were significant [Table 2]. In the non-HDT group, 7 patients had a decrease and 4 had an increase in whole bone uptake after treatment (median: -1.53, IQR: 29.05) and 8 patients showed an increase and 3 had a decrease in pelvic NaF uptake (median: -2.56, IQR: 27.91) [Figures 3b and 3d, respectively] and [Figure 4].

In addition, after multiplying GSUVmean to the whole-volume of each patient, in the HDT group, the mean decreased from 21797 to 17450 (Wilcoxon signed test p= 0.02), while in the non-HDT group, the mean decreased from 16411 to 15750 (Wilcoxon signed test; p= 0.86).

The changes in GSUVmean in the whole body and pelvis were strongly correlated with each other (r= 0.9, p-values < 0.001). A high level of inter-observer reliability was found in intra-class correlation (ICC for pre-treatment whole bone: 0.983, 95% CI: 0.965-0.992, post-treatment whole bone: 0.989, 95% CI: 0.978-0.995, pre-treatment whole pelvis: 0.998, 95% CI: 0.996-0.999, post-treatment whole pelvis: 0.996, 95% CI: 0.991-0.998) [Table 3].

Discussion

This is the first study that compared changes in NaF uptake before and after high-dose therapy (consisting of HDC/ASCT) to changes before and after conventional-dose
chemotherapy in MM using a global assessment approach. We observed a statistically significant decrease in NaF uptake in the HDT group. This result is in accordance with the previous studies that have shown that bone turnover is reduced in recipients of stem cell transplants and their preparatory regimens including high-dose chemotherapy [23-26]. Laroche et al. [26] evaluated the effect of HDC followed by ASCT on bone turnover in 39 MM patients by measuring phosphorus and calcium parameters, bone turnover markers, and BMD at different time points: after diagnosis, before ASCT, 6 months and 1 year after ASCT. They showed that high-dose therapy leads to decreased bone resorption as well as osteoblastic activity [26]. Sachpekidis et al. [27] showed that the uptake of NaF was reduced significantly after high-dose therapy including ASCT in MM patients. They observed that the NaF uptake (SUVaverage and SUVmax), as well as the kinetic parameters $K_1$, and $Ca^{2+}$ influx from reference skeleton significantly decreased after high-dose therapy ($p < 0.001$) [27].

The changes in NaF uptake in the whole bone, pelvis and femoral neck of the patients who received conventional-dose chemotherapy was not significant [Figure 5]. This result can be in accordance with a clinical study by Banfi et al demonstrating that patients with breast cancer or non-Hodgkin's lymphoma undergoing high-dose chemotherapy had a 50% reduction in the number of stromal osteoprogenitors in the bone marrow, whereas conventional-dose chemotherapy and pre-chemotherapy groups’ bones were unaffected [28].

Currently, metabolic bone diseases are evaluated primarily through dual energy X-ray absorptiometry. However, there are some significant limitations that exist in using bone mineral densitometry (BMD) and other method of evaluation of bone turnover such as bone biopsy studies. BMD, as an indirect method, has the low sensitivity in detecting bone disorders at earlier stages; therefore, BMD is only able to detect osteoporosis in
advanced stages of the disease. Bone biopsies are an invasive alternative which introduces difficulty in future follow-ups [29]. Recently, PET has emerged as an increasingly accurate and noninvasive option. Several radiotracers may be candidates for these applications, yet tracers with shorter half-lives, such as NaF (labeled with $^{18}$F) and $^{99m}$Tc-labeled phosphates, are preferred to minimize radiation exposure. Both tracers are able to quantify bone formation in the skeleton but several technical advantages promote the use of NaF PET as the preferred procedure including superior spatial resolution, tomographic as opposed to projection images, enhanced differentiation of osseous and soft tissue structures, and the increased specificity of NaF deposition in bone [29]. Further, PET provides quantitative data that cannot be achieved by bone scintigraphy.

This study applied a global assessment methodology in conjunction with SUVmean parameters to assess the whole skeletal uptake of NaF, which may provide a better expression of systemic osseous metabolism. Therefore, this methodology represents a novel approach in contrast to previous NaF-PET studies that attempted to assess bone metabolism in MM patients with conventional method of PET quantification such as SUVmax [30, 31]. SUVmax only represents the highest metabolic activity of a single voxel within the ROI and is adversely affected by noise [32, 33]. As a result, SUVmax may have increased variability and not be truly representative of the uptake in the structure or lesion of interest [34]. A global metabolic measurement, such as the method suggested in this study, could be useful in determining the magnitude of bone involvement in MM patients [35, 36]. We observed a high level of agreement between two observers performing the measurements. In a study by Lin et al, the reproducibility of NaF PET/CT–derived SUV$_\text{max}$, SUV$_\text{mean}$, and SUV$_\text{total}$ was assessed for both lesion-level and patient-level ROIs in a multicenter prospective [37]. The investigators found low repeatability coefficients, high
ICCs, and small coefficients of variation in test–retest scans. They also observed that patient-level repeatability was slightly superior to lesion-level repeatability, justifying the use of SUV both in individual lesions and across the whole body. They reported an excellent ICC (> 0.95) for all SUV metrics [37]. In this study, we observed an excellent ICC for our measurements (ICC for pre-treatment whole bone: 0.983, 95% CI: 0.965-0.992, post-treatment whole bone: 0.989, 95% CI: 0.978-0.995, pre-treatment whole pelvis: 0.998, 95% CI: 0.996-0.999, post-treatment whole pelvis: 0.996, 95% CI: 0.991-0.998) [Table 3].

In addition to MM, NaF has been used in other cancers, mainly for prediction of survival. For instance, in a study, the researchers demonstrated that skeletal tumor burden on NaF-PET/CT, quantified by the method of obtaining the total fluoride skeletal metastatic lesion uptake (TLF10 ,SUVmax threshold = 10) is a strong and independent prognostic biomarker in breast cancer patients [38]. In another study, in addition to TLF10, fluoride tumor volume above an SUVmax of 10 (FTV10) was determined for Ninety-eight consecutive patients who underwent NaF PET/CT scans for evaluation of skeletal metastatic disease [30]. On the basis of these values, the investigators concluded that an SUVmax threshold of 10 is able to exclude normal bone from the volumetric calculations [30]. In another study, the researchers tried to identify predictive factors on baseline NaF PET/CT of early response to radium-223 dichloride after 3 cycles of treatment in metastatic castration-resistant prostate cancer patients [40]. They showed that SUVmax and SUVmean on baseline NaF PET/CT were independent predictors of bone lesions’ response to 3 cycles of radium-223 dichloride [39].

In addition to the global assessment in whole bone and pelvis of MM patients, we evaluated the uptake of NaF in three different areas of femoral neck on both sides (right and left). The results for the medial compartment of femoral neck assessment in the HDT group were not significant. The femoral neck is one of the best sites for the assessment
of bone turnover in the body [40] and Gandhi et al. showed a significant and continued bone loss in the femoral neck of MM patients after stem cell transplantation [41]. The group analyzed BMD changes with respect to relevant determinants in 44 patients who received stem cell transplant. They observed a significant decline in BMD at the femoral neck (P = 0.01) after 3 months post treatment [41].

An important factor that should be considered for interpreting our results is that the MM patients underwent the high-dose therapy eight weeks after the end of treatment. In some studies, it has been shown that osteoblast activity may increase following high-dose therapy, but the effect may take several weeks to emerge. For instance, Clark et al. evaluated the effect of high-dose chemotherapy and autografting in MM patients by assessing biochemical markers of bone turnover [42]. They evaluated 32 myeloma patients after a blood or marrow transplant and high-dose treatment with melphalan. Bone formation was assessed by serum concentrations of bone-specific alkaline phosphatase (BSAP) and procollagen 1 extension peptide (P1CP). The authors found that, in most patients, high-dose treatment normalized abnormal bone resorption, but this effect may take several weeks to emerge and was accompanied by an increase in markers of bone deposition such as P1CP and/or BSAP several months post-transplant [42]. In another study, Terpos et al. showed that bone formation markers such as osteocalcin and bone-alkaline phosphatase and osteocalcin started to increase after the 9th and 11th month post-ASCT, providing an indication that bone formation may be delayed after intensive therapy [43].

There are some limitations in this study. To start, differences from baseline were assessed after 8 weeks in the HDT group and after 2 weeks for the non-HDT group. As a result,
time from baseline may confound the observed differences between treatment groups. If the non-HDT group had been assessed at 8 weeks, we predict that more bone recovery would be present, resulting in greater NaF uptake after therapy and increasing the observed differences between treatment groups. Additionally, there was a relatively low number of patients in each group. Further studies with higher numbers of patients may support the results that we observed in this prospective study. Furthermore, we used two different PET scanners to collect the cases, but since we compared the percentage of change from before to after treatment and each patient underwent imaging by the same PET scanner, the results are minimally affected.

**Conclusion**

Uptake of NaF in the whole bone, pelvis and femoral neck of MM patients was assessed by applying a semi-automated method of PET/CT quantification. The uptake of NaF significantly decreased after the treatment in the HDT group. There was also a trend, but not statistically significant, of decreased NaF uptake after treatment in the non-HDT group. A high level of agreement was observed for the global quantification method that we used in this study. Further studies in the future are needed to evaluate long-term effects of the treatment on the bone turnover of patients with MM.

Compliance with Ethical Standards: The project was funded by the Region of Southern Denmark, University of Southern Denmark, Odense University Hospital, Harboe Foundation, The A.P.Møller Foundation (Fonden til lægevidenskabens fremme), Aase & Ejnar Danielsen Foundation, The Family Hede Nielsen Foundation.
Conflict of Interest: All authors declare that they have no conflict of interest.

Ethics: The protocol was approved by the Danish Ethics Committee (S-20120209), the Danish Data Protection Agency (2008-58-0035) and registered at clinicaltrials.gov (NCT02187731 and NCT01724749).

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

References:


35. Zadeh MZ, Raynor WY, Seraj SM, Ayubcha C, Kothekar E, Werner T, et al. Evolving Roles of Fluorodeoxyglucose and Sodium Fluoride in Assessment of Multiple Myeloma Patients:
Introducing a Novel Method of PET Quantification to Overcome Shortcomings of the Existing Approaches. PET Clinics. 2019.
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>HDT (y)</th>
<th>Non-HDT (y)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.5± 5.6</td>
<td>70.9± 7.2</td>
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<td>Gender</td>
<td>15 Males</td>
<td>8 Males</td>
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</tr>
<tr>
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<td>----------</td>
<td>---------</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>4 Females</td>
<td>3 Females</td>
<td></td>
</tr>
<tr>
<td>Hgb (g/dl)</td>
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<td>7.2± 1.1</td>
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<tr>
<td>B2M (mg/L)</td>
<td>239.8± 78.2</td>
<td>267.7± 102.8</td>
<td>0.4</td>
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<td>Calcium</td>
<td>1.3± 0.1</td>
<td>1.3± 0.1</td>
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<tr>
<td>Albumin (g/L)</td>
<td>38.2 ± 4.4</td>
<td>35.5 ± 6.4</td>
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<td>LDH (U/L)</td>
<td>234.3± 61.2</td>
<td>212.3± 45.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Creatinine (micromole/L)</td>
<td>84.4± 16.5</td>
<td>83.2± 19.8</td>
<td>0.9</td>
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<td>IgG positive</td>
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<td>8 patients</td>
<td>0.6</td>
</tr>
<tr>
<td>IgA positive</td>
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</tr>
<tr>
<td></td>
<td>Unknown=1</td>
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</table>

Abbreviations HDT: high dose therapy, non-HDT: non-high dose therapy, B2M: beta-2 microglobulin, ISS: international staging system, R- ISS: revised international staging system
Table 2. Changes in whole bone, pelvis and femoral neck NaF uptake
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean± SD (pre-treatment)</th>
<th>Mean± SD (post-treatment)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Whole Body (HDT)</td>
<td>4.21± 1.25</td>
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<td>Pelvis (HDT)</td>
<td>4.60± 1.19</td>
<td>3.68± 0.95</td>
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<td>Whole Body (non-HDT)</td>
<td>3.31± 0.83</td>
<td>3.10± 0.84</td>
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<tr>
<td>Pelvis (non-HDT)</td>
<td>3.74± 0.96</td>
<td>3.47± 0.99</td>
<td>0.37</td>
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<tr>
<td>Lateral Right Femoral neck (HDT)</td>
<td>4.15± 2.21</td>
<td>3.47± 1.61</td>
<td>0.04</td>
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<tr>
<td>Lateral Left Femoral Neck (HDT)</td>
<td>3.95± 2.10</td>
<td>3.38± 1.63</td>
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<tr>
<td>Medial Right Femoral Neck (HDT)</td>
<td>4.13± 2.25</td>
<td>3.77± 2.02</td>
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<td>Medial Left Femoral Neck (HDT)</td>
<td>4.07± 2.29</td>
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<td>4.16± 2.22</td>
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<tr>
<td>Whole Left Femoral Neck (HDT)</td>
<td>4.03± 2.20</td>
<td>3.42± 1.56</td>
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* The results of the femoral neck analysis for the non-HDT group were not shown in this table
Table 3. Intra-class correlation analysis for inter-observer reliability

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<thead>
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<th>Parameter</th>
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<th>95% CI</th>
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<td>0.965-0.992</td>
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<td>Whole bone (post-treatment)</td>
<td>0.989</td>
<td>0.978-0.995</td>
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<tr>
<td>Whole pelvis (pre-treatment)</td>
<td>0.998</td>
<td>0.996-0.999</td>
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<tr>
<td>Whole pelvis (post-treatment)</td>
<td>0.996</td>
<td>0.991-0.998</td>
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Functional Imaging in Multiple Myeloma (MM) (FULIMA)
Patients with possible MM diagnosis w/o prior chemotherapy

-28 of the participants excluded:
-12 SMM
-9 MGUS
-1 amyloidosis
-1 primary plasmacytoma
-1 participant did not have any sort of plasma cell diseases
-1 participant included by mistake (< 50 years old)
-3 patients deliberately withdrew

70 subjects recruited

42 patients with MM

12 patients were excluded because of lacking NaF-PET/CT at either baseline or EOT

HDT including ASCT

19 Patients

non-HDT

11 Patients

Fig. 1 Flowchart of patient inclusion
Fig. 2 (a) The following images reflect a single coronal slice of a whole-body scan. The middle image is a co-registered and fused NaF-CT and PET scan, where NaF activity is indicated by the red color scale. The next image illustrates the initial semi-automated CT-based segmentation ROI. The right most image shows the final whole-body ROI after a closing procedure was applied. (b) The left most illustrates the semi-automated CT-based segmentation ROI which is rendered in three dimensions on the right. (c) The images reflect the pre-determined anatomical criteria for segmenting the whole femoral neck.
Fig. 3 Percentage of change in NaF uptake in the whole bone after high-dose therapy (HDT) (a) and after non-HDT (b). Percentage of change in NaF uptake in the pelvis after HDT (c) and non-HDT (d). In the HDT group, 14 patients had a decrease (red bars) and 5 patients had an increase (green bars) in NaF uptake after treatment in the whole bone (range: -57.89 to 26.36%) as well as pelvis (range: -55.66 to 26.07%) (a and c). In the non-HDT group, 7 patients had a decrease (red bars) and 4 patients had an increase (green bars) after the treatment in the whole body (range: -50.29 to 93.47) (b). In addition, eight patients showed decrease (red bars) and 3 patients showed increase (green bars) after the treatment in the pelvis (range: -50.29 to 92.75) (d)
Fig 4 Box Plots show changes in NaF uptake in the whole bone and pelvis after treatment in the HDT and non-HDT groups. NaF uptake after treatment decreased significantly in the whole body (median: -12.45, IQR: 41.29) as well as pelvis (median: -17.20, IQR: 31.41) of the HDT group (a and b, respectively). There was a decrease, but not statistically significant, in the non-HDT group, after treatment in the whole body (median: -1.53, IQR: 29.05) as well as the pelvis (median: -2.56, IQR: 27.91) (c and d, respectively).
Fig 5 Scans above demonstrate the changes in NaF uptake after treatment in a patient from the HDT group (left) and a patient from the non-HDT group (right)