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Repeatability of Quantitative ^{18}F-DCFPyL PET/CT Measurements in Metastatic Prostate Cancer.

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ABSTRACT

Quantitative evaluation of radiolabeled Prostate-Specific Membrane Antigen (PSMA) PET scans may be used to monitor treatment response in patients with prostate cancer (PCa)**.** To interpret longitudinal differences in PSMA uptake, the intrinsic variability of tracer uptake in PCa lesions needs to be defined. The aim of this study was to investigate the repeatability of quantitative ^{18}F-DCFPyL (a second generation ^{18}F-PSMA-ligand) PET/CT measurements in patients with PCa. **Methods:** Twelve patients with metastatic PCa were prospectively included, of which 2 were excluded from final analyses. Patients received two whole-body ^{18}F-DCFPyL PET/CT scans (median dose 317 MBq; uptake time 120 min), within median 4 days (range 1-11 days). After semi-automatic (isocontour-based) tumor delineation, the following lesion-based metrics were derived: Tumor-to-Blood ratio (TBR_{mean}, TBR_{peak}, and TBR_{max}), Standardized Uptake Value (SUV_{mean}, SUV_{peak}, SUV_{max}, normalized to bodyweight), tumor volume, and total lesion tracer uptake (TLU). Additionally, patient-based Total Tumor Volume (sum of PSMA-positive tumor volumes; TTV) and Total Tumor Burden (sum of all lesion TLUs; TTB) were derived. Repeatability was analyzed using repeatability coefficients (RC) and intra-class correlations (ICC). Additionally, the effect of point spread function (PSF) image reconstruction on the repeatability of uptake metrics was evaluated. **Results:** In total, 36 ^{18}F-DCFPyL PET positive lesions were analyzed (up to 5 lesions per patient). RCs of TBR_{mean}, TBR_{peak}, and TBR_{max} were 31.8%, 31.7%, and 37.3%, respectively. For SUV_{mean}, SUV_{peak}, SUV_{max} the RCs were 24.4%, 25.3% and 31.0%, respectively. All ICC were ≥0.97. Tumor volume delineations were well repeatable, with RC 28.1% for individual lesion volumes and RC 17.0% for TTV. TTB had a RC of 23.2% and 33.4%, when based on SUV_{mean} and TBR_{mean}, respectively. Small lesions (<4.2mL) had worse repeatability for volume measurements. The repeatability of SUV_{peak}, TLU, and all patient-level metrics were not affected by PSF-reconstruction. **Conclusion:** ^{18}F-DCFPyL uptake measurements are well repeatable and can be used for clinical validation in future treatment response assessment studies. Patient-based TTV may be preferred for multicenter studies since its repeatability was both high and robust to different image reconstructions.

Keywords: PSMA, ^{18}F-DCFPyL, prostate cancer, repeatability

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men worldwide, with an estimated annual number of deaths over 350.000(*1*). Prostate-Specific Membrane Antigen (PSMA) Positron Emission Tomography (PET) is increasingly used for PCa diagnostics(*2*). PSMA is a class II trans-membrane glycoprotein that provides a valuable target for radiolabeled imaging, as its expression is upregulated in malignant prostate cells and associated with aggressive disease characteristics(*3*). Due to larger availability, ^{68}Gallium-labeled PSMA tracers have been studied most frequently to date, demonstrating high detection rates for metastatic disease(*2,4*). Alternatively, ^{18}Fluorine-labeled tracers have been developed, including ^{18}F-DCFPyL (2-(3-(1-carboxy-5-[(6-^{18}F-fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid), a second-generation small-molecule ligand that strongly binds to PSMA(*5,6*). The ^{18}F-radionuclide provides for PET-images with a higher resolution compared to ^{68}Ga, due to a shorter positron range and higher positron yield(*2*).

Quantitative analysis of PSMA uptake may be used to predict or evaluate treatment response, as changes in PSMA uptake over time may indicate response to treatment or progression of disease(*7-9*). Recently, we performed a full pharmacokinetic analysis of ^{18}F-DCFPyL to validate simplified methods for tumor uptake quantification. Tumor-to-Blood Ratios (TBR; tracer activity concentration in the tumor normalized to the whole blood activity concentration on PET) were found to best describe the tumor tracer uptake(*10*). For reliable use of quantitative PSMA PET metrics in clinical practice, it is important to determine their repeatability. Only changes that exceed random variability should be interpreted as treatment response or disease progression. To the best of our knowledge, this is the first study reporting on the day-to-day variability of ^{18}F-DCFPyL uptake in PCa lesions. The aim of this study was to evaluate the repeatability of quantitative ^{18}F-DCFPyL PET/CT measurements in patients with metastatic PCa.

MATERIALS AND METHODS

Patients

Twelve patients were prospectively included in the Amsterdam UMC between January and May 2019. Inclusion criteria were: (1) histologically proven PCa; (2) at least two metastases, detected by any imaging modality; and (3) at least one metastasis of ≥1.5cm in size (to minimize partial-volume effects). Patients with multiple malignancies and claustrophobia were excluded.

The study was approved by the ethical review board of the Amsterdam UMC and all subjects signed informed consent. This trial was registered under EudraCT number 2017-000344-18 and the Netherlands Trial Registry number 6477. Personal and demographic data regarding age, length, body weight, Gleason score, prostate-specific antigen level (ng/mL) at the time of PET/CT, and information on prior therapy were collected.

Data Acquisition

All patients underwent two ^{18}F-DCFPyL PET/CT scans within 4 days (median, range 1-11 days). PET/CT imaging adhered to routine clinically used protocols. ^{18}F-DCFPyL was synthesized under Good Manufacturing Practices conditions at the Amsterdam UMC (Radionuclide Center), using the precursor of ABX GmbH® (Germany) (Supplemental Text 1(*11*)). No fasting was required and no diuretics were administered prior to imaging. PET was performed using an European Association of Nuclear Medicine Research Ltd (EARL) calibrated hybrid Philips Ingenuity TF scanner (Philips Healthcare®, the Netherlands/USA)(*12,13*). Our imaging protocol included a target injected ^{18}F-DCFPyL dose of 300 MBq, with an uptake interval after injection of 120 minutes. First, a CT scan was made for attenuation correction (30-120 mAs; 120 kV). Next, whole-body PET acquisitions were then acquired from mid-thigh to skull base (4 minutes per bed position).

Images were corrected for decay, scatter, random coincidences, and photon attenuation. Images were reconstructed using the (EARL1-compliant(*13*)) Ordered Subsets Expectation Maximization with Time-of-Flight algorithm (3 iterations; 33 subsets). Additionally, images were post-processed using a Point Spread Function (PSF) reconstruction (Lucy-Richardson iterative deconvolution)(*14*). Using a NEMA-NU-2 Image Quality Phantom, the full-width-at-half-maximum of this reconstruction was calibrated at 7.0mm for adequate signal recovery complying with novel EARL2 guidelines(*15*).

Data Analysis

All scans were controlled for image-quality(*16*) and visually interpreted by an experienced nuclear medicine physician (DO), who identified suspicious PCa metastases in bone and/or lymph nodes. Lesions were semi-automatically delineated using in-house developed software (*ACCURATE-tool*, previously benchmarked against commercially available image-analysis tools(*17*)) using a 50% isocontour of SUV_{peak} (sphere of 1.2 cm diameter, positioned to maximize its mean value) with correction for local background uptake to obtain volumes-of-interest (VOIs)(*18*). Blood activity concentrations (for TBR calculation) were measured in the ascending aorta using: i) a single image slice 3x3 voxel VOI, and ii) a 3x3 voxel VOI in 5 consecutive slices(*10*). VOIs were created on both original (EARL1) and PSF-reconstructions (EARL2).

From each VOI, the following metrics were recorded on a lesion-level: tumor volume (mL), TBR (tumor VOI activity concentration/blood activity concentration), SUV, and total lesion uptake (TLU). TBR was calculated using both the mean, peak, and max activity within the VOI, yielding TBR_{mean}, TBR_{peak}, and TBR_{max}, respectively. SUV variants included SUV_{max} (maximum SUV within the VOI), SUV_{peak} (mean SUV within a 12mm diameter sphere positioned within the VOI to yield the highest value), and SUV_{mean} (mean SUV within the VOI). SUV was normalized to body weight. TLU was defined as lesion SUV_{mean} or TBR_{mean} multiplied by lesion volume, yielding TLU_{SUV} and TLU_{TBR}, respectively. Additionally, two patient-level metrics were derived: Total PSMA-positive Tumor Volume (TTV) and PSMA Total Tumor Burden (TTB). TTV

was defined as the sum of the delineated tumor volumes within a patient. TTB was defined as the sum of the TLU_{SUV} and TLU_{TBR} within a patient, yielding TTB_{SUV} and TTB_{TBR}, respectively. As recommended by PERCIST guidelines for PET response assessment(*19*), and to balance the number of analyzed lesions between patients, for lesion-based analyses we selected the 5 hottest lesions in case of >5 PSMA-avid lesions. For patient-level analysis, all suspicious PSMA-avid lesions were included.

Statistical Analysis

To assess difference in uptake intervals and injected dosages between test and retest scans we used the Wilcoxon singed-rank test for paired data. Repeatability of quantitative PET metrics was quantified using repeatability coefficients (RC; in percentages). The RCs were calculated as 1.96 times the standard deviation of relative test-retest differences *d,* that were calculated as follows:

$$d = \frac{X2-X1}{\bar{X}} * 100 \qquad \text{Equation 1}$$

Where *X1* and *X2* are the lesion- or patient-level metrics on day 1 (test) and day 2 (retest), respectively. $\bar{X}$ is the average between *X1* and *X2*. Bland-Altman plots were used for visual inspection of test-retest differences. Also, intra-class correlations (ICC; two-way mixed model with an absolute agreement definition) were calculated between test and retest data. The Pitman-Morgan test was used to test for differences in repeatability between paired data (correlated variances)(*20*), with α set at 0.05. P-values were corrected for multiple comparisons using Holms-Bonferroni method(*21*). The Levene's test was used to compare variances of independent groups in subgroup analysis (bone vs. lymph node metastases, >4.2mL lesions vs <4.2mL lesions). SPSS version 22.0 (IBM) and Excel (Microsoft) worksheets were used for statistical analyses.

RESULTS

Patients

Twelve patients were enrolled, of which two patients could not be analyzed. Patient characteristics and disease stage of the ten finally evaluated patients are presented in Table 1. Seven (70%) patients were using androgen-deprivation therapy (luteinizing hormone–releasing hormone agonist), all of which had been treated for at least 3 months at time of PET. In one excluded patient reliable comparison of the ^{18}F-DCFPyL scans was impeded due to significant radiolysis of the tracer (evident from a visually altered biodistribution as well as highly abnormal bone uptake(*16*)). The radiolysis was likely caused by a relatively high radioactivity concentration in the production batch (268 MBq/mL), combined by a long interval between delivery of the tracer and injection (>3 hours). Tracer logistics and storage were improved after this incidental finding and no other radiolysis problems occurred during this study. Another patient was excluded because of unconfirmed malignancy upon performing post-hoc CT-guided histological biopsy during clinical follow-up for two highly suspicious bone lesions on ^{18}F-DCFPyL PET. There were no significant differences between uptake intervals, injected dosages, and injected masses between test and retest scans (P = 0.799, P = 0.499, and P = 0.878 respectively).

Repeatability of Lesion-Level Metrics

In total, 36 ^{18}F-DCFPyL PET-avid lesions were analyzed, including 21 bone lesions (58.3%), 12 lymph node metastases (33.3%), and 3 intraprostatic foci (8.3%). Descriptive values of the analyzed PET parameters are shown in Table 2 (PSF-reconstruction data in Supplemental Table 1). The best repeatability was observed for SUV_{mean} (RC 24.4%) and SUV_{peak} (RC 25.3%). SUV_{max} had poorer repeatability (RC 31.0%; Table 3), but the differences between repeatability of SUVs were not significant (p=0.06-0.60). Blood activity derived from a 1-slice and 5-slice VOI had a repeatability of 23.1% and 17.3%, respectively. Consequently, calculating TBR using 5-slice blood measurements had better repeatability compared to

single-slice measurements (RC 31.7-37.3% versus 34.1-40.1%) and was used henceforth. Overall, TBRs had worse repeatability than SUVs, but only repeatability of TBR_{mean} was significantly lower than that of SUV_{mean} (RC 31.8% versus 24.4%, *p*=0.03; Figure 1).

Repeatability of semi-automatic tumor volume measurement was 28.1%. Repeatability of TLU_{TBR} (RC 39.3%) was non-significantly lower than that of TLU_{SUV} (RC 32.1%, p=0.08). Bland-Altman plots did not demonstrate a skewed variability, but variability of SUV and TBR tended to be less for higher values (Figure 2). In subgroup analysis, no significant differences between repeatability of metrics derived from bone versus lymph node metastases were observed (p=0.06-0.98). Only volume measurements had a significantly different repeatability for lesions >4.2mL versus <4.2mL (RC 17.6% and 36.8%, respectively; *p*=0.015).

Repeatability of Patient-Level Metrics

The highest repeatability was observed for TTV (RC 17%). TTB_{SUV} had better repeatability than TTB_{TBR}, albeit non-significantly (RC 23.2% versus 33.4%, p=0.19). Bland-Altman plots demonstrated no skewed variability (Figure 3).

Effect of PSF-Reconstruction on Repeatability

PSF-reconstruction worsened repeatability significantly for the TBRs, SUV_{mean}, and SUV_{max} (p≤0.005; Supplemental Table 2). However, the repeatability of tumor volume (RC 32.0%, *p*=0.43), SUV_{peak} (RC% 27.8%, p=0.15), TLU_{SUV} (RC 30.3%, p=0.62), and TLU_{TBR} (RC 41.3%, p=0.70) was not affected. Notably, repeatability of all patient-level metrics was not significantly affected by the PFS-reconstruction (*p*=0.15-0.59; Supplemental Table 2).

DISCUSSION

In this study we investigated the repeatability of ^{18}F-DCFPyL uptake and volume measurements in metastatic PCa patients. Knowledge of the day-to-day variation in these metrics is indispensable for use of ^{18}F-DCFPyL metrics as novel biomarkers for assessment of response to systemic treatments. We conclude that ^{18}F-DCFPyL uptake metrics are highly repeatable (ICC ≥0.97) and are thus suited for response monitoring purposes. SUV metrics tend to have higher repeatability than TBRs. The best repeatability was observed for patient-based TTV measurements.

In routine static PET acquisitions, ^{18}F-DCFPyL pharmacokinetics are most accurately quantified using the TBR(*10*), which demonstrated a repeatability of 31.8% in this study. Hence, a change in TBR exceeding 32% may indicate a change in tumoral ^{18}F-DCFPyL-uptake that exceeds the physiological variability, due to (e.g.) disease progression, treatment response, a true flare phenomenon, or an imaging protocol deviation. Repeatability of tumor SUV_{mean} was superior to TBR (Figure 1), which can be explained by added variability of blood pool activity measurements used in TBR calculation (blood pool RC 17.3%). Still, in our pharmacokinetic analysis we concluded that SUV measurements do not universally correlate with the underlying ^{18}F-DCFPyL pharmacokinetics (K_i), as intrapatient tumor volumes appear to affect the bioavailability of the tracer (a so-called sink-effect)(*10,22*). At higher tumor loads, SUV tends to underestimate ^{18}F-DCFPyL uptake in lesions, while TBR (partly) corrects for this and thus better reflects changes in ^{18}F-DCFPyL during response monitoring. These findings are in line with other prostate cancer radiotracers (^{18}F-fluoromethylcholine, ^{18}F-fluordihydrotestosterone) where tumor uptake measurements normalized to blood pool activity are more accurate metrics for tracer quantification than SUV, but have worse repeatability(*23,24*). All taken together, TBR may be preferred over SUV metrics despite its lower repeatability, which we recently illustrated in a clinical case(*22*). The higher variability of TBR compared to SUV will only have a negative impact on response assessment in patients with small tumor volumes with small treatment effect sizes.

Interestingly, the semi-automatically delineated total intrapatient tumor volume (TTV) demonstrated the highest overall repeatability (RC 17%). These favorable outcomes are likely explained by the high tumor to background ratio that ^{18}F-DCFPyL provides (and PSMA tracers in general), permitting reliable (semi)automatic identification of tumor extent. On a lesion-basis, however, variability of volume measurements was larger (RC 28.1%), which can at least partly be explained by the volume-dependency of its variability. The high repeatability of TTV may be of benefit for longitudinal assessments of total PSMA burden in patients receiving systemic treatments. Especially for PSMA-targeted radioligand therapies (e.g. ^{177}Lutetium-PSMA), assessment of changes in the total tumor volume as a whole, instead of individual lesion responses, may be clinically useful.

In multicenter studies, use of different PET/CT systems with varying image-reconstruction protocols require quantitative metrics that are robust to such factors. Advanced reconstruction methods may improve lesion detection (*25*), but repeatability may be hampered by the inherent image noise propagation. In line with previous observations for ^{18}F-fluorodihydrotestosterone(*26*), we observed lower repeatability of several metrics when using an image reconstruction with improved signal recovery, adhering to novel imaging guidelines (EARL2). However, repeatability of SUV_{peak}, TLU and patient-level measurements were not affected by the PSF-reconstruction, rendering them fit for use in multicenter studies were PET imaging protocols differ between centers. As blood activity measurements are susceptible to noise, repeatability of TBR was negatively affected by PSF-reconstruction. Overall, non-PSF reconstruction images (EARL1-compliant) may therefore be preferred for quantitative assessment.

Our study has limitations, most notably the small patient sample. Still, results were in line with findings on other ^{18}F-labeled PCa radiotracers, as well as ^{18}F-FDG(*19,23,24*). Factors contributing to the total variability in quantitative PET-metrics include biological variation in tracer uptake, image noise, scan protocol deviations between scans, and the analysis software used. We acknowledge the patients'

heterogeneity in terms of disease stages (primary metastatic disease, biochemical recurrence, castration-resistance), but subgroup analysis per disease stage was not feasible at the current sample size. We have no reason to assume that tracer uptake variability attributable to tumor biology will differ between disease stages, however. In our single-center evaluation, only a single type of PET-scanner and analysis software package was used – multicenter variability may be higher. We welcome other investigators using ^{18}F-DCFPyL to repeat our study in their own center, or even in a multicenter setting, to validate our current findings in a larger cohort. In the present study, the tracer uptake time and injected dosages of both test and retest scan were similar (Table 1). As our pharmacokinetic data indicated that tumor ^{18}F-DCFPyL uptake continues to rise at 120 min after injection (*10*), test-retest variability might be higher in clinical practice, where uptake times between scans may vary more. Clinical imaging protocols for ^{18}F-DCFPyL regarding uptake time intervals, total scan duration, and patient positioning (*i.e.* feet first or head first) should be stringently adhered to, especially in response assessment studies.

CONCLUSIONS

In this study we assessed the repeatability of quantitative ^{18}F-DCFPyL PET/CT measurements in patients with metastatic PCa, concluding that ^{18}F-DCFPyL uptake metrics are well repeatable. The variability limits proposed in this study should be validated in future clinical studies. To this end, any change in TBR exceeding 32% can be considered a change in tracer uptake beyond physiologic day-to-day variability (in case of comparable image-acquisition parameters). Additionally, as TTV measurements are highly repeatable (RC 17%) they may be specifically suitable for longitudinal assessment of PSMA-targeted radioligand therapy effects. The repeatability of SUV_{peak}, Total Lesion Uptake, and patient-level metrics (TTV and TTB) of ^{18}F-DCFPyL uptake is robust to differences in image reconstructions.

DISCLOSURES

Dr. R. Boellaard reports to have a scientific collaboration with Philips Healthcare, the Netherlands/USA. The other authors have no disclosures or potential conflicts of interest to this manuscript.

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KEY POINTS

QUESTION: What is the repeatability of quantitative ^{18}F-DCFPyL PET/CT measurements in patients with metastatic prostate cancer?

PERTINENT FINDINGS: In this prospective test-retest study, we demonstrate that quantitative ^{18}F-DCFPyL PET/CT measurements are well repeatable and may thus be used for treatment response monitoring.

IMPLICATIONS FOR PATIENT CARE: In case of comparable image-acquisition parameters, any change in Tumor-to-Blood ratio exceeding 32% will indicate a change beyond physiological day-to-day variability that should trigger further evaluation. Total Tumor Volume measurements may be specifically suitable for longitudinal assessment of PSMA-targeted radioligand therapies.

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Table 1: Patient and scan characteristics of the patients included in the repeatability analysis (*n*=10).

Patient Characteristics	Median	Range
Age (years)	74	(61-79)
Initial Gleason score	8	(6-9)
PSA at PET/CT (ng/mL)	9	(1-2796)
Length (cm)	178	(168-192)
Weight (kg)	88	(68-94)
PCa stage:	*n*	%
Primary metastastic	2	20.0
Biochemically recurrent	3	30.0
Castration-resistant	5	50.0
Analyzed lesion type:	*n*	%
Bone	21	58.3
Lymph node	12	33.3
Intraprostatic	3[a]	8.3
	n	%
Androgen Deprivation at PET/CT	7	70.0
prior docetaxel	3	30.0
Injected activity: Test (MBq)	317	(280-331)
Injected activity: Retest (MBq)	313	(254-341)
Uptake time: Test (min)	120	(118-153)
Uptake time: Retest (min)	122	(111-149)
Test-Retest diff. injected activity (MBq)[b]	28	(8-63)
Test-Retest diff. uptake time (min)[b]	3	(0-22)

[b]two intraprostatic foci in one patient; [a] differences were not significant ($p>0.05$).

Table 2: Descriptive data of lesion and patient-based uptake metrics on test and retest scans.

	Test		Retest	
	Median	*IQR*	*Median*	*IQR*
Lesion-level				
Volume	4.6	2.8 – 8.7	4.6	2.5 – 8.6
SUV_{mean}	16.6	9.5 – 24.4	17.1	9.7 – 28.0
SUV_{peak}	21.7	10.5 - 28.3	21.6	11.4 – 32.2
SUV_{max}	28.1	16.0 – 41.0	29.8	17.2 – 51.2
TBR_{mean}	13.4	7.1 – 24.1	14.6	8.6 – 22.7
TBR_{peak}	17.7	7.7 – 28.4	18.8	9.8 – 26.7
TBR_{max}	25.0	11.7 – 40.9	23.6	14.1 – 38.8
TLU_{SUV}	85.6	32.3 – 192.7	80.1	30.1 – 194.0
TLU_{TBR}	67.6	24.6 – 189.4	66.7	23.5 – 152.6
Patient-level				
TTV	21.4	10.6 – 63.2	21.8	10.3 – 69.7
TTB_{SUV}	317.8	70.4 – 1920.7	285.5	70.6 – 1846.4
TTB_{TBR}	236.6	63.2 – 1920.1	224.9	68.2 – 1720.0

IQR = interquartile range; SUV = Standardized Uptake Value; TBR = Tumor-to-Blood Ratio; TLU = Total Lesion Uptake; TTV = Total Tumor Volume; TTB = Total Tumor Burden

Table 3: Repeatability of lesion- and- patient-based ^{18}F-DCFPyL uptake metrics.

Parameter	Mean test-retest difference %	RC%	ICC (95% CI)
Lesion-level			
Volume	-1.1	28.1	1.00 (0.99-1.00)
SUV_{mean}	1.0	24.4	0.99 (0.98-0.99)
SUV_{peak}	1.8	25.3	0.99 (0.97-0.99)
SUV_{max}	1.9	31.0	0.97 (0.94-0.99)
TBR_{mean}	1.9	31.8	0.98 (0.96-0.99)
TBR_{peak}	2.6	31.7	0.98 (0.96-0.99)
TBR_{max}	2.7	37.3	0.97 (0.94-0.98)
TLU_{SUV}	-0.1	32.1	0.99 (0.98-1.00)
TLU_{TBR}	-3.5	39.3	0.98 (0.96-0.99)
Patient-level			
TTV	-2.2	17.0	1.00 (0.99-1.00)
TTB_{SUV}	-0.2	23.2	0.99 (0.97-1.00)
TTB_{TBR}	-2.1	33.4	0.98 (0.91-0.99)

IQR = interquartile range; SUV = Standardized Uptake Value; TBR = Tumor-to-Blood Ratio; TLU = Total Lesion Uptake; TTV = Total Tumor Volume; TTB = Total Tumor Burden

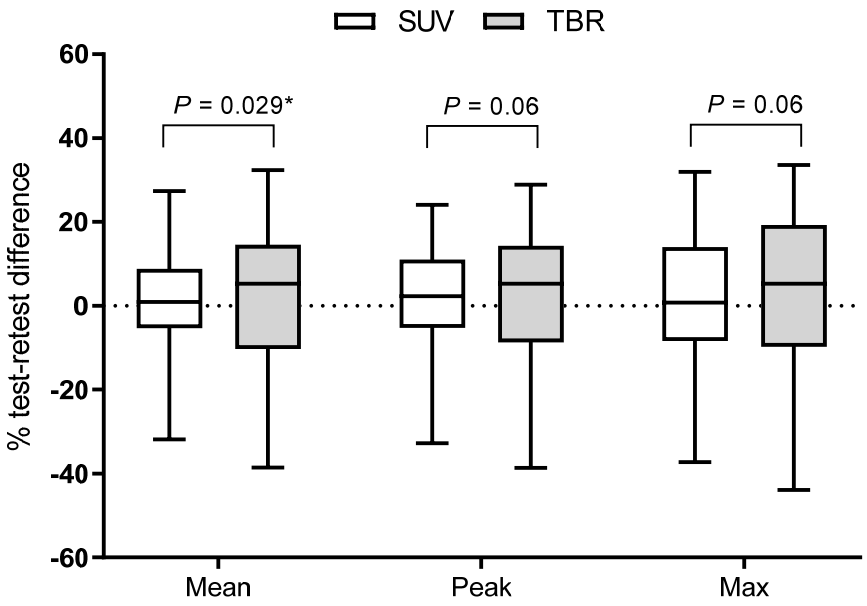

Figure 1: Test-retest variability of SUV and TBR variants. Significant differences have been indicated with an asterix (Holms-Bonferroni corrected *p*-values). Differences in repeatability between SUVs and between TBRs were not significant.

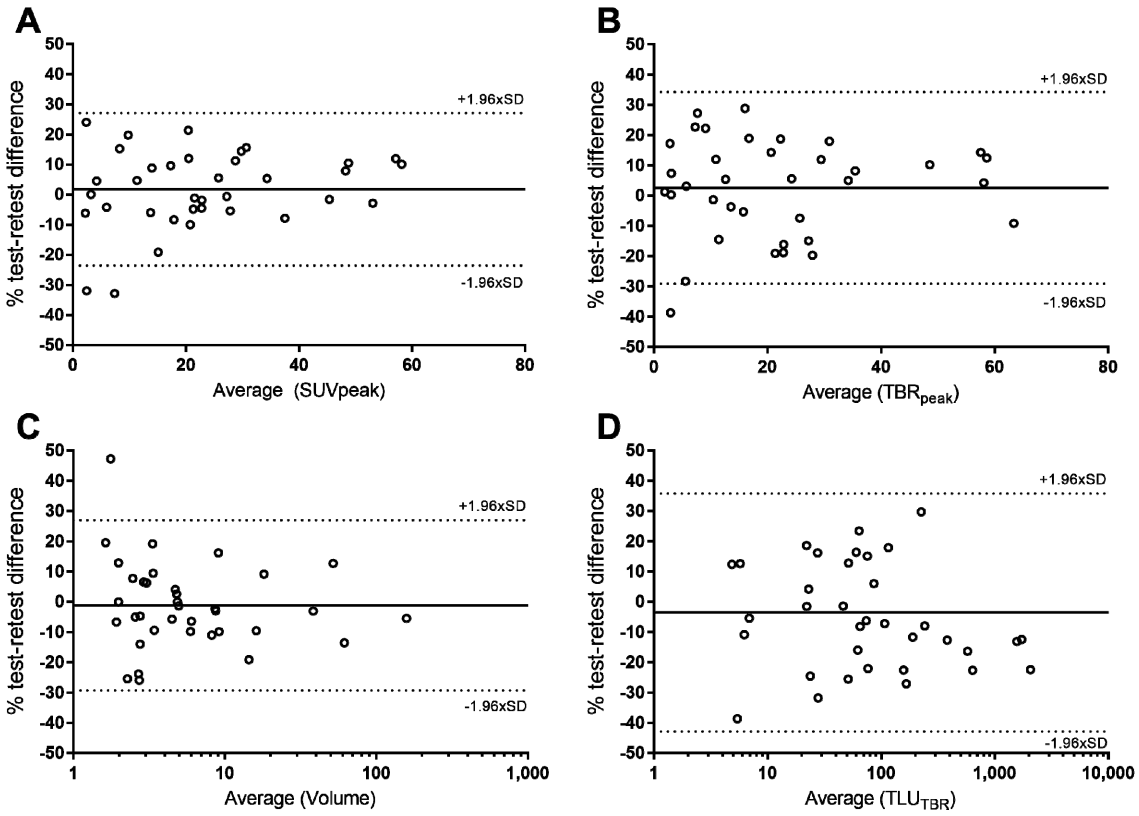

Figure 2: Bland-Altman plots of lesion-level metrics (A) SUV$_{peak}$, (B) TBR$_{peak}$, (C) volume, and (D) TLU$_{TBR}$. Y-axis in (C) and (D) were log-scaled for visual interpretation.

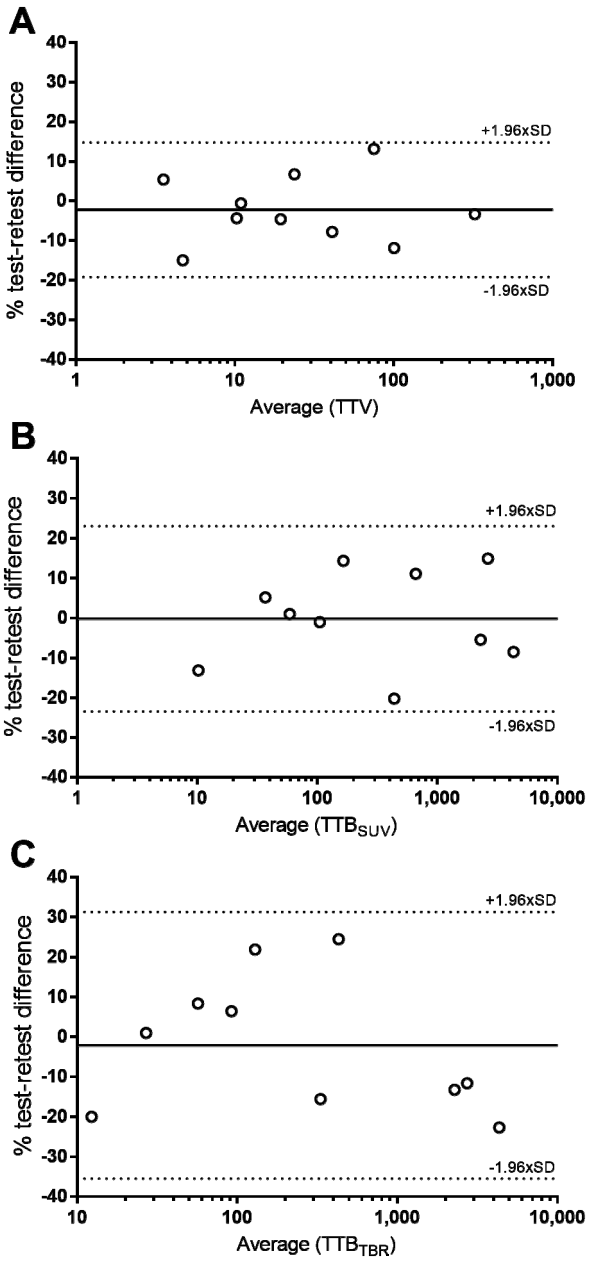

Figure 3: Bland-Altman plots of patient-level metrics TTV, TTB$_{SUV}$, and TTB$_{TBR}$. Y-axes were log-scaled for visual interpretation.

SUPPLEMENTARY FILES

Supplementary Table 1: Descriptive data of lesion- and- patient-based uptake metrics on test and retest scans for PSF-reconstruction images.

	Test		**Retest**	
	Median	*Range*	*Median*	*Range*
Lesion-level				
Volume	3.4	2.0 – 7.8	3.6	1.9 – 7.5
SUV_{mean}	25.0	15.0 – 40.3	24.2	14.9 – 47.2
SUV_{peak}	27.2	15.3 – 38.8	29.5	16.3 – 48.8
SUV_{max}	52.9	29.2 – 93.9	47.1	29.5 – 98.6
TBR_{mean}	19.7	11.6 – 33.7	19.4	13.1 – 34.1
TBR_{peak}	23.8	10.4 – 37.7	23.0	13.2 – 36.0
TBR_{max}	49.3	22.0 – 83.3	36.8	26.9 – 76.1
TLU_{SUV}	100.3	38.5 – 223.0	99.9	35.6 – 240.9
TLU_{TBR}	84.0	29.2 – 213.1	82.2	27.1 – 255.7
Patient-level				
TTV	17.2	7.5 – 46.0	17.9	7.8 – 47.0
TTB_{SUV}	375.3	74.6 – 1909.1	340.9	77.4 – 2094.6
TTB_{TBR}	276.9	66.3 – 1933.5	263.5	74.8 – 2215.6

IQR = interquartile range; SUV = Standardized Uptake Value; TBR = Tumor-to-Blood Ratio; TLU = Total Lesion Uptake; TTV = Total Tumor Volume; TTB = Total Tumor Burden

Supplementary Table 2: Repeatability of lesion and patient-based uptake metrics for PSF-reconstruction images. *P*-value indicates a significant differences in repeatability between original (non-PSF) and PSF-reconstructions.

Parameter	Mean test-retest difference %	RC%	ICC (95% CI)	***p*-value** *non-PSF vs. PSF*
Lesion-level				
Volume	0.1	32.0	1.00 (1.00-1.00)	0.427
SUV_{mean}	0.6	32.3	0.97 (0.95-0.99)	**0.005**
SUV_{peak}	2.2	27.8	0.98 (0.97-0.99)	0.147
SUV_{max}	-0.9	52.1	0.87 (0.77-0.93)	**<0.001**
TBR_{mean}	2.2	41.7	0.96 (0.92-0.98)	**<0.001**
TBR_{peak}	3.7	38.1	0.97 (0.94-0.98)	**<0.001**
TBR_{max}	0.7	58.9	0.88 (0.78-0.94)	**<0.001**
TLU_{SUV}	0.7	30.3	0.99 (0.98-0.99)	0.616
TLU_{TBR}	2.2	41.3	0.97 (0.95-0.99)	0.699
Patient-level				
TTV	1.7	13.9	1.00 (1.00-1.00)	0.152
TTB_{SUV}	1.9	23.4	0.99 (0.98-1.00)	0.952
TTB_{TBR}	3.9	37.6	0.98 (0.92-1.00)	0.588