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ORIGINAL ARTICLE

Prognostic significance of normalized FDG-PET parameters in patients with multiple myeloma undergoing induction chemotherapy and autologous hematopoietic stem cell transplantation: a retrospective single-center evaluation

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Abstract

Purpose The purpose of this study was to determine retrospectively, through a single-center evaluation, whether FDG PET-CT normalized semi-quantitative parameters may predict response to induction chemotherapy (iChT) and hematopoietic stem cell transplantation (HSCT), as well as disease progression and progression-free survival in multiple myeloma (MM) patients, thus becoming a tool of personalized medicine.

Methods Patients undergoing iChT and HSCT with baseline and post-treatment FDG PET-CTs from January 2008 to July 2015 were included. The following baseline and post-treatment parameters were obtained: SUVmax, SUVmean, SUVpeak, MTVsum, TLGsum, rPET (lesion SUVmax/liver SUVmax) and qPET (lesion SUVpeak/liver SUVmean). Baseline-to-post-treatment changes (Δ) were also calculated. Metabolic and clinical laboratory progression or response at follow-up were noted; time-to-metabolic-progression (TMP) was defined as the interval from post-treatment scan to eventual progression at follow-up FDG PET-CTs. Possible association between each functional parameter and metabolic/clinical-laboratory progression or response was determined. Kaplan-Meier curves allowed to depict the TMP trend according to FDG PET-CT parameters.

Results Twenty-eight patients were included. Significantly higher ΔrPET and ΔqPET values were observed in ten patients with "metabolic response", with respect to 18 patients having "metabolic progression" (median 0.62 [IQR 0.32 – 1.34] vs median 0.00 [IQR -0.25 – 0.49] for ΔrPET; $P = 0.045$; median 0.51 [IQR 0.32 – 1.13] vs median 0.00 [IQR -0.31 – 0.67] for ΔqPET; $P = 0.035$). Neither normalized nor non normalized parameters differed significantly between the 20 patients with "clinical-laboratory response" and the eight patients with "clinical-laboratory progression". ΔrPET value lower than 0.38 and ΔqPET value lower than 0.27 predicted a significantly shorter TMP ($P = 0.003$ and $P = 0.005$, respectively).

Conclusions Normalized semi-quantitative parameters are effective in predicting persistent response to treatment and shorter TMP in patients with MM undergoing iChT and HSCT.

Keywords Multiple myeloma · Induction chemotherapy · Hematopoietic stem cell transplantation · Normalized parameters · Time-to-metabolic progression · Personalized medicine

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Introduction

Multiple myeloma (MM) accounts for 1% of all neoplasms in adults, with a mean age at onset of 68 years in men and 70 years in women [1]. MM is a haematological malignant condition deriving from the uncontrolled proliferation of plasma cells in bone marrow or, less frequently, in extra-medullary sites. Clinical manifestations may be quite unspecific and common to several haematological conditions: anaemia, bone

fragility and increased risk of pathological fractures, increased occurrence of infections and eventually renal failure [2–5]. Nowadays, there are several therapeutic options. Particularly in symptomatic MM occurring in younger patients, the main therapeutic option is induction chemotherapy (iChT) followed by autologous hematopoietic stem cell transplantation (HSCT). In case of feasibility of autologous HSCT, iChT is based on administration of proteasome inhibitors (bortezomib, carfilzomib) and immunomodulatory imide drugs (thalidomide, lenalidomide), in association with dexamethasone [6–9].

PET-CT using ^{18}F-FDG is the most widely performed nuclear medicine diagnostic technique for staging and evaluation of response to treatment in MM patients, because of its several advantages: assessment of all possible sites of disease (skeletal or extra-skeletal) with high sensitivity and within a single examination; identification of metabolically active disease in patients with no morphological alterations at whole-body skeletal survey or CT; early distinction between active and non-active disease at post-treatment evaluation [10–15].

Qualitative (visual) evaluation of sites of metabolically active disease is often inaccurate or not reliable, mainly because of significant inter-observer variability. This is the reason why semi-quantitative parameters have been validated in clinical practice for years, to obtain an accurate definition of tracer uptake and to achieve a more accurate comparison between baseline and post-treatment examinations [16–20]. The most common semi-quantitative parameters are those derived from Standard Uptake Value (SUV): SUVmax, SUVmean and SUVpeak; further semi-quantitative parameters useful to describe the metabolic burden of lesions are Metabolic Tumor Volume (MTV) and Total Lesion Glycolisis (TLG). However, such parameters can be influenced by several factors, partly depending on single patient's characteristics (height and body weight, blood glucose level, possible kidney function impairment or other concurrent pathological conditions, etc.) and partly inherent to the PET-CT acquisition or reconstruction method (injected activity, time interval from injection to images acquisition, PET scanner technical specifications including presence/absence of time-of-flight acquisition, time per bed position, etc.) [21]. Moreover, such factors may vary from baseline to post-treatment examination.

Internal normalization of these parameters may allow to overcome the aforementioned factors, possibly with a greater prognostic impact on patient management.

The aim of our study is to determine whether internally normalized semi-quantitative parameters may predict response to treatment and disease progression, as well as patients' progression-free survival, thus underlining their additional prognostic value in comparison to conventional non-normalized semi-quantitative parameters and thus proving to be a tool of personalized medicine.

Materials and methods

Study design and inclusion criteria

Patients affected by multiple myeloma (MM) undergoing ^{18}F-FDG PET-CT at our PET-CT center for staging of initial disease or restaging of suspected disease relapse in the time period between January 2008 and July 2015 were retrospectively evaluated. The study, designed in the perspective of a personalized diagnostic and therapeutical path, was approved by our Ethical Committee and informed consent was obtained by all patients.

Inclusion criteria were:

- High-dose iChT followed by autologous HSCT performed as the first-line therapy in patients with newly diagnosed MM or as treatment of disease relapse in patients with previously diagnosed MM;
- ^{18}F-FDG PET-CT performed both before and after high-dose iChT and autologous HSCT (in particular, post-treatment PET-CT had to be performed no more than 9 months after HSCT);
- Evidence of at least one skeletal or extra-skeletal lesion from MM with high uptake of ^{18}F-FDG at baseline PET-CT;
- Minimum 2 years follow-up with at least one ^{18}F-FDG PET-CT performed on site during the follow-up in order to assess the functional response or progression of MM lesions over time.

Laboratory data concerning plasma cell infiltration of bone marrow at baseline (Base-%PC) and post-treatment (Post-%PC) and the presence and type of the monoclonal component at baseline (Base-MC) and post-treatment (Post-MC), measured in international units, were recorded and reported for all patients. In order to be eligible for this study, only Base-%PC and Base-MC measured no more than 6 months before baseline ^{18}F-FDG PET-CT as well as Post-%PC and Post-MC measured no more than 6 months after post-treatment ^{18}F-FDG PET-CT were considered.

PET-CT protocol

^{18}F-FDG (mean activity dose 280 MBq, range 185–390 MBq, according to each patient's body mass index) was injected intravenously after at least 6 h fasting and with glucose blood levels not exceeding 200 mg/dl.

Acquisition of PET-CT images was performed about 70 min (range 60–85 min) after ^{18}F-FDG administration using a PET-CT scanner and covering a field of view from the vertex of skull to the extremities of feet in order to include all skeletal segments. For the acquisitions of baseline and post-treatment examinations we used: before July 2013, two Philips™

scanners (DUAL and GEMINI GXL); after July 2013, also a Siemens™ scanner equipped with "time-of-flight" technology (BIOGRAPH mCT). Before each PET acquisition, a low-dose (40–60 kV) non-contrast enhanced CT scan was performed covering all PET field of view. PET images were acquired with 3D mode lasting 25–30 min (BIOGRAPH mCT) or about 45–50 min (DUAL and GEMINI GXL).

Image reconstruction implied iterative algorithms (3D-RAMLA or OS-EM and TRUEX-TOF); therefore, reconstructed images were loaded on a dedicated report workstation equipped with visualization software Syngo.via (Siemens™) and displayed on high-resolution monitors in transaxial, coronal and sagittal planes.

Analysis of PET-CT images

Qualitative (visual) analysis was first performed in order to determine the number and sites of lesions with increased ^{18}F-FDG uptake and qualitative variations in number and uptake degree of the same lesions from the baseline to the post-treatment scan.

Subsequently, a semi-quantitative analysis of the same images was performed by placing volumes of interest (VOIs) on focal sites of increased ^{18}F-FDG uptake (regardless of the presence of morphological alterations on low-dose CT) in order to obtain several non-normalized parameters: SUVmax, SUVmean and SUVpeak of the lesion with the highest ^{18}F-FDG uptake at baseline and post-treatment PET-CT; MTV and TLG of the sum of all functionally detectable lesions (called MTVsum and TLGsum, respectively). Particularly, SUVmax, SUVmean and SUVpeak were obtained by placing a VOI on the lesion with the highest ^{18}F-FDG uptake; MTVsum and TLGsum were obtained by contouring with VOIs all the functionally active lesions (particularly, in patients with more than five detectable lesions, VOIs were placed around the five sites of more intense pathological ^{18}F-FDG uptake, while in patients with maximum five active lesions, VOIs were placed around all the lesions themselves).

In order to obtain normalized parameters, ratios between the lesional VOIs and a reference organ were calculated: a standard 30 cm^3 VOI was placed on the right hepatic lobe between the 8th and 7th segment in order to be far from hepatic edges (Fig. 1), then liver SUVmax and liver SUVmean were obtained at baseline and post-treatment examination. These normalized parameters were called rPET and qPET: rPET is the ratio between the SUVmax of the lesional VOI and the liver SUVmax; qPET is the ratio between the SUVpeak of the lesional VOI and the liver SUVmean. Each parameter was calculated at both baseline and post-treatment PET-CT; baseline to post-treatment variation (Δ value) was also calculated for each parameter (ΔSUV max, ΔSUV mean, ΔSUV peak, ΔMTVsum, ΔTLGsum, ΔrPET and ΔqPET).

Definition of outcome during the follow-up

In all included patients, disease response or progression was established according both to clinical and laboratory parameters (increase or appearance of monoclonal component during follow-up) and to the evolution of metabolic activity in lesions during the follow-up PET-CT(s) performed after the post-treatment scan over minimum 2 years follow-up. Particularly, the further decrease or the complete disappearance/absence of previously active lesions in follow-up PET-CT(s) was defined as a "metabolic response"; on the other hand, the occurrence of new functionally active lesions in follow-up PET-CT(s) was defined as a "metabolic progression".

The time interval (in months) from the post-treatment scan to the eventual first evidence of progression at follow-up ^{18}F-FDG PET-CT(s) was calculated and denominated time to metabolic progression (TMP). In patients in which there was no evidence of metabolic progression at follow-up PET-CT(s), TMP was defined as the interval between the post-treatment scan and the last date of follow-up for this study set at 30th September 2017.

Statistical analysis

Shapiro-Wilk's test was applied in all patients in order to determine whether the distribution of the aforementioned quantitative variables (baseline, post-treatment and Δ values) was parametric or not. Since a non-parametric distribution was found for all parameters, Mann-Whitney test was used to determine whether a significant difference in each functional parameter's median values (baseline, post-treatment and Δ) was evident in patients with metabolic or clinical-laboratory progression in comparison with patients without metabolic or clinical-laboratory progression.

Furthermore, Mann-Whitney test was used to determine whether each functional parameter (baseline, post-treatment and Δ value) significantly differed between patients with evidence of increase in %PC (Post-%PC > Base-%PC) with respect to patients with decrease in %PC (Post-%PC < Base-%PC); similarly, this was performed to determine whether each functional parameter (baseline, post-treatment and Δ value) significantly differed between patients with evidence of detectable Post-MC in comparison with patients without detectable Post-MC.

In order to assess possible differences in TMP in patients depending on their baseline, post-treatment and Δ values for each parameter, a cut-off value was obtained for each parameter (normalized and non-normalized ones) by using discriminant analysis which allowed to dichotomize the population in two classes (parameter higher or lower than the cut-off). Cut-off values were obtained using discriminant function analysis which provides data

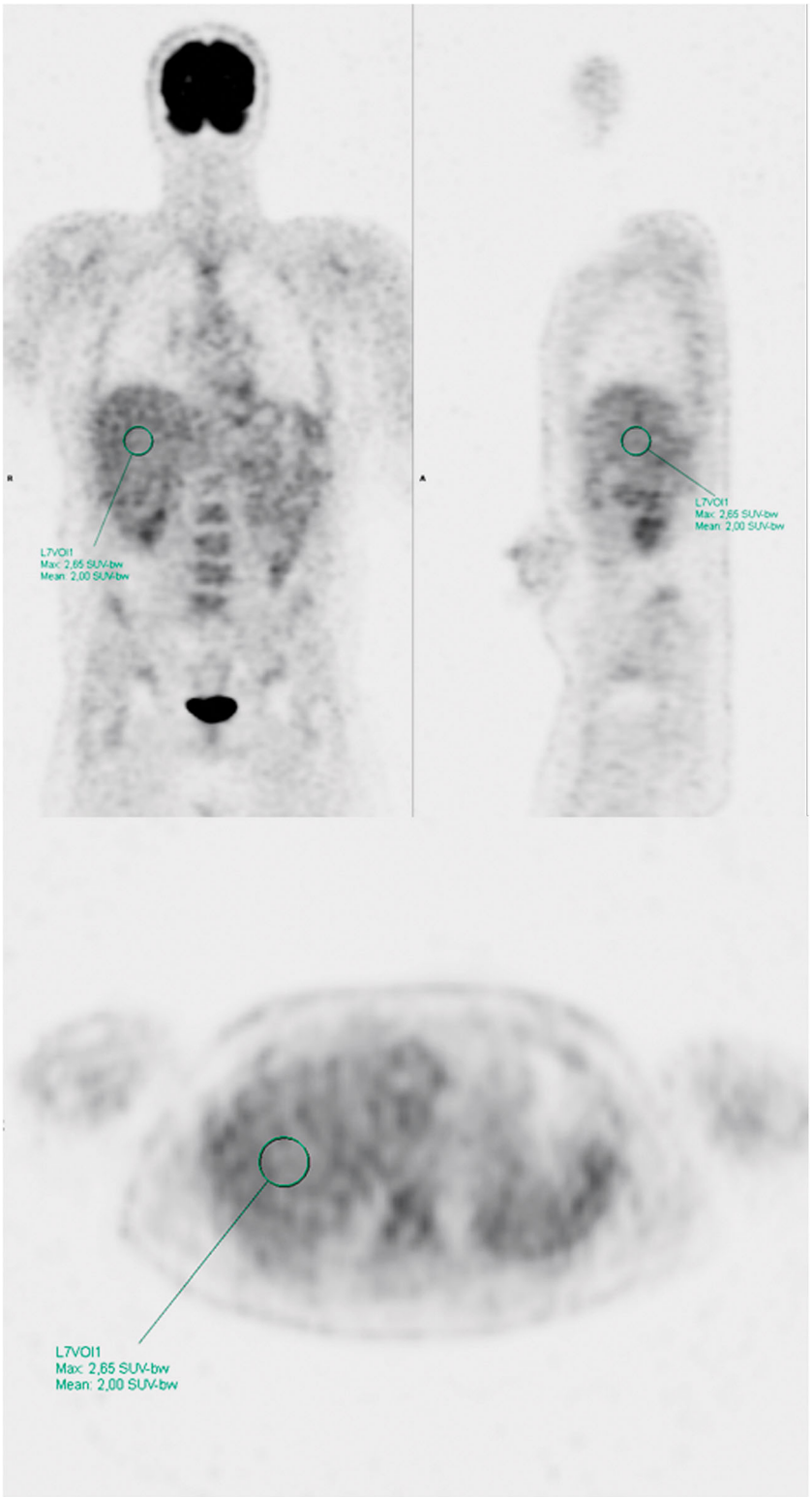

Fig. 1 Correct placement of standard circular 30 cm^3 VOI on the right liver lobe, based on the coronal, sagittal and transaxial PET images

distribution in the two groups (each semi-quantitative parameter vs time to progression) to be converted to two centroid functions whose mean value ($D_{cut\text{-}off}$ or mean of centroid functions) was calculated; correlation coefficient (C) and correlation constant (K) were also derived; the desired cut-off value ($X_{cut\text{-}off}$) for each semi-quantitative parameter was calculated using the inverse canonical function: $X_{cut\text{-}off} = (D_{cut\text{-}off} - K)/C$. Kaplan-Meier survival

curves were constructed by plotting, for each class of patients, TMP and % of patients with functional progression. Log-rank Mantel-Cox function was used to determine whether possible differences in TMP between the two classes of patients were significant.

Software SPSS v.18 was used for all statistical analyses and P values <0.05 were considered significant.

Results

Patient population characteristics

Twenty-eight patients (14 male, 14 female, median age 57 years, range 48-65) with focal ^{18}F-FDG-positive disease at baseline PET-CT were selected retrospectively from the whole population of 78 patients undergoing high-dose iCht and autologous HSCT. Baseline ^{18}F-FDG PET-CT was performed for initial disease staging in 6 patients with recent diagnosis of multiple myeloma (MM) and for disease restaging in 22 patients with suspected relapse. Baseline ^{18}F-FDG PET-CT was performed using Philips™ Gemini DUAL in three patients, Philips™ Gemini GXL in 14 patients while in 11 patients it was performed using the more recent Siemens™ Biograph mCT.

Post-treatment ^{18}F-FDG PET-CT was performed 4.8 ± 1.5 months after treatment completion using Philips™ Gemini DUAL in two patients, Philips™ Gemini GXL in 11 patients and the more recent Siemens™ Biograph mCT in 15 patients.

Therefore, five patients performed post-treatment ^{18}F-FDG PET-CT on a different scanner than their respective baseline: particularly, one patient shifted from Philips™ Gemini DUAL to Philips™ Gemini GXL and four patients shifted from Philips™ Gemini GXL to Siemens™ Biograph mCT.

Mean follow-up lasted 48.2 ± 9.8 months for each patient; during follow-up each patient performed 4.2 ± 2.1 ^{18}F-FDG PET-CT examinations. Two patients died during follow-up for extra-skeletal disease progression.

Determination of baseline bone marrow plasma cell percent involvement (Base-%PC) and/or post-treatment bone marrow plasma cell percent involvement (Post-%PC) was available in 22 patients; determination of baseline monoclonal component (Base-MC) and/or post-treatment monoclonal component (Post-MC) was available in 27 patients; determination of baseline free light chains determination (Base-FLC) and/or post-treatment free light chains (Post-FLC) was available in 26 patients. Detectable Base-%PC was observed in 15/19 patients (median 4.3%) while detectable Post-%PC was observed in 5/22 patients (median 0.3%). Base-MC was present in 23/25 patients; Post-MC was present in 18/27 patients.

Qualitative (visual) evaluation

Baseline ^{18}F-FDG PET-CT showed a total of 97 focal sites of pathological uptake in 28 patients; post-treatment ^{18}F-FDG PET-CT showed a total of 72 focal sites of pathological uptake in 24 patients. Most focal sites of pathological uptake were found in the axial bone (vertebrae, ribs and pelvis) accounting for 79 sites (81%) at baseline and 53 sites (74%) at post-treatment examination, while the remainder were observed in the appendicular long bones (femurs and humerus). No extra-medullary focal sites of disease were noticeable at both baseline and post-treatment scans. A reduction in number of ^{18}F-FDG-positive sites at post-treatment PET-CT was observed in ten patients while in four patients FDG-positive sites completely disappeared at post-treatment PET-CT and slightly increased in number at post-treatment PET-CT in eight patients; no significant changes in number and visual uptake degree of focal sites of pathological uptake of ^{18}F-FDG were observed in six patients. Morphological evaluation of skeletal myeloma lesions was not always feasible because of the methodological limitations inherent to "low-dose" CT co-registered with PET images and because of the presence of osteoporotic changes in most patients that could affect the depiction of myeloma-related bone alterations.

Semi-quantitative evaluation (non-normalized parameters)

Distribution characteristics of non-normalized semi-quantitative parameters (SUVmax, SUVmean, SUVpeak, MTVsum and TLGsum) at baseline ^{18}F-FDG PET-CT, post-treatment ^{18}F-FDG PET-CT and their baseline to post-treatment variation (Δ) are summarized in Table 1. No linear correlation was found between baseline value for each parameter and its respective post-treatment value ($R^2 \sim 0$).

Semi-quantitative evaluation (normalized parameters)

Distribution characteristics of normalized semi-quantitative parameters (rPET and qPET) at baseline ^{18}F-FDG PET-CT, post-treatment ^{18}F-FDG PET-CT and their baseline to post-treatment variation (Δ) are summarized in Table 1. No linear correlation was found between baseline value for each parameter and its respective post-treatment value ($R^2 \sim 0$). Distributions of baseline rPET and qPET values in the study population were similar ($R^2 = 0.95$), as were post-treatment rPET and qPET ($R^2 = 0.81$) as well as ΔrPET and ΔqPET ($R^2 = 0.93$). Significantly higher ΔrPET and ΔqPET values were observed in nine patients with negative Post-MC ($P = 0.016$ and $P = 0.018$, respectively).

Table 1 Median values (interquartile range) of normalized and non-normalized parameters in the studied population at baseline and post-treatment PET-CT, and their variations (Δ)

Parameter	Baseline	Post-treatment	Δ
SUVmax	3.41 (2.79; 5.05)	2.46 (1.81; 3.17)	1.08 (−0.01; 2.75)
SUVmean	2.31 (1.81; 3.18)	1.86 (1.34; 2.16)	0.70 (−0.01; 1.76)
SUVpeak	2.83 (2.08; 4.00)	2.06 (1.54; 2.60)	0.92 (−0.03; 2.04)
MTVsum	9.64 (3.71; 22.83)	5.79 (2.64; 22.95)	1.05 (−2.18; 5.70)
TLGsum	18.99 (7.14; 54.35)	10.47 (4.56; 52.69)	5.90 (−4.68; 37.34)
rPET	1.21 (1.03; 1.62)	0.94 (0.73; 1.26)	0.30 (−0.18; 0.92)
qPET	1.32 (1.10; 1.70)	1.06 (0.84; 1.33)	0.26 (−0.01; 0.95)

Semi-quantitative evaluation vs patients' outcome

Ten patients were considered as having "metabolic response" (35%) and 18 as having "metabolic progression" (65%).

As reported in Table 2, significantly higher ΔrPET and ΔqPET values were observed in ten patients with "metabolic response" with respect to the 18 patients having "metabolic progression" (median 0.62 [IQR 0.32 – 1.34] vs median 0.00 [IQR -0.25 – 0.49] for ΔrPET; $P = 0.045$; median 0.51 [IQR 0.32 – 1.13] vs median 0.00 [IQR -0.31 – 0.67] for ΔqPET; $P = 0.035$). PET-CT images of patients showing either "metabolic progression" or "metabolic response" at follow-up are reported in Figs. 2 and 3, respectively.

Table 2 Median values (interquartile range) of normalized and non-normalized parameters in patients with either "metabolic response" or "metabolic progression"; P values derived from Mann-Whitney U-test ($P < 0.05$ in bold)

Parameter	Metabolic progression	Metabolic response	P-value
Baseline			
SUVmax	3.31 (2.44; 3.66)	4.13 (2.75; 6.82)	0.36
SUVmean	1.99 (1.64; 2.81)	2.52 (2.03; 4.49)	0.24
SUVpeak	2.46 (1.90; 3.05)	2.88 (2.11; 5.79)	0.52
MTVsum	9.34 (3.69; 19.14)	11.58 (4.12; 38.83)	0.73
TLGsum	15.78 (6.91; 37.92)	45.94 (7.07; 133.27)	0.40
rPET	1.14 (0.91; 1.48)	1.25 (1.06; 2.34)	0.59
qPET	1.15 (0.92; 1.43)	1.43 (1.10; 2.52)	0.36
Post-treatment			
SUVmax	2.93 (1.95; 4.97)	2.15 (1.39; 3.17)	0.25
SUVmean	1.94 (1.48; 2.48)	1.73 (1.13; 2.18)	0.52
SUVpeak	2.46 (1.65; 2.65)	1.87 (1.34; 2.81)	0.48
MTVsum	6.08 (3.12; 20.94)	5.50 (1.48; 31.33)	0.52
TLGsum	10.84 (4.60; 43.34)	10.09 (2.10; 63.95)	0.48
rPET	1.03 (0.70; 1.59)	0.85 (0.64; 1.21)	0.39
qPET	1.07 (0.84; 1.41)	0.93 (0.74; 1.39)	0.97
Data			
ΔSUVmax	0.49 (−0.42; 1.65)	2.36 (0.49; 4.08)	0.12
ΔSUVmean	0.17 (−0.53; 0.71)	1.58 (0.29; 2.71)	0.07
ΔSUVpeak	0.35 (−0.06; 1.86)	1.35 (1.01; 2.08)	0.32
ΔMTVsum	0.65 (−3.01; 5.98)	2.43 (−0.01; 12.25)	0.36
ΔTLGsum	0.85 (−5.65; 18.79)	18.02 (1.12; 68.24)	0.33
ΔrPET	***0.00 (−0.25; 0.49)***	***0.62 (0.32; 1.34)***	***0.045***
ΔqPET	***0.00 (−0.31; 0.67)***	***0.51 (0.32; 1.13)***	***0.035***

We also performed a sub-analysis of the 22 patients who underwent PET-CT for restaging of suspected disease relapse: 13 patients had evidence of "metabolic progression" while nine patients had evidence of "metabolic response" during the follow-up. Significantly higher ΔrPET values were observed in nine patients with "metabolic response" with respect to the 13 patients with "metabolic progression" (median 0.76 [IQR 0.10-1.35] vs median − 0.18 [IQR -0.47-0.41]; $P = 0.025$); significantly lower post-treatment rPET values were observed in nine patients with "metabolic response" with respect to the 13 ones with "metabolic progression" (median 0.82 [IQR 0.59-1.08] vs median 1.27 [IQR 0.86-1.69]; $P = 0.014$). A trend to higher ΔqPET values was found in patients with "metabolic response" (median 0.58 [IQR 0.18-1.17] vs median − 0.06 [IQR -0.29-0.49], although this was not significant ($P = 0.06$). Sub-group analysis on the six patients undergoing PET-CT for staging of newly diagnosed multiple myeloma was not performed because of the small sample size.

Conversely, the non-normalized semi-quantitative parameters considered (SUVmax, SUVmean, SUVpeak, MTVsum and TLGsum) did not significantly differ between patients with "metabolic response" and patients with "metabolic progression", although a trend to slightly lower Δ values was observed in patients with "metabolic progression".

Twenty patients were considered as having a "clinical-laboratory response" (71%) and eight as having a "clinical-laboratory progression" (29%).

As reported in Table 3, neither normalized nor non normalized semi-quantitative parameters differed significantly between patients having a "clinical-laboratory response" and patients having a "clinical-laboratory progression".

PET parameters-based survival analysis

The TMP was calculated for each patient. Median TMP was 19.3 months (IQR 15.3–24.8) in 18 patients with "metabolic

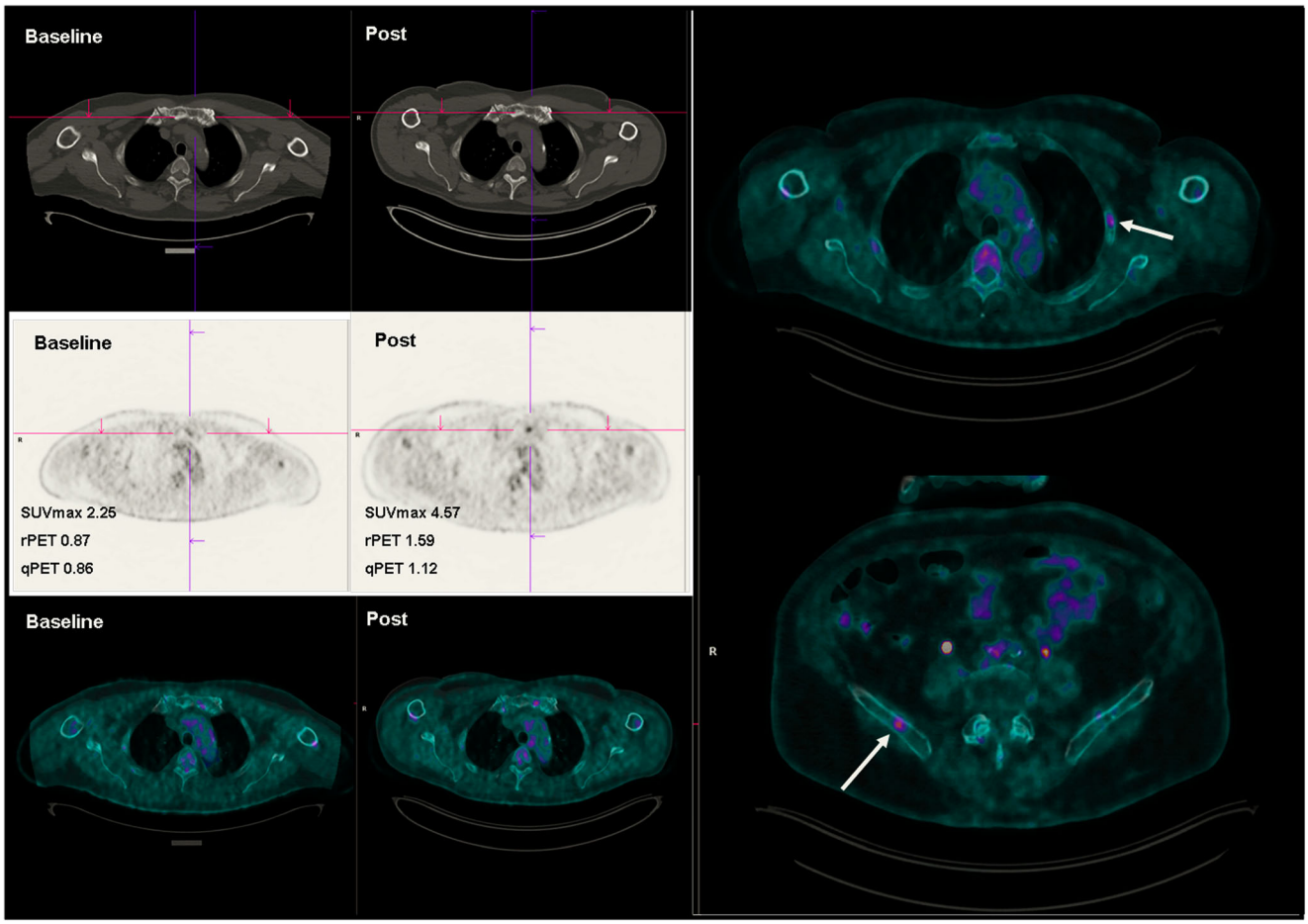

Fig. 2 A 65-year-old male. Baseline PET-CT shows a single area of focal ^{18}F-FDG uptake on left sternum (SUVmax 2.25; rPET 0.87; qPET 0.86) in the absence of structural alterations; post-treatment PET-CT shows further increase in ^{18}F-FDG uptake at the same location (SUVmax 4.57; rPET 1.59; qPET 1.12). Δ values obtained (ΔSUVmax −2.32; ΔrPET −0.72; ΔqPET −0.26) predict metabolic progression with evidence of two additional uptake sites at follow-up PET-CT (third left rib and right iliac crest, as shown by *arrows*) with very short TMP (15 months)

progression" while in ten patients with "metabolic response" it was 33.2 months (IQR 28.5–40.3).

Kaplan-Meier survival curves obtained from the 28 patients (Fig. 4) showed that a ΔrPET value lower than 0.38 (cut-off value for ΔrPET obtained using discriminant function analysis) and a ΔqPET value lower than 0.27 (cut-off value for ΔqPET obtained using discriminant function analysis) predicted a shorter TMP. Median TMP was 18.5 [IQR 15.2–28] months in 16 patients with ΔrPET lower than 0.38 vs median 31.7 [IQR 26.7–38.2] months in 12 patients with ΔrPET higher than 0.38; median TMP was 19.5 [IQR 16.4–29] months in 15 patients with ΔqPET lower than 0.27 vs median 30.2 [IQR 23.5–38] in 13 patients with ΔqPET higher than 0.27. Log-rank test assessed the difference was statistically significant ($P = 0.003$ for ΔrPET; $P = 0.005$ for ΔqPET). A slight tendency to a shorter median TMP was found in patients with post-treatment rPET higher than 1.02 (cut-off value for rPET obtained using discriminant function analysis): median TMP was 24.2 [IQR 16.5–30.7] months when post-treatment rPET was higher than 1.02 vs median TMP of 29.7 [IQR 21.5 – 42.3] months when post-treatment rPET was lower than 1.02; however, this did not reach statistical significance ($P = 0.181$).

Kaplan-Meier survival curves obtained from the 22 patients with suspected disease relapse (Fig. 5) showed that a ΔrPET value lower than 0.36 (cut-off value for ΔrPET obtained using discriminant function analysis) and a ΔqPET value lower than 0.35 (cut-off value for ΔqPET obtained using discriminant function analysis) predicted a shorter TMP. Median TMP was 18 [IQR 15.5–33] months in 12 patients with ΔrPET lower than 0.36 vs median 30 [IQR 25.7–36.3] months in ten patients with ΔrPET higher than 0.36; median TMP was 19 [IQR 16.5–33] months in 11 patients with ΔqPET lower than 0.35 vs median 30 [IQR 25.5–33.5] months in 11 patients with ΔqPET higher than 0.35. Log-rank test assessed the difference was statistically significant in both cases ($P = 0.013$ for ΔrPET; $P = 0.041$ for ΔqPET). Sub-group survival analysis on the six patients undergoing PET-CT for staging of newly diagnosed multiple myeloma was not performed because of the small sample size.

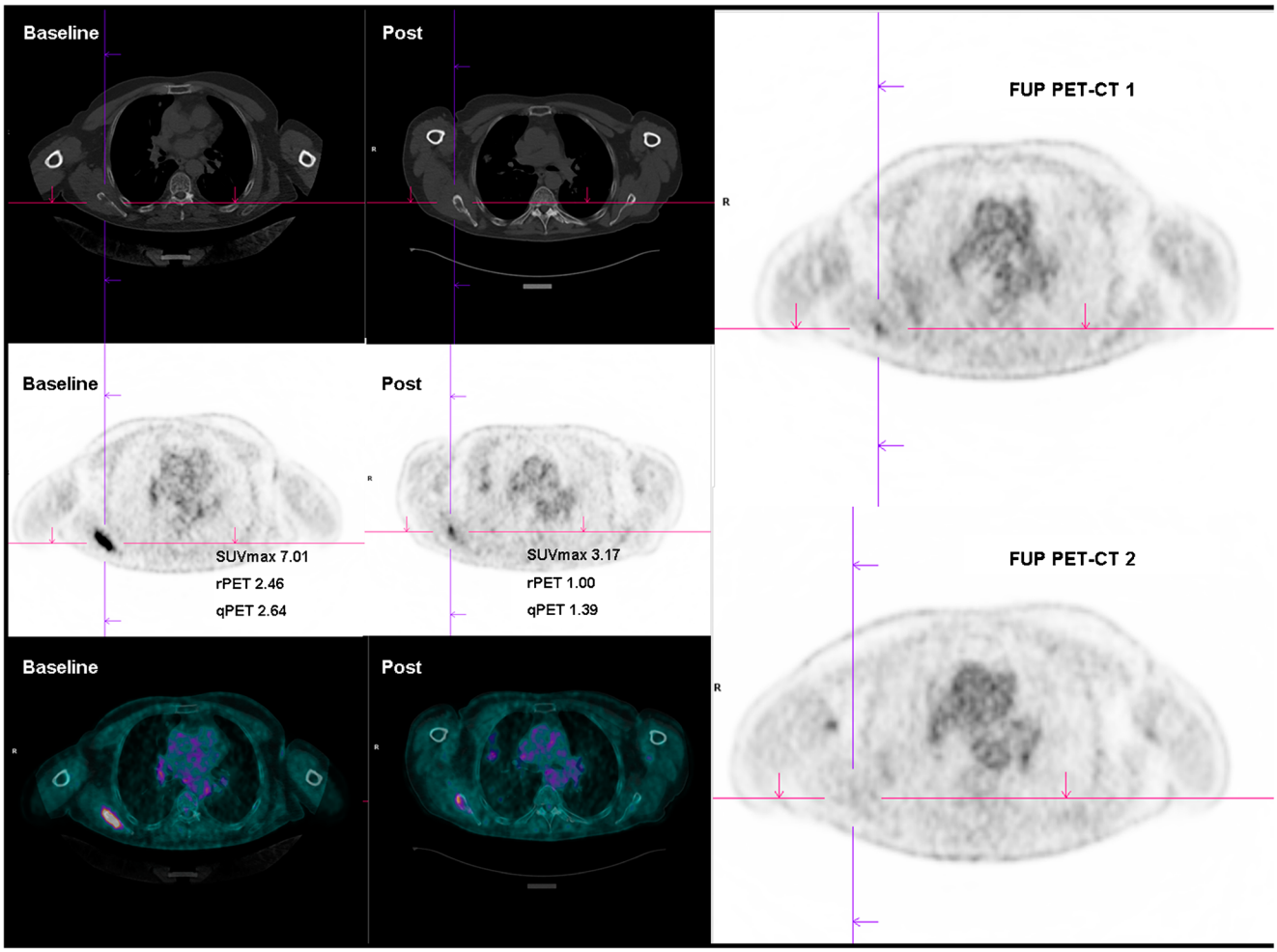

Fig. 3 A 54-year-old male. Baseline PET-CT shows a single area of focal ^{18}F-FDG uptake on a lytic lesion involving right scapula (SUVmax 7.01; rPET 2.46; qPET 2.64); post-treatment PET-CT shows a decrease in ^{18}F-FDG uptake by the same lesion (SUVmax 3.17; rPET 1.00; qPET1.39), morphologically stable. Δ values obtained (ΔSUVmax 3.84; ΔrPET 1.46; ΔqPET 1.25) predict metabolic response with evidence of further decrease in ^{18}F-FDG uptake by the same lesion at follow-up PET-CTs (FUP PET-CT 1 and 2), as well as in the absence of new uptake sites and with a long TMP (32 months)

Conversely, time to "clinical-laboratory progression" did not significantly differ between patients with ΔrPET or ΔqPET values higher or lower than their respective cut-offs obtained using discriminant function analysis. Particularly, median time to "clinical-laboratory progression" was 26.1 [IQR 15.8–39.6] months in 16 patients with ΔrPET lower than 0.38 vs median 29.6 [IQR 20.2–41.5] months in 12 patients with ΔrPET higher than 0.38; median time to "clinical-laboratory progression" was 28.3 [IQR 15.5–43.8] months in 15 patients with ΔqPET lower than 0.27 vs median 29.3 [IQR 20.5–34.3] in 13 patients with ΔqPET higher than 0.27.

Discussion

^{18}F-FDG PET-CT provides unique functional information regarding skeletal and extra-skeletal involvement in patients with MM, both in disease staging/restaging in order to suggest the best therapeutical strategy, and in the early (4–6 weeks) evaluation of treatment effectiveness. Its diagnostic and prognostic role also has been widely demonstrated, even when in combination with other methods [22, 23]. Semi-quantitative parameters may be useful for a more precise and reliable assessment of ^{18}F-FDG accumulation in lesional sites [16–20]. However, they are prone to a number of interferences, partly derived from patient's features and partly inherent to the diagnostic procedure itself [21].

Normalized semi-quantitative parameters may be useful to overcome these issues: since they are a ratio between the degree of uptake of a lesion and the degree of uptake of a reference organ (generally not involved by the specific disease), they should not be affected by the aforementioned biological and technical factors. Thus, they may reduce inter-variability between baseline and post-treatment evaluation in order to make better assessment of patients' response to treatment aiming at a better clinical management. To the best of our

Table 3 Median values (interquartile range) of normalized and non-normalized parameters in patients with either "clinical-laboratory response" or "clinical-laboratory progression"; P values derived from Mann-Whitney U-test

Parameter	Clinical-laboratory progression	Clinical-laboratory response	P-value
Baseline			
SUVmax	3.53 (2.29; 6.65)	3.28 (2.51; 5.03)	0.54
SUVmean	2.17 (1.67; 4.14)	2.42 (1.79; 3.89)	0.98
SUVpeak	2.91 (1.99; 5.20)	2.72 (1.84; 3.89)	0.35
MTVsum	10.57 (4.93; 18.95)	6.73 (2.63; 34.62)	0.60
TLGsum	23.22 (14.52; 54.18)	13.92 (4.63; 83.47)	0.37
rPET	1.26 (0.94; 2.40)	1.20 (1.02; 1.50)	0.70
qPET	1.41 (1.02; 2.48)	1.25 (1.05; 1.43)	0.73
Post-treatment			
SUVmax	2.61 (1.93; 3.04)	2.73 (1.76; 4.42)	0.70
SUVmean	1.71 (1.33; 1.99)	1.97 (1.47; 2.45)	0.26
SUVpeak	2.09 (1.53; 2.63)	2.35 (1.54; 2.82)	0.70
MTVsum	7.51 (3.36; 26.44)	4.70 (2.00; 22.95)	0.42
TLGsum	14.47 (4.60; 51.88)	7.54 (4.06; 52.68)	0.70
rPET	0.91 (0.69; 1.26)	1.01 (0.71; 1.56)	0.52
qPET	0.96 (0.67; 1.39)	1.10 (0.84; 1.43)	0.51
Delta			
ΔSUVmax	1.68 (−0.27; 3.94)	0.74 (−0.14; 2.14)	0.54
ΔSUVmean	0.70 (−0.18; 2.65)	0.43 (−0.14; 1.42)	0.45
ΔSUVpeak	0.62 (−0.06; 2.04)	0.54 (−0.08; 1.96)	0.45
ΔMTVsum	1.34 (−3.12; 5.70)	0.65 (−0.10; 7.82)	0.91
ΔTLGsum	11.62 (−6.97; 37.34)	2.95 (−4.50; 38.84)	0.94
ΔrPET	0.33 (−0.08; 1.36)	0.16 (−0.21; 0.69)	0.26
ΔqPET	0.36 (−0.03; 1.14)	0.15 (−0.30; 0.55)	0.20

knowledge, no previous studies investigating the prognostic role of ^{18}F-FDG PET-CT derived normalized semi-quantitative parameters, consequently aiming for a personalized clinical practice, in patients with MM have been published yet.

One of the normalized parameters used in our study is rPET (ratio between SUVmax of the target lesion and SUVmax of the right liver lobe measured on a standard 30 cm^3 VOI). We have calculated rPET at baseline, post-treatment PET-CT and the baseline to post-treatment variation (ΔrPET) for each

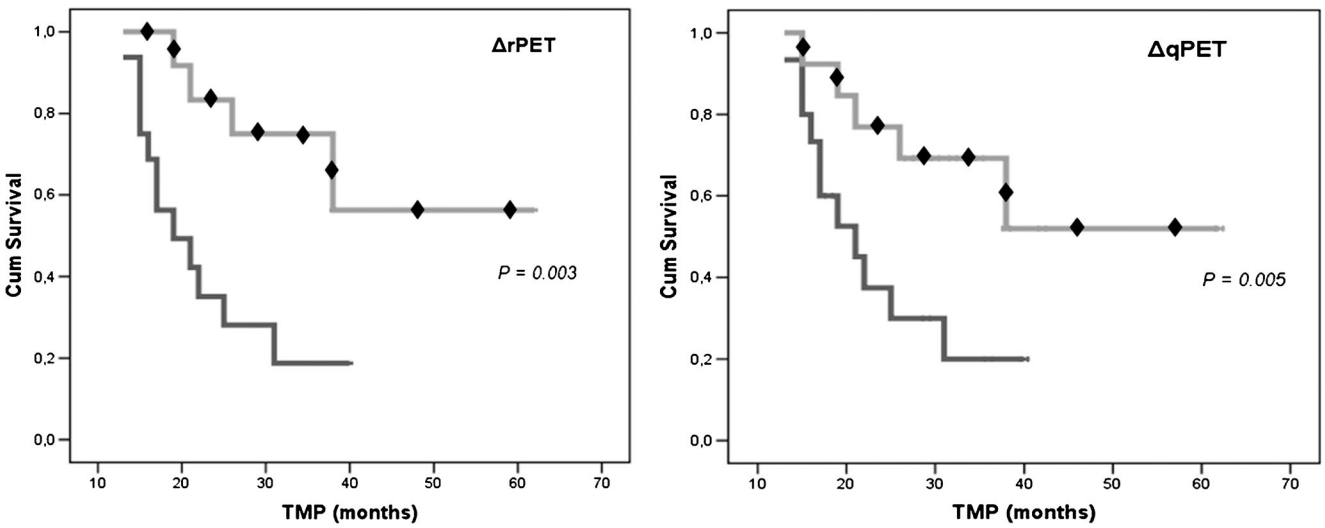

Fig. 4 Kaplan-Meier survival curves showing TMP according to ΔrPET and ΔqPET values. *Dotted line*: patients with value higher than cut-off. *Continuous line*: patients with value lower than cut-off

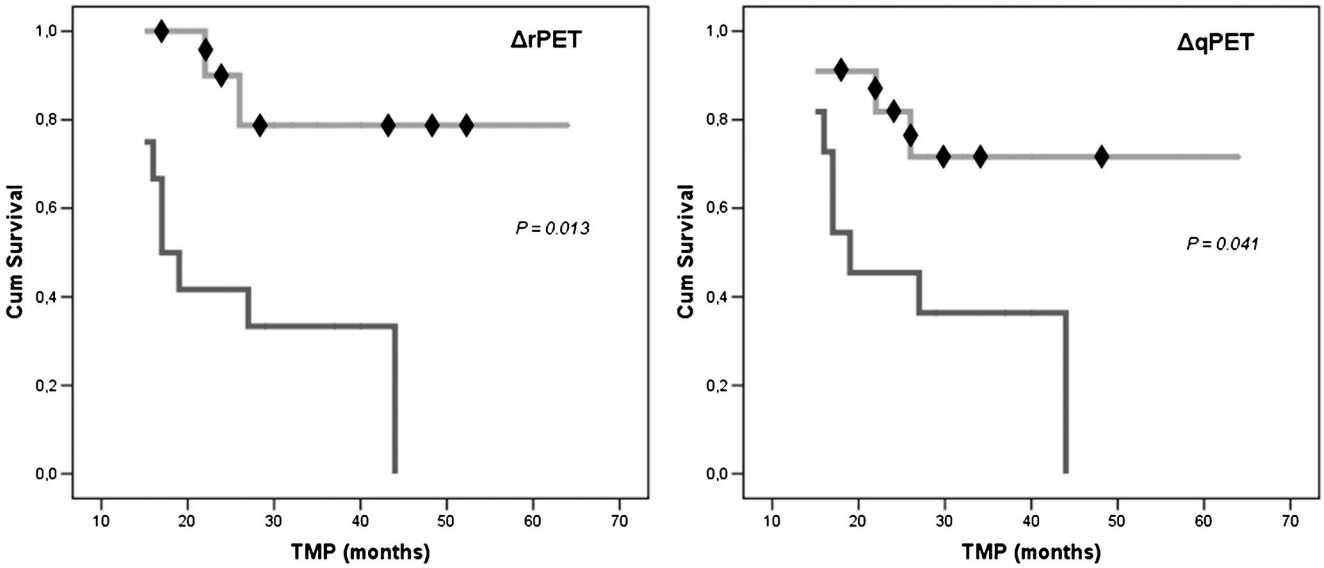

Fig. 5 Kaplan-Meier survival curves showing TMP according to ΔrPET and ΔqPET values in patients undergoing PET-CT for restaging purposes. *Dotted line*: patients with value higher than cut-off. *Continuous line*: patients with value lower than cut-off

patient, demonstrating that a higher ΔrPET was observed more frequently in patients with evidence of "metabolic response" during follow-up, whilst a ΔrPET <0.38 predicted a significantly shorter TMP. On the contrary, neither baseline nor post-treatment rPET were significantly associated with the presence or absence of "metabolic progression" or "clinical-laboratory progression", nor to a significantly shorter TMP. In the smallest cohort of the 22 patients undergoing restaging for suspected disease relapse, higher ΔrPET values were observed in patients with "metabolic response" and post-treatment rPET values were significantly lower in patients with "metabolic response" during follow-up; furthermore, a ΔrPET <0.36 predicted a significantly shorter TMP. Nowadays, the use of rPET is reported in the literature only in patients with Hodgkin's lymphoma [18]: in this retrospective study on 68 patients evaluated after two cycles of ABVD, a rPET >1.14 obtained at interim ^{18}F-FDG PET-CT predicted a poor survival after 2 years of follow-up (PFS 15 vs 87%). Noteworthy is that our post-treatment rPET cut-off (1.02) was similar to the one (1.14) reported by Annunziata and co-workers [18].

The other normalized parameter used in our study is qPET (ratio between SUVpeak of the target lesion and SUVmean of the right liver lobe measured on a standard 30 cm^3 VOI). In our study the SUVpeak has been calculated automatically by the contouring software as the mean uptake of a standard 1 cm^3 VOI centered on the highest uptake spot; this method may lead to an underestimation of the SUVmax in patients with very low residual burden of functionally active disease at the post-treatment PET-CT, since the standard 1 cm^3 could be wider than the active lesion itself.

Other calculation strategies have been proposed recently, notably the mean value of the SUVmax voxel and the three surrounding voxels with the highest uptake [19], although comparison studies on a wide population have not been published yet. A spherical VOI was preferred to obtain the reference liver uptake since it allows an accurate determination of both SUVmax and SUVmean provided that the liver was not involved by the disease and the VOI was far from liver edges. Despite the assessment that lesion SUVpeak may be trickier than that of lesion SUVmax, we have considered qPET in addition to rPET, since liver SUVmean is expected to be more accurate for assessing heterogeneity of hepatic ^{18}F-FDG distribution, compared to liver SUVmax,

rPET was calculated at both baseline and post-treatment examinations, and the baseline to post-treatment variation (ΔqPET) has been derived. Neither baseline nor post-treatment qPET were associated with presence or absence of "metabolic progression" or "clinical-laboratory progression"; baseline qPET >1.55 and post-treatment qPET >1.23 were not predictive of shorter TMP. Conversely, higher ΔqPET values were observed in patients with "metabolic response" during follow-up and a ΔqPET <0.27 predicted a significantly shorter median TMP. In the smallest cohort of the 22 patients undergoing restaging for suspected recurrent disease, a ΔqPET value lower than 0.35 predicted a shorter TMP. The only previous study investigating qPET in 898 paediatric patients with Hodgkin's lymphoma was authored by Hasenclever et al. [19]. In his paper post-treatment qPET <1.3 is associated with the absence of residual disease in 97% of patients. In our cohort median ΔrPET and ΔqPET values in patients showing "metabolic progression" was 0, that is, patients with no evidence of baseline to post-treatment variation of lesion uptake (with respect to the liver background) had progressed during the subsequent follow-up. On the contrary, a positive variation is always predictive of "metabolic response" during follow-up.

Conversely, the non-normalized semi-quantitative parameters considered (SUVmax, SUVmean, SUVpeak, MTVsum and TLGsum) did not significantly differ between patients with either "metabolic response" or "metabolic progression".

It has to be noticed that in our study a positive association was found between higher ΔrPET or ΔqPET values and the absence of Post-MC; such behaviour seems to be a further confirmation of the possible use of ΔrPET and ΔqPET as indirect indices of treatment effectiveness.

A discrepancy has been observed between the metabolic and clinical-laboratory evolution in the follow-up: six patients with evidence of "clinical-laboratory response" showed "metabolic progression"; three patients with evidence of "clinical-laboratory progression" showed "metabolic response". Accordingly, sensitivity and specificity of "metabolic progression" in disclosing "clinical-laboratory response" at the time of evaluation is far than optimal (62.5 and 70%, respectively). Therefore the evolution of the functionally active disease at PET-CT does not always fit with the evolution of clinical-laboratory symptoms and signs of the disease, at least partly explaining why the ΔrPET and ΔqPET predict the "metabolic progression" but not the "clinical-laboratory" one. It is noteworthy from our results that when ΔrPET or ΔqPET values are lower than their respective cut-offs TMP is quite shorter (8–9 months) than the time to "clinical-laboratory progression". However, these data should be considered as preliminary and further studies ad hoc designed may be needed to confirm them.

In our 28 patients with focal MM involvement the visual (qualitative) evaluation of PET-CT examinations depicted the presence of at least three foci of ^{18}F-FDG-positive disease in 11/28 patients at baseline and at least two residual foci of ^{18}F-FDG-positive disease in 14/28 patients at post-treatment evaluation (four patients reached complete disappearance of ^{18}F-FDG-positive lesions). Zamagni et al. [24] in a prospective study on 192 patients with MM at diagnosis have demonstrated that the presence of at least three ^{18}F-FDG-positive focal lesions at baseline PET-CT was an unfavourable prognostic factor in terms of progression-free survival (PFS) after iChT and single/double autologous HSCT (50 vs 68% 4 years after treatment completion). Similar results have been obtained by Usmani et al. [25] in the widest population ever studied for this purpose (239 patients), assessing that shorter (30 months) progression-free (66 vs 87%) and overall survival (OS, 73 vs 90%) were evident in patients with more than three ^{18}F-FDG-positive lesions at baseline PET-CT, and the absence of residual metabolically active lesions after iChT and autologous HSCT was a significant favourable prognostic factor in terms of PFS and OS. Patriarca et al. [26] have studied retrospectively 67 patients undergoing ^{18}F-FDG PET-CT before allogeneic HSCT, in which the presence of at least two ^{18}F-FDG-positive lesions at baseline PET-CT implied shorter PFS (21 vs 56%) and OS (49 vs 72%) as early as after two years of follow-up. Moreover, in the same study the presence of at least one ^{18}F-FDG-positive lesion at post-treatment PET-CT was an independent unfavourable prognostic factor associated with a shorter OS.

Furthermore, several studies have investigated the prognostic role of the most well-known conventional semi-quantitative parameters, primarily SUVmax, in patients with MM undergoing autologous or allogeneic HSCT [27–30]. Particularly, a SUVmax threshold of 4.2 was found to be useful in distinguishing patients with either better or worse PFS and OS when measured on the most active lesion at post-treatment ^{18}F-FDG PET-CT in patients undergoing autologous HSCT (PFS 44 vs 75%; OS 69 vs 88% for SUVmax values higher or lower than 4.2, respectively) as demonstrated by Zamagni et al. [24], or when measured on the most active lesion at baseline ^{18}F-FDG PET-CT in patients undergoing allogeneic HSCT (PFS 21 vs 56%; OS 49 vs 72% for SUVmax values higher or lower than 4.2, respectively) as demonstrated by Patriarca et al. [26]. In the latter study multivariate analysis also showed the independent prognostic role of baseline SUVmax >4.2 in predicting worse OS. Based on the analysis of our population, SUVmax >4.2 was found in 9/28 patients with focal ^{18}F-FDG-positive lesions at baseline and 5/24 patients with focal ^{18}F-FDG-positive lesions at post-treatment PET-CT. No significant differences were found in terms of time to "metabolic progression" (TMP) or "clinical-laboratory" progression according to this SUVmax threshold (please note that 4.2 was very next to the 4.16 threshold for baseline SUVmax found in our population using the discriminant analysis), although bias due to the low number of patients with SUVmax >4.2 cannot be excluded.

The role of MTV and TLG in patients with MM also has been explored recently by Fonti et al. [16] and McDonald et al. [17] demonstrating their prognostic role in this diagnostic setting in terms of PFS and/or OS. On the contrary, in our population neither MTVsum nor TLGsum predicted the risk and time to disease progression in terms of "metabolic progression" or "clinical-laboratory" progression during the follow-up.

In our cohort, only four patients had performed their baseline scan on a non-TOF scanner and their post-treatment scan on a TOF scanner (the reverse never occurred); however, although a sub-analysis regarding TOF vs non-TOF PET-CTs was not feasible because of the high discrepancy of respective sample sizes (4 vs 24 patients who did not change their tomograph specifications), it is expected for normalized parameters not to be negatively affected since different scanner specifications, as well as other patient-related or scanner-related factors, are to weigh similarly on both lesional and liver uptake.

The most relevant limitation of our study was its retrospective design which could have affected negatively the data collection, particularly with respect to laboratory measures that

were not available in all included patients both at baseline and post-treatment. Retrospective design also could have been responsible for a certain degree of inhomogeneity in number and time interval of PET-CT examinations performed during each patient's follow-up, although treatment strategies including high dose iChT and autologous HSCT are standardized enough and well experienced at our Haematology Service.

A possible treatment bias cannot be fully excluded since patients with the evidence of increase on metabolic tumour burden at PET-CT performed after high-dose iChT and autologous HSCT are expected to undergo a more intense treatment (and a possible change in treatment strategy) during their follow-up compared to patients with the evidence of reduction in metabolic tumour burden; nevertheless, in our study higher ΔrPET and ΔqPET are confirmed to be effective predictors of "metabolic response" during follow-up while ΔrPET and ΔqPET values lower than the calculated respective cut-offs were predictors of a significantly shorter TMP. Therefore, treatment bias, although present, should have not played a significant role.

Conclusion

Our study has demonstrated, on a small cohort of patients, that semi-quantitative internally normalized PET-CT parameters ΔrPET and ΔqPET are effective in predicting a persistent response to treatment in patients with MM undergoing high-dose iChT and autologous HSCT, with a better performance than non-normalized ones. Moreover, they are useful prognostic indices in predicting the risk of rapid disease progression in the same patients, possibly dealing with a more effective identification of those who would benefit a more intense treatment and, after all, dealing with a better management of the disease in the perspective of a personalized clinical practice. Prospective cohort studies on a wider population and, eventually, with a longer-term follow-up should be necessary in order to confirm our findings.

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