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Original paper

Treatment response assessment in [^{18}F]FDG-PET/CT oncology scans: Impact of count statistics variation and reconstruction protocol

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ABSTRACT

Purpose: To investigate influences of reconstruction algorithms and count statistics variation on quantification and treatment response assessment in cancer patients, by using a large field of view-FOV scanner.
Methods: 54 cancer patients underwent PET/CT scan: 1) at baseline: 1.5 min/FOV, reconstructed by ordered-subset expectation maximization + point-spread-function-OSEM-PSF and bayesian penalised-likelihood-BPL algorithm 2) at restaging: 2 min/FOV, reconstructed also at 1.5 and 1 min/FOV, using OSEM-PSF and BPL. SUL (lean-body mass SUV) peak and max were measured for each target-lesion (n = 59). Differences in quantification obtained from datasets with different reconstruction algorithms and different time/FOV were evaluated. For any pair of PET datasets, metabolic response was assessed by using SULpeak, with a threshold of 30% in variation considered as significant.
Results: Both at baseline and restaging, SULpeak and max values were higher in BPL reconstructions than in OSEM-PSF ($p < 0.0001$). SULpeak at different time/FOV reconstructions showed no statistically significant differences both with OSEM-PSF and BPL; SULmax depended on acquisition time ($p < 0.05$). In 56/59 lesions (95%) therapy response was concordant regardless count statistics variation and reconstruction algorithm; 2/59 (3%) showed different responses according to count statistics, both for OSEM-PSF and BPL; in 1/59 lesion (2%) response was different depending on reconstruction algorithm used.
Conclusions: BPL provided higher SULpeak and max than OSEM-PSF. With a large FOV/high sensitivity scanner, variation of time/FOV in restaging PET scans gave stable and reproducible results in terms of SULpeak, both for OSEM-PSF and BPL. Thus, metabolic response defined by SULpeak variation proved to be quite independent from count statistics.

1. Introduction

[^{18}F]FDG PET/CT (^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography) is commonly used for treatment response evaluation in oncology [1–5]. Therapy response assessment for most solid tumors is usually obtained by semiquantitative PET data such as SUV (Standardized Uptake Value) max or SUV peak [6–7]. SUV measurements can be influenced by many factors, both biological (i.e. patients preparation, blood glucose, lesions dimensions, tumor type) and technological (i.e. scanner physical performances, acquisition protocols and reconstruction parameters) [8]. Standardization of PET procedures is considered mandatory in order to obtain comparable PET results [7,9,10], however in clinical routine practice can be difficult to strictly adhere to these recommendations. In this contest, the possibility to obtain reliable and reproducible semiquantitative data even when some PET acquisition parameters are changed could be of great interest and further consolidate the role of PET in therapy response assessment, both in clinical routine and research. Nowadays, PET/CT scanners with large FOV and high sensitivity [11] and new reconstruction algorithms such as the regularized ones [12] are available, both concurring to reduce acquisition time and injected activity, while preserving image quality. In this scenario the aim of this study was to investigate the influence of reconstruction algorithms and count statistics variation on SUV values and treatment response assessment using a large FOV and

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high sensitivity scanner.

2. Materials and methods

2.1. Patients population and target lesions selection

From March 2016 to December 2017, in Nuclear Medicine Department of San Gerardo Hospital (Monza, Italy) 54 [^{18}F]FDG PET/CT cases were selected among patients with solid tumors submitted to the examination for treatment monitoring. PET/CT was performed as a part of their diagnostic and therapeutic workflow; all selected patients were examined by a baseline scan before treatment (baseline PET scan) and a restaging study after therapy (restaging PET scan). Up to 2 target lesions were selected in each patient, with size ≥1 cm and significant FDG uptake at baseline. The present study was approved by the Ethical Committee of Our Institution and all patients signed an informed consent.

2.2. Baseline and restaging PET scan protocol

All target lesions were evaluated both at baseline and restaging with a 5 BGO rings Discovery IQ scanner (GE Healthcare, Milwaukee, Wisconsin, US). 5R-DIQ scanner has a large axial FOV of 26 cm and high sensitivity: 23.3 cps/kBq and 19.5 cps/kBq at FOV centre and 10 cm off-centre respectively, as measured according to NEMA NU-2 2012 procedures.

Patients fasted for at least 8 hours and blood glucose was tested before the tracer administration (threshold 170 mg/dL). Each patient was administered with 3.7 MBq/kg of [^{18}F]FDG and median uptake time was 64 (range 56–102 min) and 66 (range 55–98 min) minutes at baseline and restaging scans respectively. During the uptake time patients were asked to hydrate orally (500 mL of water) and to empty their bladder immediately before positioning for the scan. A scout view was acquired to define scan volume. CT was acquired first, during shallow breathing with 120 kVp, tube rotation 0.5 s, auto mA modulation, slice thickness 3.27 mm and Q.AC algorithm reconstruction. No oral or intravenous contrast media were administered to the patients for CT component of PET/CT studies. CT images were used for attenuation correction of PET data. Acquisition time at baseline scans was 1.5 min/FOV and images were reconstructed both with OSEM algorithm (6 iterations, 12 subsets, Gaussian post filter 6.4 mm) with PSF correction (OSEM-PSF) and with a regularized algorithm (BPL), with a beta factor of 350 (as optimized in our clinical practice). Restaging acquisition scans were acquired with 2.0 min/FOV and images were reconstructed using LIST data in three datasets of images at 2.0, 1.5 and 1.0 min/FOV respectively, both with OSEM-PSF and BPL algorithms.

2.3. Semiquantitative parameters calculation

SUL (lean body mass standardized uptake value) peak and SUL max were calculated for each target lesion at baseline and restaging in PET datasets reconstructed at any time/FOV, both in OSEM-PSF and BPL images, by using dedicated software PETVCAR on AW 4.6 workstation (GE Healthcare, Milwaukee, Wisconsin, US).

2.4. Data analysis and statistics

A dedicated database was created to collect SUL values, patients data (age, sex, body mass index, blood glucose, injected activity, uptake time) and lesions parameters (dimension at CT and organ site). Quantification data were determined for both reconstruction algorithms (OSEM-PSF and BPL) and compared: SUL peak and SUL max obtained from OSEM-PSF images were compared to those obtained from BPL images using Wilcoxon test, both at baseline and restaging PET studies (any time/FOV); differences in SUL peak and max values obtained from OSEM-PSF and BPL reconstructions at baseline were evaluated also using Bland-Altman analysis. SUL variability was determined as a function of count statistics variation in terms of time/FOV: SUL peak and SUL max values calculated from 1.0 min/FOV to 2.0 min/FOV were compared by using Kruskall-Wallis test, both for OSEM-PSF and BPL reconstructions; analysis of agreement in quantification according to different time/FOV was also performed using the Bland-Altman method. Differences between distributions were determined using Kolmogorov-Smirnov test. Stata software 9.0 (Stata Corporation, College Station, Texas, USA) was used to perform statistical analysis and a p-value < 0.05 was considered as significant.

The difference in term of therapy response to treatment obtained from the comparison of datasets with different count statistics was analyzed, both for OSEM-PSF and BPL reconstructions: each baseline PET scan (1.5 min/FOV) was compared to correspondent restaging PET scans (1 min/FOV, 1.5 min/FOV, 2 min/FOV). For any pair of datasets metabolic response for each lesion was assessed on the base of SUL peak variation with a threshold of 30% of variation considered as significant [7]. Therapy metabolic response was defined as follows:

- complete response (CR): complete disappearance of the pathological uptake (residual uptake not distinguishable from the local background activity);
- partial response (PR): reduction of SUL peak ≥ 30%;
- stable disease (SD): SUL peak variation < 30%;
- progression of disease (PD): increase of SUL peak ≥ 30%.

For any pair of datasets, changes in level of response (CR, PR, SD, PD) depending on different count statistics and/or reconstruction algorithm were assessed.

Acquisition time of 1.5 min/FOV was considered the standard reference for routine clinical use, as defined by internal protocol of our Department: quantitative parameters and level of therapy response derived from PET/CT datasets with count statistics other than 1.5 min/FOV were not used for clinical purpose and did not affect the management of patients.

3. Results

54 patients were enrolled and 6 of them were excluded due to differences in injection protocol. 59 target lesions (median lesion dimension 2.5 cm, range 1.5–10) were selected in 48 patients affected by solid tumors (median age 71 years, range 51–84, median body mass index 24 kg/m^2, range 20–30). Anatomical site of the lesions is shown in Table 1.

At baseline both SUL peak and SUL max values were higher in BPL reconstructions than in OSEM-PSF: mean SUL peak values were 6.4 and 6.9 for OSEM-PSF and BPL algorithms respectively ($p < 0.0001$) and mean SUL max values were 8.2 and 9.0 for OSEM-PSF and BPL respectively ($p < 0.0001$). Mean ± standard deviation (SD), median and range values for SUL peak and SUL max for OSEM-PSF and BPL reconstructions are summarized in Table 2. Furthermore, in restaging PET scans both SUL peak and SUL max values increased using BPL with respect to OSEM-PSF and the difference was statistically significant for each time/FOV acquisition ($p < 0.0001$, see Table 3). Differences in SUL peak and max values obtained from OSEM-PSF and BPL reconstructions at baseline are also shown in Fig. 1.

Table 1
Lesions distribution.

Lesion site	N° (%)
Lung	23 (39%)
Liver	6 (10%)
Lymph nodes	18 (31%)
Other organs (esophagus, breast, uterus, peritoneal nodules, adrenal gland, solid tissue in head/neck and retroscapular region)	12 (20%)

Table 2
SUL peak and SUL max at baseline. No differences between distributions were observed (Kolmogorov-Smirnov test p = 0.650 for both SUL peak and SUL max at baseline).

BASELINE N = 59 lesions	OSEM-PSF	BPL	Wilcoxon test p-value
	Mean ± SD median (range)		
SUL peak	6.4 ± 3.5 5.0 (1.8–19.5)	6.9 ± 3.9 5.5 (2.0–20.6)	< 0.0001
SUL max	8.2 ± 4.4 6.7 (2.9–22.9)	9.0 ± 4.9 7.8 (3.5–24.7)	< 0.0001

The impact of time/FOV on quantification is summarized in Table 3; SUL peak values associated to different time/FOV showed no statistically significant differences both with OSEM-PSF and BPL reconstructions, while SUL max values showed a dependence on acquisition time ($p < 0.05$). The Bland-Altman method was also used and analysis confirmed SUL peak did not tend to vary when time/FOV changed both in OSEM-PSF and BPL reconstructions, unlike SUL max (Figs. 2 and 3 respectively).

Fig. 4 shows PET/CT images of a patient studied at baseline and after therapy (different time/FOV); to be noted the higher SUL peak values in BPL reconstructions compared to OSEM-PSF ones, both at baseline and restaging, and SUL peak slight variation across different time/FOV in restaging scans, both in OSEM-PSF and BPL reconstructions.

In 56 out of 59 lesions (95%) treatment response assessment was concordant regardless count statistics variation (1.0, 1.5, 2.0 min/FOV) and reconstruction algorithm (OSEM-PSF and BPL): level of therapy response in these lesions was defined as 9/56 PD, 18/56 SD, 20/56 PR and 9/56 CR. Only three lesions out of 59 (5%) showed slight differences in therapy response assessment; in particular in the first case response to treatment shifted from “stable disease” at 1.0 and 1.5 min/FOV to “partial response” at 2.0 min/FOV both in OSEM-PSF and BPL images; in the second case response shifted from “progression disease” to “stable disease” only in BPL reconstruction at 1.0 min/FOV; in the third case response shifted for all time/FOV datasets from “stable disease” in OSEM-PSF to “partial response” in BPL reconstructions. The variation in quantification of the above mentioned 3 cases is detailed in Table 4.

4. Discussion

Variation of glucose metabolism occurs earlier than tumor shrinking during the treatment and the ability of [^{18}F]FDG PET to predict treatment response in individual patients is currently of great interest; in particular, accurate early differentiation of *responders* from *not responders* using [^{18}F]FDG PET/CT could be relevant to avoid unnecessary drug toxicities, to allow an early change of treatment [1–4,13,14] and to optimize economic costs, that can be not negligible particularly in case of new biological targeted therapies.

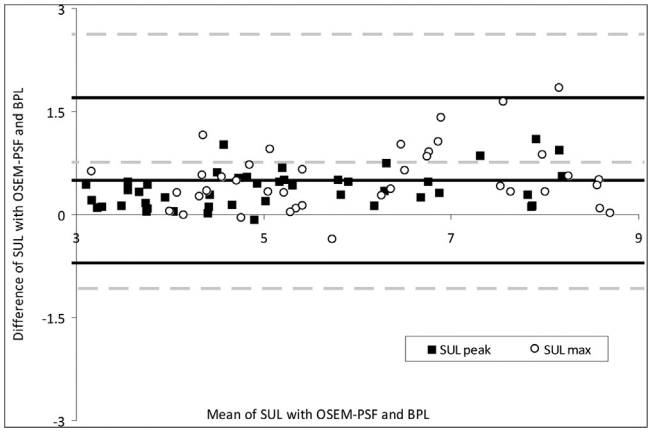

Fig. 1. Bland Altman plot combining OSEM-PSF and BPL results at baseline.

Treatment response assessment for most solid tumors is usually obtained by semiquantitative PET data such as SUV max, mean and, lately, SUV peak [6,7]. SUV peak overcomes SUV max and SUV mean limitations by measuring activity concentration in a 1 cm^3 sphere centered on the SUV max of a metabolic active lesion, as to maximize the enclosed average SUV [15]. In particular, SUL peak is the parameter considered by PERCIST (PET evaluation response criteria in solid tumors) in order to define metabolic response to treatment [7]; SUL is typically more consistent from patient to patient than SUV normalized to body weight, as patients with high body mass index have high normal organ SUVs because FDG does not significantly accumulate in white fat in the fasting state [16].

Reproducibility of PET quantification is crucial to ensure accurate therapy response assessment and standardization of PET procedures is considered mandatory to obtain comparable quantitative PET results [17]. Determination of SUV values is dependent on patient preparation and adequate scan quality, that must be kept as similar as possible between the baseline and restaging studies. Particularly, scans should be performed on the same scanner with comparable injected doses of [^{18}F]FDG and comparable uptake times. Standardization of PET protocols is required also for scan acquisition and image reconstruction parameters [6–10,18]. However, in routine practice many factors related both to patients and clinical workflow can make difficult to strictly adhere to all recommendations; in particular, in case of reduced compliance a faster PET acquisition (reduced time/FOV) can become necessary for patient’s comfort and to reduce the probability of motion artifacts. A lower administered activity without compromising diagnostic quality would be advisable in any case to achieve a significant dose reduction [19]. Another issue is a reduced tracer supply by the vendor; in this case a faster acquisition (lowered time/FOV) or a lower administered activity (no change in time/FOV) could allow performing all the patients scheduled for that day.

Table 3
Difference in quantification obtained from PET datasets with different time/FOV. No differences between distributions at different acquisition-times were observed (Kolmogorov-Smirnov test p = 0.999 for SUL peak and p = 0.920 for SUL max).

RESTAGING		1 MIN	1.5 MIN	2.0 MIN	Kruskall-Wallis test p-value
SUL peak	OSEM-PSF	4.1 ± 2.3 3.8 (0.9–9.7)	4.1 ± 2.3 3.9 (0.8–9.7)	4.1 ± 2.3 3.9 (1.0–9.6)	0.421
	BPL	4.4 ± 2.5 4.1 (0.9–10.3)	4.4 ± 2.5 4.0 (0.8–10.4)	4.3 ± 2.5 4.0 (0.8–10.4)	0.244
Wilcoxon test p-value		< 0.0001 (all time/FOV)			
SUL max	OSEM-PSF	5.5 ± 3.0 5.2 (1.3–12.6)	5.4 ± 3.0 5.2 (1.3–12.5)	5.3 ± 2.9 5.3 (1.3–12.4)	< 0.05
	BPL	6.0 ± 3.4 5.8 (1.3–15.6)	5.8 ± 3.3 5.7 (1.2–15.4)	5.7 ± 3.3 5.6 (1.2–15.1)	< 0.05
Wilcoxon test p-value		< 0.0001 (all time/FOV)			

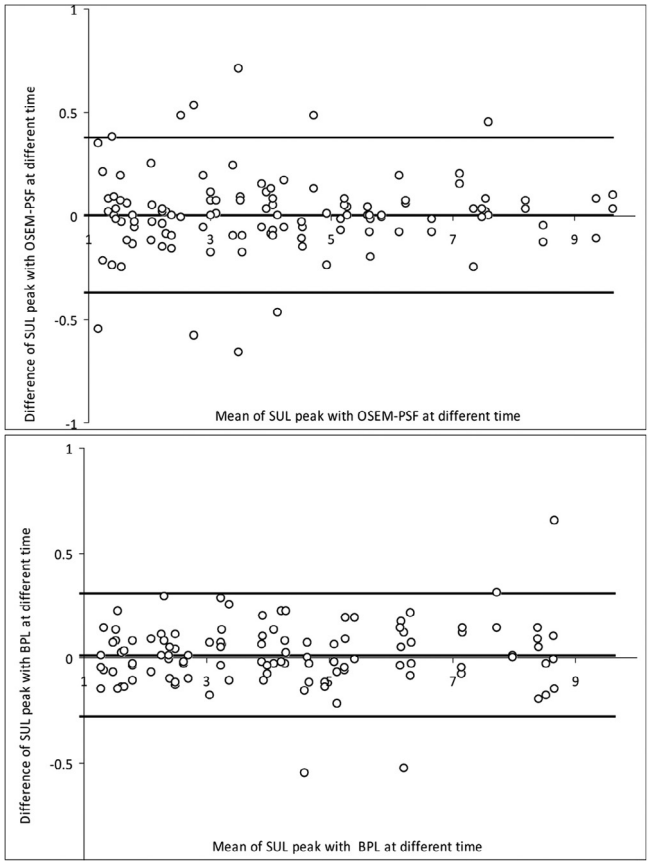

Fig. 2. Bland Altman plot of SUL peak, OSEM-PSF and BPL reconstructions, respectively; limits of agreements are indicated by straight lines.

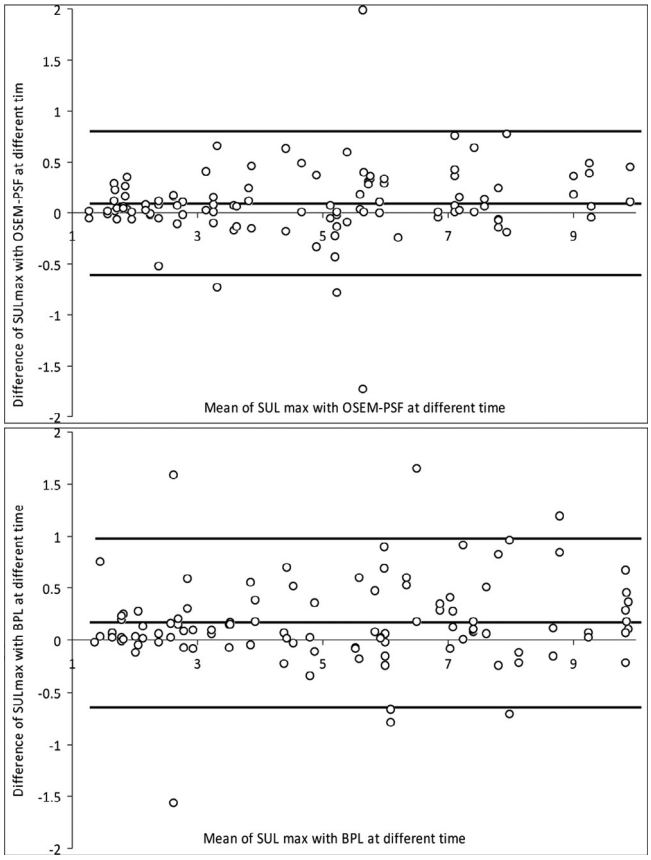

Fig. 3. Bland Altman plot of SUL max, OSEM-PSF and BPL reconstructions, respectively; limits of agreement are indicated by straight lines.

In the present study we investigated if new PET technologies such as large FOV/high sensitivity scanners (Discovery IQ) and regularized reconstruction algorithms (BPL) could allow a greater flexibility in performing PET scans. In particular, we investigated the influence of reconstruction algorithm and count statistics variation in terms of time/FOV on SUL quantification and the impact of SUL variability on therapy response assessment when defined on SUL peak variation.

For the aim of the present work, both SUL peak and SUL max have been considered, since the last one was the most frequently used semiquantitative PET parameter over the last years [5–7].

In this study BPL algorithm gave higher results in quantification since both SUL peak and SUL max values were higher when compared to those from OSEM-PSF datasets, both at baseline and restaging PET scans at any time/FOV ($p < 0.0001$). These data are probably due to the specific characteristics of regularized algorithms: the very high number of iterations ($n = 25$) allows to reach data convergence while Beta factor controls the noise. At the opposite, OSEM algorithms can use only a limited number of iterations (commonly 2–6) to avoid noisy images, without full data convergence and increased quantification. The increase in quantification could improve detectability (in particular for small lesions) and image quality [20], leading to better image reading both at baseline exams for initial assessment of disease and at restaging ones for therapy response definition.

An interesting issue is the quantification stability found in the current study. No significant variation was observed in SUL peak values in different time/FOV datasets, both in OSEM-PSF and BPL reconstructions. Conversely, SUL max showed a dependence on count statistics variation, regardless of the reconstruction protocol ($p < 0.05$, both OSEM-PSF and BPL); in particular the current results showed that SUL max values were higher at lower time/FOV, both in OSEM-PSF and BPL reconstructions. This could probably be due to the intrinsic nature of radioactive decay: shorter/time acquisitions are generally characterized by higher variability if compared to longer ones, with the possibility of higher SUL max values.

These results confirm what already described in recent literature, showing that SUV max can be more affected by noise-induced bias reflecting statistical fluctuations likely leading to a higher level of uncertainty in quantification, while SUL peak is less sensitive to this factor as it is calculated on an average value within a ROI/VOI [18]. This is the reason why SUL peak is now commonly used to define response to treatment according to PERCIST criteria [5]. As a direct consequence of SUL peak stability, we observed a very good agreement in the definition of therapy response according to SUL peak percentage variations.

Overall, only in 3/59 target lesions (5%) the level of therapy response was different according to time/FOV (2/3 cases) or reconstruction algorithm (1/3 cases). However, it should be pointed out that in all these cases the variation in terms of treatment response was related to percentage variation of semiquantitative data close around to the established threshold of 30%; furthermore SUL peak absolute values showed only slight variations, likely not significant in a clinical setting. A potential limitation of the current work is the fact that in many patients up to two target lesions only were considered to define treatment response, also in patients with more than two. Further studies are needed to evaluate also the robustness of PET radiomic features [21].

Nevertheless, it has to be considered that the current work aimed to validate the consistence of more flexible PET protocols (changes in time/FOV) and to assess the effect of this flexibility in terms of quantification with a large FOV scanner. We did not aim to assess the effect of methodological changes in a clinical scenario, as this approach would require a larger patient population with a clinical follow up to confirm the imaging data. Finally, we observed SUL peak stability at different time/FOV both with OSEM-PSF and BPL algorithms and a

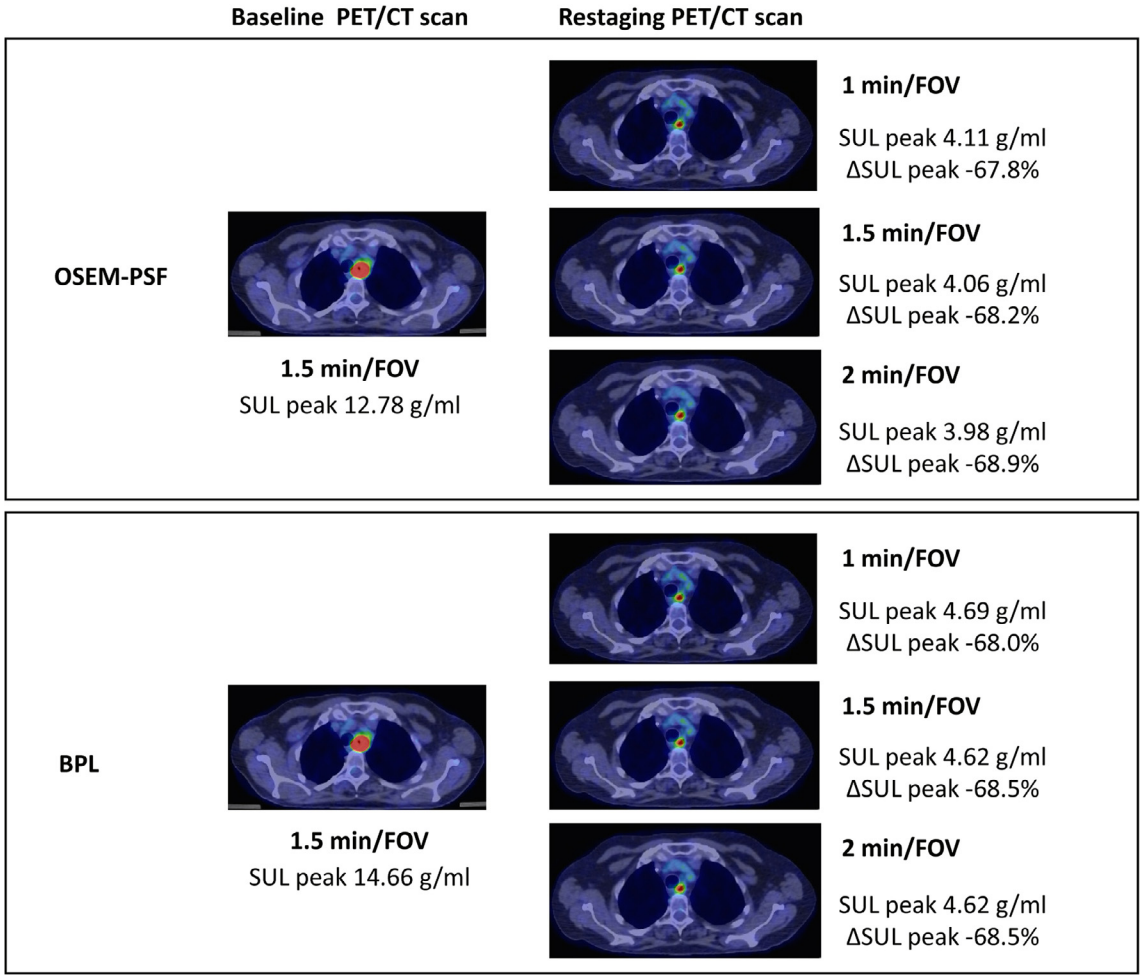

Fig. 4. PET/CT fused images of a patient with oesophageal adenocarcinoma, partial response (PR) after radio-chemotherapy.

Table 4
SUL peak between baseline and restaging PET/CT scan relative to the three cases for which metabolic response assessment turned out to be dependent on count statistics variation and/or reconstruction algorithm.

	Lesion size (mm)^ baseline	SUL peak baseline		Lesion size (mm)^ restaging	SUL peak restaging (% variation)					
		OSEM-PSF	BPL		OSEM-PSF			BPL		
					1 min	1.5 min	2 min	1 min	1.5 min	2 min
Case 1	29	5.65	6.14	20	4.00 (−29.2)	3.97 (−29.7)	3.86 (−31.7)	4.39 (−28.5)	4.37 (−28.8)	4.15 (−32.4)
Case 2	30	3.53	3.97	38	4.77 (+35.1)	5.01 (+41.9)	5.00 (+41.6)	4.96 (+24.9)	5.18(+30.5)	5.25 (+32.2)
Case 3	na*	13.15	16.06	na*	9.32 (−29.1)	9.43 (−28.3)	9.35 (−28.9)	10.28 (−36.0)	10.35 (−35.6)	10.38 (−35.4)

^ Highest axial diameter.
* Not available: size was not measurable because lesion consisted of a large solid tissue in retroscapular region not clearly delimited from surrounding anatomical structures (sarcoma).

good agreement between OSEM-PSF and BPL datasets in treatment response definition. Although BPL quantitative data are statistically higher than OSEM-PSF ones, the results seems to indicate that Discovery IQ features (very large FOV and high sensitivity) allow to obtain accurate and stable quantification, maintained also with standard OSEM reconstruction algorithms. However, quantification stability could allow to change acquisition parameters (i.e. time/FOV) preserving reliability of quantification (SULs peak), that could be very useful in routine clinical workflow. In painful patients not tolerating prolonged acquisition time, a faster acquisition could be of great advantage; similarly, a faster acquisition time could allow to perform a higher number of PET scans per day, thus reducing long waiting lists for the examination.

5. Conclusions

In this study both SUL peak and SUL max showed a dependence on reconstruction algorithm, with BPL providing better results than OSEM-PSF both at baseline and restaging PET studies at any time/FOV; this should be taken into account when standardization and harmonization

of PET procedures are recommended, in particular for comparison of PET scans for therapy response assessment.

Variation of count statistics (time/FOV) at restaging PET scans did not affect results in terms of SUL peak, both for OSEM-PSF and BPL algorithms; consequently, metabolic response assessment defined as SUL peak percentage variation proved to be independent from count statistics. Thus, when a large FOV/high sensitivity scanner is used, SUL peak is a robust parameter for quantification even in case of differences in scan durations; standardization of PET procedures is a crucial point to obtain reproducible and comparable PET results, but new PET/CT technologies could in part overcome these constraints allowing some flexibility in PET protocols, in particular for acquisition time.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

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

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