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Standardized Uptake Values are Adequate Measures of Lesional ^{18}F-DCFPyL Uptake in Patients with Low Prostate Cancer Disease Burden.

Running title: SUV versus TBR in ^{18}F-DCFPyL PET/CT

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ABSTRACT

Rationale: In prostate cancer (PCa) patients, the Tumor-to-Blood ratio (TBR) has been validated as the preferred simplified method for lesional ^{18}F-DCFPyL (a radiolabeled Prostate-Specific Membrane Antigen (PSMA) ligand) uptake quantification on positron emission tomography (PET). In contrast to standardized uptake values (SUV), the TBR accounts for variability in arterial input functions caused by differences in total tumor-burden between patients (the 'sink effect'). However, TBR depends strongly on tracer uptake interval, has worse repeatability and is less applicable in clinical practice than SUVs. We investigated whether SUV could provide adequate quantification of ^{18}F-DCFPyL uptake on PET/computed tomography (CT) in a patient cohort with low prostate cancer (PCa) burden. **Methods**:

A total of 116 patients with PCa undergoing ^{18}F-DCFPyL PET/CT imaging were retrospectively included. All ^{18}F-DCFPyL-avid lesions suspect for PCa were semi-automatically delineated. SUV_{peak} was plotted against TBR for the most intense lesion of each patient. The correlation of SUV_{peak} and TBR was evaluated using linear regression, and was stratified for patients undergoing PET/CT for primary staging, restaging at biochemical recurrence and in metastatic castration-resistant PCa. Moreover, the correlation was evaluated as a function of tracer uptake time, prostate-specific antigen (PSA) levels and PET-positive tumor volume. **Results:** A total of 436 lesions was delineated (median 1 per patient, range 1-66). SUV_{Peak} correlated well to TBR in patients with PCa and a total tumor volume of <200 ml (R^2=0.931). The correlation between SUV and TBR was not affected by disease setting, PSA levels or tumor volume. SUV_{peak} depended less on tracer uptake time than TBR. **Conclusion:**

For ^{18}F-DCFPyL PET/CT, SUV_{peak} highly correlates with TBR. Therefore, it is a valuable simplified semi-quantitative measurement in patients with low volume prostate cancer (<200 ml). SUV_{peak} can therefore be applied in ^{18}F-DCFPyL PET assessment as an imaging biomarker to characterize tumors and to monitor treatment outcomes.

KEY WORDS

^{18}F-DCFPyL, PSMA, prostate cancer, standardized uptake values, tumour to blood ratio

INTRODUCTION

Prostate cancer (PCa) is the second most prevalent cancer disease in men worldwide (*1*). Conventional imaging studies such as computed tomography (CT), bone scintigraphy and magnetic resonance imaging (MRI) have moderate sensitivity for the detection PCa metastases (*2,3*). The recent Prostate-Specific Membrane Antigen (PSMA) positron-emission tomography/computed tomography (PET/CT) scans are showing more promising results in detecting metastases, in primary staging but especially in the recurrent stage of the disease (*4,5*). In addition, PSMA tracers are usually labeled with ^{68}Gallium (i.e. ^{68}Ga-PSMA-11) or ^{18}Fluorine (^{18}F-DCFPyL or ^{18}F-PSMA-1007) (*6*).

Recent studies demonstrated a benefit of using semi-quantitative measures of radiolabeled PSMA ligand uptake on PET for prognostication, as imaging biomarker to characterize tumors and monitor treatment outcomes (*7,8*). A requisite for reliable clinical use of semi-quantitative PET uptake parameters is that they correlate with the underlying tracer kinetics in vivo (*9*). For ^{18}F-DCFPyL uptake, our group recently validated the Tumor-to-Blood ratio (TBR) as the preferred simplified method, demonstrating a strong correlation with the reference pharmacokinetic parameter based on Patlak analyses (*10,11*). We observed that for ^{18}F-DCFPyL , high tumor volumes (1000-2000 ml) had an effect on the tracer plasma input functions. This renders SUV invalid for such patients, as it assumes that plasma input functions between patients are similar. In contrast with SUV, using TBR can correct for differences in plasma input functions between patients. Unfortunately, TBR poses some disadvantages, as summarized in Table 1, as it depends more on uptake interval, has worse repeatability, and is more labor intensive as compared to SUV (*12-14*).

The extraordinary high tumor volumes that affected ^{18}F-DCFPyL kinetics in previous studies are relatively rare and only seen in end stage disease (*15,16*). Even in metastasized castration-resistant prostate cancer (mCRPC) patients, only 6.2% has a tumor volume of 500ml or higher(*17*). In clinical practice, the majority of patients with PCa that receive a PSMA PET/CT scan in both the primary and recurrent PCa setting have relatively low-volume disease (*18-20*). We hypothesized that SUV might be a valid alternative to TBR for lesional ^{18}F-DCFPyL quantification in the majority of PCa patients with a low disease burden, defined as 200ml or less. The aim of this study was to validate SUV against TBR in PCa patients with commonly seen low tumor burdens and potentially define a tumor volume threshold below which SUV remains a valid parameter for ^{18}F-DCFPyL uptake quantification. Secondly, we illustrated the

influence of uptake interval on SUV versus TBR based on the hypothesis that SUV will be less dependent on uptake intervals than TBR.

MATERIALS AND METHODS

Patients

A retrospective analysis was performed in 124 patients with histologically proven PCa, included in Amsterdam University Medical Centers (location VUmc). As an inclusion criterion, all patients that underwent a ^{18}F-DCFPyL PET/CT scan within variable stages of disease were eligible. We performed a secondary analysis of data pooled from 4 studies conducted from November 2017 and August 2019, that encompassed patients with primary PCa, recurrent PCa and metastasized castration-resistant prostate cancer (mCRPC) (*5,14,16,21*). All 4 studies were approved by the local medical ethical committee (review numbers 2017.543, 2017.565 (combined for 2 studies) and 2018.453). The main analysis included 116 patients, with 81 patients receiving a ^{18}F-DCFPyL PET/CT scan for primary PCa, 25 patients having a ^{18}F-DCFPyL PET/CT scan in the recurrent setting, and 10 patients with mCRPC. The 81 patients who received a ^{18}F-DCFPyL PET/CT in the primary staging setting were patients who underwent ^{18}F-DCFPyL PET/CT imaging before surgery, so it is assumed that these patients had low-volume disease. Additionally, dynamic PET acquisitions from 8 patients with end-stage, metastasized CRPC was available and used for time-dependent analyses (see below). All subjects signed informed consent when enrolled in the original studies being approved by the institutional review board of VUmc, explicitly allowing secondary analysis of their study data.

Image Acquisition

^{18}F-DCFPyL was synthesized under Good Manufacturing Practices conditions at the on-site cyclotron(*22,23*). Image-acquisitions were performed using a Philips Ingenuity TF (Philips Healthcare®, the Netherlands/USA) PET/CT system. The scan trajectory included mid-thighs to skull base (static scans), with 4 min per bed position. All PET scans were combined with a low-dose or high-dose CT scan without intravenous contrast (30-110mAs, 110-130kV). Images were corrected for decay, scatter, random coincidences, and photon attenuation. Images were reconstructed with a Binary Large OBject-based Ordered-Subsets Expectations Maximization algorithm (3 iterations; 33 subsets).

Scan Assessment

PET/CT scans of the primary cohort of 116 patients were analyzed and all tumor deposits were delineated according to the available clinical reports. All local tumors, lymph node metastases and bone/visceral metastases were delineated individually, as a volume of interest (VOI). An automatically

generated SUV_{peak} isocontour of 50% with correction for background uptake was used to create the VOI in the tissues suspect for malignancy (*24*). Per VOI, tumor volume (in ml) and SUV_{peak} were calculated. SUV_{peak} was chosen because it is less variable and has less inherent intra-patient bias compared to $SUV_{max,}$ and does not require exact tumor borders as compared to SUV_{mean} (*25,26*). Per patient, total tumor volume (TTV) and the total lesion uptake (TLU) were calculated. TTV was defined as the sum of the delineated tumor volumes within one patient, and TLU was defined as the lesional mean uptake multiplied by the lesion volume, as a percentage of injected dose. Additionally, a 3x3 VOI was placed in the ascending aorta on 5 consecutive slices of the CT scan (*27*) yielding the blood pool activity used for the calculation of TBR. TBR was determined by dividing the SUV_{peak} of the lesions by the SUV_{peak} of the aortic blood pool. Delineation was performed using the in-house developed ACCURATE tool © (*28*).

Effect of Uptake Interval on SUV versus TBR

In a sub-analysis, 8 patients with mCRPC who were dynamically scanned with ^{18}F-DCFPyL PET/CT were reinvestigated to define their correlation of SUV_{peak} versus TBR over time (*16*). These patients received a low-dose CT scan (30 mAs, 120 kV) followed by a dynamic PET scan from 0 to 120 min after injection of ^{18}F-DCFPyL (median dose, 313 MBq; range, 292–314 MBq) with a 30-min break in acquisitions, for patient comfort, 60 minutes after the first dynamic scan. Similarly to the scans of the main cohort, data were corrected for decay, dead time, scatter, and random coincidences; photon-attenuation correction was performed using the low-dose CT scans. Patient demographic data can be found in the primary publication (*16*)

Statistical Analysis

Numerical variables were summarized with median values and interquartile range (IQR); categorical variables with proportions (%). Data was assessed for normality using histogram analysis. The most intense lesion with highest SUV_{peak} value within each patient was compared to the corresponding TBR by linear regression analysis (R^2) using Pearson's correlation coefficient and Spearman's rank correlation coefficient. To assess whether uptake time' (time from injection to scan start) affected the correlation between SUV and TBR, three groups, were identified: uptake interval of <110min, 110-130min, and >130min. Significance level was set at $p<0.05$. Statistical analysis was performed using IBM® SPSS® Statistics for Windows®, version 26 and GraphPad Prism (version 8.0.0 for Windows, GraphPad Software).

RESULTS

Patient Characteristics

A total of 116 patients was included in the main analysis of this study. Patients had a median age of 68.0 years (range 49.0-84.0). The ^{18}F-DCFPyL PET/CT scans from 81 primary PCa patients, 25 recurrent PCa patients and 10 patients with mCRPC were analyzed. Therapy prior to ^{18}F-DCFPyL PET/CT was given in 35/116 (30.1%) patients: 14/25 (56.0%) recurrent PCa patients received radical prostatectomy, 3/25 (12.0%) received androgen deprivation therapy (ADT) combined with chemotherapy, 8/25 patients (28.0%) received radiotherapy. In the mCRPC group, 7/10 (70.0%) patients had received ADT alone, 3/10 (30.0%) patients had received ADT and chemotherapy, and in one patient prior therapy was unknown. Further details of the study population are provided in Table 2. Demographics per disease setting, are presented in Supplemental Table 1.

PET Imaging Results

The median uptake time was 120.2 minutes (range 103.1 - 163.7), with a median injected dose of 314.0 MBq (range 250.4-330.9). In total, 436 lesions were delineated (median 1 per patient, range 1-66). 69 out of 116 (59.4%) patients had a total of 1 lesion, 35 out of 116 (30.1%) patients had 2-5 lesions and 11 out of 116 (9.4%) patients had >5 lesions. We delineated 105/436 (24.1%) intra-prostatic lesions, 189/436 (43.3%) bone lesions, 141/436 (32.3%) lymph node lesions, and 1/436 (0.2%) pulmonary lesions. Median TTV was 8.1 ml (range 1.4-79.2), 24.4 ml (range 2.9-173.4) and 21.5 ml (range 5.4-473.1), respectively for the primary disease, recurrent PCa and mCRPC groups. Detailed characteristics stratified per disease setting are presented in Table 2.

Aorta SUV_{peak} as a Function of Total Tumor Volume and PSA

On a patient level, there was no correlation between the blood pool (aorta) SUV_{peak} and the TTV (R^2 = 0.001). The blood pool SUV_{peak} remained stable around increasing tumor volumes, as shown in Fig. 1a. Similarly, no correlation was noted between the blood pool SUV_{peak} and the serum PSA (as a potential surrogate marker for disease load) at the time of the scan (R^2 = 0.007), as shown in Fig. 1b.

Correlative Analysis between SUV_{peak} and TBR

Overall, SUV_{peak} correlated with TBR with a R^2 of 0.931 (most intense lesion per patient, all patients included), see Fig. 2. When plotted separately, SUV_{peak} still correlated to TBR, with an R^2 of 0.950, 0.902 and 0.957, respectively, for the primary, recurrent and mCRPC group, as presented in Fig. 3. Linear regression slopes were 1.10, 0.90, and 1.26, respectively, for the primary, recurrent and mCRPC group. PSA versus SUV_{peak} (most intense lesion) and PSA versus TBR per patient were not correlated (r=0.13,p=0.18 and r=0.14, p=0.13, respectively).

SUV_{peak} versus TBR over Injection Time.

Three patient groups were generated to stratify post-injection scan-time in minutes: respectively <110 minutes, 110-130 minutes and >130 minutes after radiotracer injection. Fig. 4. shows the linear regression analysis, with all three groups showing high correlation after the Spearman r correlation test, with a R^2 of 0.907, 0.925 and 0.955, respectively for <110 minutes, 110-130 minutes and >130 minutes after radiotracer injection. The slopes of these groups were 1.299, 1.053 and 0.9823 respectively for <110 minutes, 110-130 minutes and >130 minutes after radiotracer injection. For a sub analysis, 8 patients were scanned with a dynamic scan spanning 120 minutes. A representation of the development of the SUV_{peak} versus the TBR over time can be seen in Fig. 5. For these 8 mCRPC patients, SUV_{peak} of the maximum intense lesion showed a stable development after 20 minutes versus TBR, which showed a gradual increase until 120 minutes.

DISCUSSION

In this study we studied SUV_{peak} as a simplified method for quantification of tumor PSMA-expression on ^{18}F-DCFPyL PSMA PET/CT scans in a combined cohort of PCa patients from primary staging, recurrent PCa and mCRPC setting. A high correlation of SUV_{peak} to TBR was found for each group in cohort, as well as a high correlation of SUV to TBR in the pooled data. The correlation of SUV_{peak} and TBR in the present study thus implicates that SUV_{peak} is suitable as a simplified method for the quantification of ^{18}F-DCFPyL PSMA PET/CT in patients with a total tumor volume below 200 ml, based on the earlier findings that TBR correlates to parameters from full kinetic modeling (*16*).

When the patient cohort was stratified for tracer uptake time, all subgroups showed correlation of SUV_{peak} versus TBR. Nonetheless, inter-group evaluation showed more favorable slopes (i.e. a slope closest to 1) in favor of uptake times above 110min. This is in line with Wondergem et al., who stated 120 min is the optimal scan time enabling the visualization of an increased number of lesions (*29*). The reason why the correlation is weaker for the lower uptake times can be explained by the results from our sub-analysis of 8 additional mCRPC patients, which showed that SUV_{peak} increases rapidly after injection, and stabilizes earlier than TBR after injection time. When visually interpreting the curve as seen in Fig. 5, SUV_{peak} seemed to be less dependent on uptake interval. In addition, SUV_{peak} has a better repeatability than TBR, especially in lesions with a small volume (defined as <4,2ml), as reported by Jansen et al. . Therefore, SUV_{peak} may be a more suitable measure for clinical practice compared to TBR given the heterogeneity of scan protocols spread across hospitals. Nevertheless, TBR stands as a reliable method of semi-quantification for the whole spectrum of tumor volumes, but only when adhering to strict uptake timing protocols (*16*).

This sink effect, as described by Jansen et al. and Gaertner et al. (*16,30*), was only observed in mCRPC patients with extreme tumor volumes ranging up to 1000 or 2000 ml scanned in a research setting. Following the sink effect hypothesis, the aorta SUV_{peak} is expected to decrease with increasing tumor load (TTV), which was observed in the aforementioned studies. In another study from Werner et al., conducted in patients with lower PCa volumes (median 4.8 ml, range 0.3-98.4), the absence of a sink effect was noted after analyzing 50 ^{18}F-DCFPyL PET/CT scans (*20*). Like our study, this cohort included a variety of indications to perform a PSMA PET/CT scan, but no patient presented with a TTV higher than 100 ml. As in the study by Werner et al., a clear cut-off point for a sink effect was not established in the

present paper, since no measurable effect on ^{18}F-DCFPyL input functions was noticed as seen in Fig. 1b. This could be caused by the fact that only 1 patient with a high tumor burden (>200 ml) was included. Still, a very small slope was observed in both linear regressions, and especially the trend observed in aorta SUV_{peak} versus TTV may implicate a minor sink effect in larger PCa metastatic volumes, caused by increased tumor volumes that decreases blood pool activity, as described by Cysouw et al.(*15*). Since the majority of included patients had either primary PCa and/or lower TTV, the non-significant correlations can strengthen the argument that SUV is an applicable semi-quantitative measure for the majority of clinical PSMA scans. Still, the validity of TBR has previously been demonstrated (19).

This study carries the limitations inherent to a retrospective study, with a potential selection bias. We tried to overcome this selection bias by including a heterogeneous group of indications for ^{18}F-DCFPyL PSMA PET/CT scans. Secondly, a pharmacokinetic study (with arterial and venous blood samples) should ideally be performed on the entire cohort to verify our results. This would render a validation of SUV_{peak} versus actual pharmacodynamics, but would be very labor intensive for the amount of patients presented in this study.

Our findings imply that SUV_{peak} is a valid simplified method to quantify ^{18}F-DCFPyL PSMA-PET/CT scans in patients with PCa and a total tumor burden below 200 ml. Unfortunately, a cut-off for the sink-effect could not be identified due to the low number of patients with high tumor volumes. Therefore further research to find a sink-effect is needed in a broad range of tumor volumes, with at least a reasonable amount of tumor volumes above 200 ml, possibly even above 500 ml. Therefore, we recommend to use SUV_{peak} in tumor volumes <200 ml, as it has proven to be accurate in this study. In current clinical practice, this encompasses the vast majority of patients receiving PSMA PET scans (*14,19*). Still, TBR remains a reliable simplified quantification method in the full spectrum of tumor volumes, provided that injection to scan intervals are above 110 minutes.

CONCLUSION

For ^{18}F-DCFPyL PET/CT, standardized uptake value is a valuable simplified semi-quantitative measurement in patients with low volume prostate cancer (<200 ml), with high correlation to TBR. SUV_{peak} can therefore be potentially applied to improve precision of ^{18}F-DCFPyL PSMA PET/CT scans, as an imaging biomarker to characterize tumors, and to monitor treatment outcomes. Although the presence of a sink-effect has been demonstrated for ^{18}F-DCFPyL PET/CT previously, we could not identify the threshold tumor volume for this effect within our real-life clinical cohort.

COMPETING INTERESTS

prof. dr. Boellaard reports the receiving of a grant from Philips Healthcare, outside the submitted work. The other authors declare that they have no competing interests.

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KEY POINTS

QUESTION: Do Tumor-to-Blood ratios correlate with Standardized Uptake Values when performing quantitative evaluation of ^{18}F-DCFPyL PET/CT in clinical practice in patients with a low prostate cancer volume?

PERTINENT FINDINGS: For ^{18}F-DCFPyL PET/CT, Tumor-to-Blood ratios highly correlates with Standardized Uptake Values. Therefore, it is a valuable simplified semi-quantitative measurement in p atients with low volume prostate cancer (<200 ml).

IMPLICATIONS FOR PATIENT CARE: Tumor-to-Blood ratios and Standardized Uptake Values can be used as simplified methods to perform quantitative assessment of ^{18}F-DCFPyL PET/CT, enabling reliable interpretation of PET/CT scans and the use of tracer uptake as an imaging biomarker.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68:394-424.

2. Hovels AM, Heesakkers RA, Adang EM, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. *Clin Radiol.* 2008;63:387-395.

3. Shen G, Deng H, Hu S, Jia Z. Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis. *Skeletal Radiol.* 2014;43:1503-1513.

4. Perera M, Papa N, Roberts M, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. *Eur Urol.* 2020;77:403-417.

5. Jansen BHE, Bodar YJL, Zwezerijnen GJC, et al. Pelvic lymph-node staging with (18)F-DCFPyL PET/CT prior to extended pelvic lymph-node dissection in primary prostate cancer - the SALT trial. *Eur J Nucl Med Mol Imaging.* 2020:Epub ahead of print.

6. Ahmadzadehfar H, Essler M. Prostate-specific Membrane Antigen Imaging: A Game Changer in Prostate Cancer Diagnosis and Therapy Planning. *Eur Urol.* 2020;77:418-419.

7. Roberts MJ, Morton A, Donato P, et al. (68)Ga-PSMA PET/CT tumour intensity pre-operatively predicts adverse pathological outcomes and progression-free survival in localised prostate cancer. *Eur J Nucl Med Mol Imaging.* 2020: Epub ahead of print.

8. Uprimny C, Kroiss AS, Decristoforo C, et al. 68Ga-PSMA-11 PET/CT in primary staging of prostate cancer: PSA and Gleason score predict the intensity of tracer accumulation in the primary tumour. *European Journal of Nuclear Medicine and Molecular Imaging.* 2017;44:941-949.

9. Prasad V, Steffen IG, Diederichs G, Makowski MR, Wust P, Brenner W. Biodistribution of [(68)Ga]PSMA-HBED-CC in Patients with Prostate Cancer: Characterization of Uptake in Normal Organs and Tumour Lesions. *Mol Imaging Biol.* 2016;18:428-436.

10. Jansen BHE, Yaqub M, Cysouw MCF, et al. Reply: Quantification of (18)F-DCFPyL Uptake: TBR Versus Patlak's Analysis. *J Nucl Med.* 2019;60:1834-1835.

11. Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. *J Cereb Blood Flow Metab.* 1985;5:584-590.

12. Hoekstra CJ, Paglianiti I, Hoekstra OS, et al. Monitoring response to therapy in cancer using [18F]-2-fluoro-2-deoxy-D-glucose and positron emission tomography: an overview of different analytical methods. *Eur J Nucl Med.* 2000;27:731-743.

13. Chen W, Dilsizian V. PET assessment of vascular inflammation and atherosclerotic plaques: SUV or TBR? *J Nucl Med.* 2015;56:503-504.

14. Jansen BHE, Cysouw MCF, Vis AN, et al. Repeatability of Quantitative (18)F-DCFPyL PET/CT Measurements in Metastatic Prostate Cancer. *J Nucl Med.* 2020;27:600-601.

15. Cysouw MCF, Jansen BHE, Yaqub M, et al. Letter to the Editor re: Semiquantitative Parameters in PSMA-Targeted PET Imaging with [(18)F]DCFPyL: Impact of Tumor Burden on Normal Organ Uptake. *Mol Imaging Biol.* 2020;22:15-17.

16. Jansen BHE, Yaqub M, Voortman J, et al. Simplified Methods for Quantification of (18)F-DCFPyL Uptake in Patients with Prostate Cancer. *J Nucl Med.* 2019;60:1730-1735.

17. Seifert R, Kessel K, Schlack K, et al. PSMA PET total tumor volume predicts outcome of patients with advanced prostate cancer receiving [(177)Lu]Lu-PSMA-617 radioligand therapy in a bicentric analysis. *Eur J Nucl Med Mol Imaging.* 2020:Epub ahead of print.

18. Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol.* 2020:Epub ahead of print.

19. von Klot CJ, Merseburger AS, Boker A, et al. (68)Ga-PSMA PET/CT Imaging Predicting Intraprostatic Tumor Extent, Extracapsular Extension and Seminal Vesicle Invasion Prior to Radical Prostatectomy in Patients with Prostate Cancer. *Nucl Med Mol Imaging.* 2017;51:314-322.

20. Werner RA, Bundschuh RA, Bundschuh L, et al. Semiquantitative Parameters in PSMA-Targeted PET Imaging with [(18)F]DCFPyL: Impact of Tumor Burden on Normal Organ Uptake. *Mol Imaging Biol.* 2020;22:190-197.

21. Jansen BHE, Jansen RW, Wondergem M, et al. Lesion Detection and Interobserver Agreement with Advanced Image Reconstruction for (18)F-DCFPyL PET/CT in Patients with Biochemically Recurrent Prostate Cancer. *J Nucl Med.* 2020;61:210-216.

22. Bouvet V, Wuest M, Jans HS, et al. Automated synthesis of [(18)F]DCFPyL via direct radiofluorination and validation in preclinical prostate cancer models. *EJNMMI Res.* 2016;6:40.

23. Ravert HT, Holt DP, Chen Y, et al. An improved synthesis of the radiolabeled prostate-specific membrane antigen inhibitor, [(18) F]DCFPyL. *J Labelled Comp Radiopharm.* 2016;59:439-450.

24. Frings V, Velden FHPv, Velasquez LM, et al. Repeatability of Metabolically Active Tumor Volume Measurements with FDG PET/CT in Advanced Gastrointestinal Malignancies: A Multicenter Study. *Radiology.* 2014;273:539-548.

25. Akamatsu G, Ikari Y, Nishida H, et al. Influence of Statistical Fluctuation on Reproducibility and Accuracy of SUVmax and SUVpeak: A Phantom Study. *J Nucl Med Technol.* 2015;43:222-226.

26. Lodge MA, Chaudhry MA, Wahl RL. Noise considerations for PET quantification using maximum and peak standardized uptake value. *J Nucl Med.* 2012;53:1041-1047.

27. Jansen BHE, Kramer GM, Cysouw MCF, et al. Healthy Tissue Uptake of (68)Ga-Prostate-Specific Membrane Antigen, (18)F-DCFPyL, (18)F-Fluoromethylcholine, and (18)F-Dihydrotestosterone. *J Nucl Med.* 2019;60:1111-1117.

28. Boellaard R. Quantitative oncology molecular analysis suite: ACCURATE. *J Nucl Med.* 2018;59:1753.

29. Wondergem M, van der Zant FM, Knol RJJ, Lazarenko SV, Pruim J, de Jong IJ. (18)F-DCFPyL PET/CT in the Detection of Prostate Cancer at 60 and 120 Minutes: Detection Rate, Image Quality, Activity Kinetics, and Biodistribution. *J Nucl Med.* 2017;58:1797-1804.

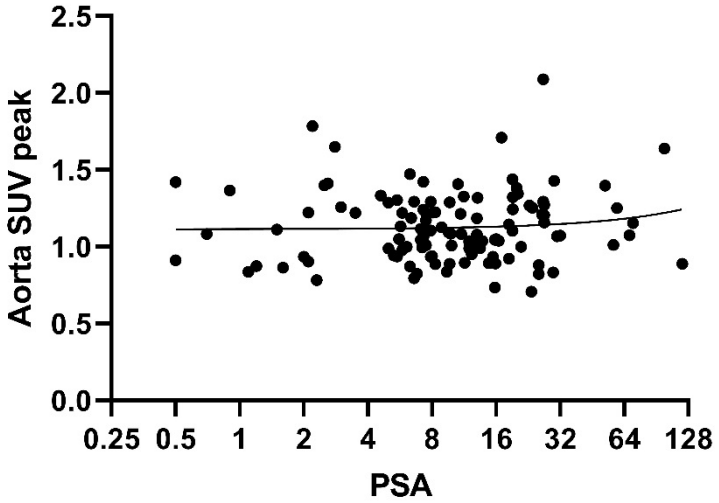
30. Gaertner FC, Halabi K, Ahmadzadehfar H, et al. Uptake of PSMA-ligands in normal tissues is dependent on tumor load in patients with prostate cancer. *Oncotarget.* 2017;8:55094-55103.

31. van den Hoff J, Oehme L, Schramm G, et al. The PET-derived tumor-to-blood standard uptake ratio (SUR) is superior to tumor SUV as a surrogate parameter of the metabolic rate of FDG. *EJNMMI Res.* 2013;3:77.

32. Hofheinz F, Hoff J, Steffen IG, et al. Comparative evaluation of SUV, tumor-to-blood standard uptake ratio (SUR), and dual time point measurements for assessment of the metabolic uptake rate in FDG PET. *EJNMMI Res.* 2016;6:53.

Figure 1. (A) Linear regression of aorta SUV_{peak} versus PSA with exclusion of the PSA outlier on a Log 2 scaled X-axis. A slightly positive slope of 0.001 is visible, with $R^2 = 0.007$. With an Aorta SUV_{peak} of 0.994, the outlier with a PSA of 2790,0 did not alter the results and was therefore excluded from the graph. (B) Linear regression of Aorta SUV_{peak} versus Total tumor volume on a Log 2 scaled X-axis. Both R2 and the correlation coefficient r were highly insignificant (R2 = 0.001; r = 0.038).

(A)



(B)

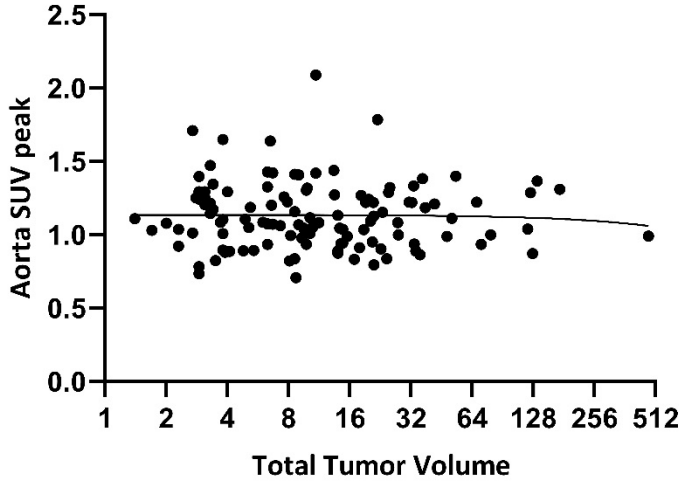


Figure 2. Linear regression of maximal SUV_{peak} versus TBR values of the most intense lesion suspect for PCa on ^{18}F-DCFPyL PET/CT in 114 patients. R^2 measured 0.931, and the slope of the regression was 1.032.

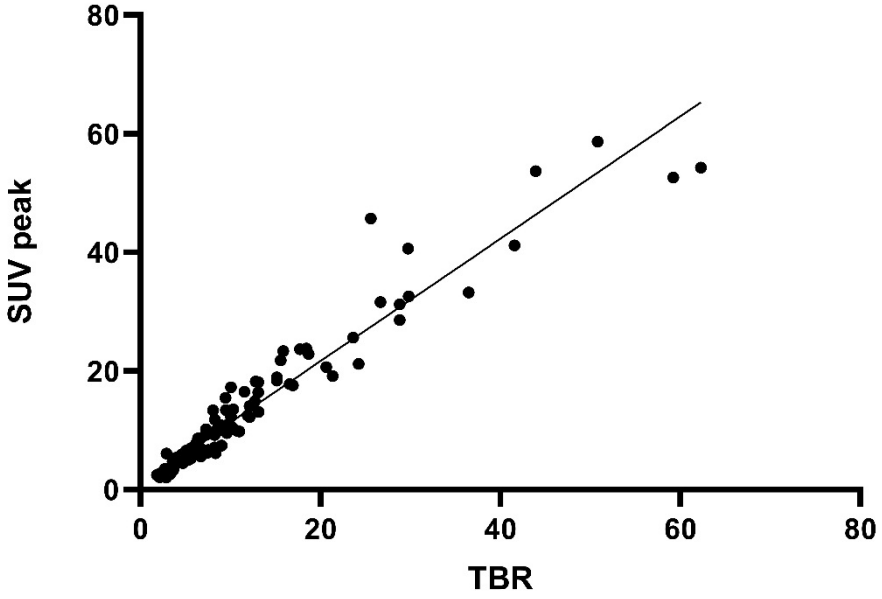


Figure 3. Linear regression of SUV_{peak} versus TBR values of the most intense lesion suspect for prostate cancer on ^{18}F-DCFPyL PET/CT with stratification for different groups: mCRPC (green), recurrent PCa (blue) and primary PCa (red). This plot emphasizes the high correlation for primary (R^2 0.957) and recurrent PCa (R^2 0.950) and somewhat lesser correlating mCRPC (R^2 0.902) group, as individuals.

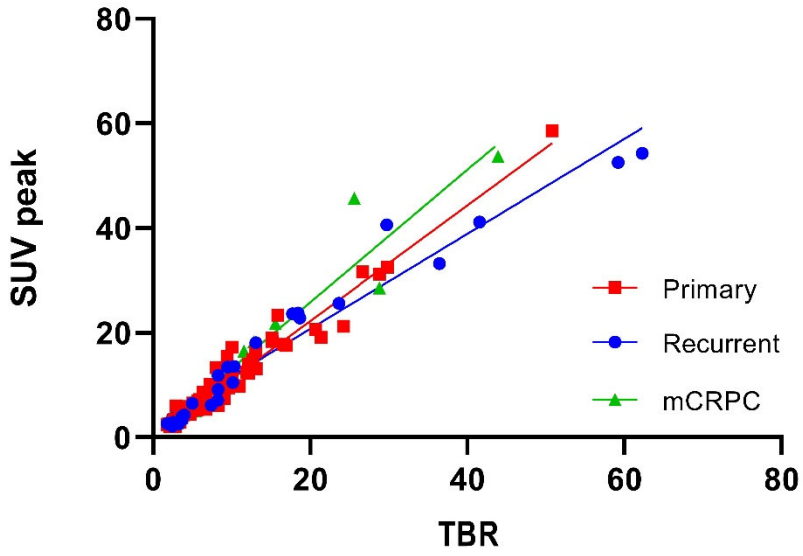


Figure 4. Linear regression of SUV_{peak} versus TBR values of the most intense lesion suspect for PCa on ^{18}F-DCFPyL PET/CT stratified for injection time. R^2 in ascending order for uptake time was 0.907, 0.925 and 0.955.

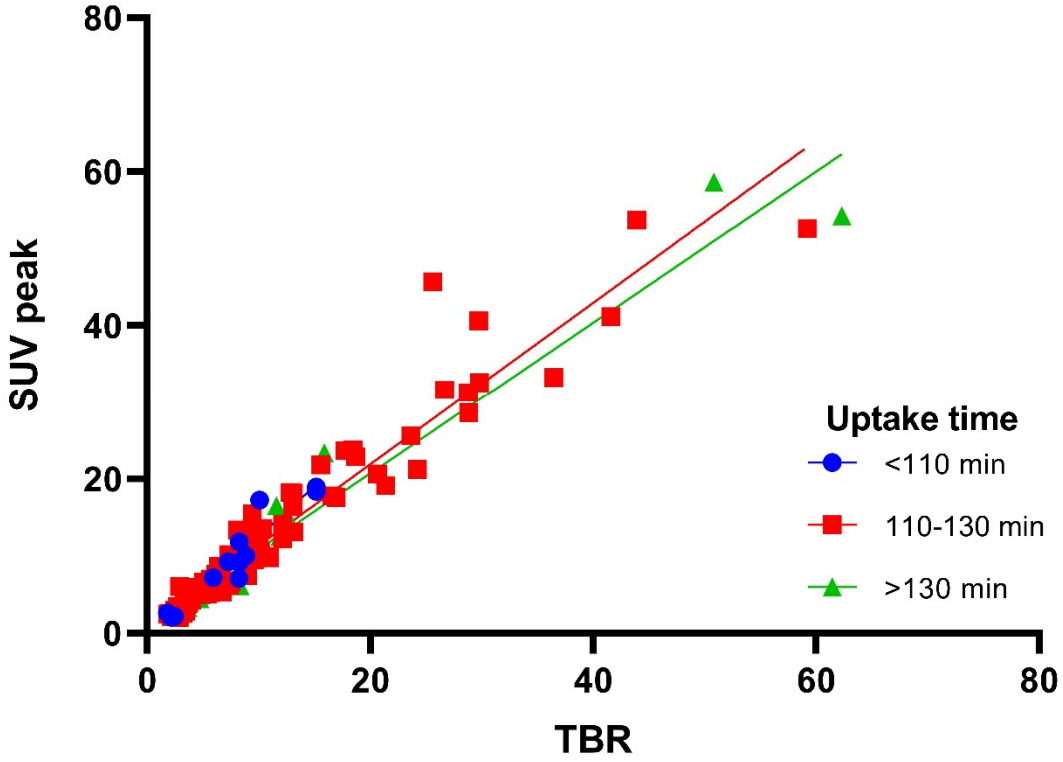
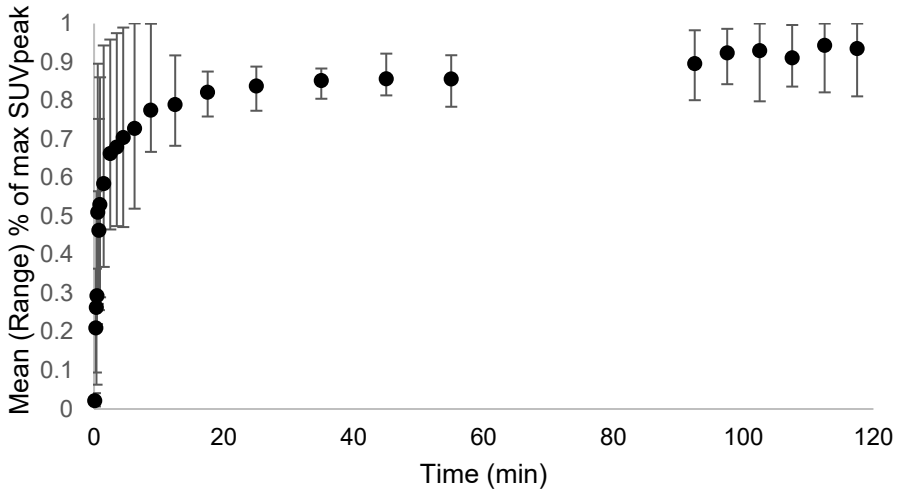
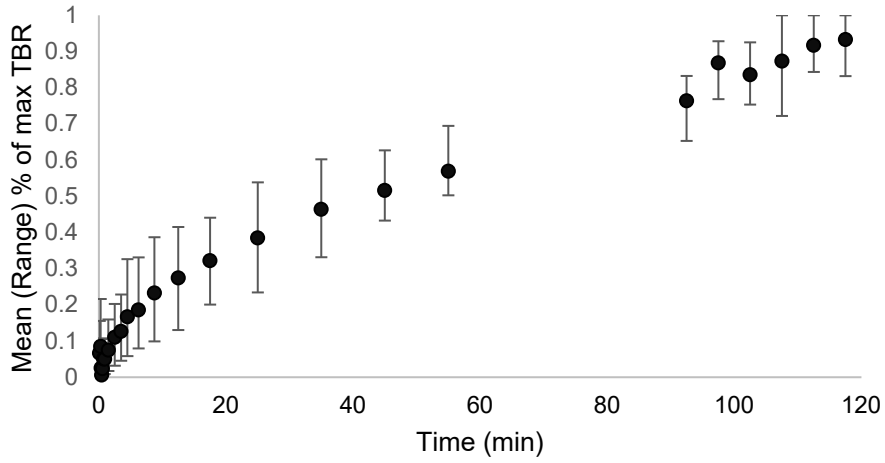


Figure 5. Development of mean (range) SUV_{peak} and TBR of the most intense lesions as function of uptake interval of 8 mCRPC patients. SUV and TBR are presented as the percentage of the maximum value measured per respective patient.





TABLES AND FIGURES

Table 1. Overview of Advantages and disadvantages of Standardized uptake value (SUV) versus Tumor-to-Blood-ratio (TBR)

SUV		TBR	
Pro	**Con**	**Pro**	**Con**
-Single measurement without additional data acquisition and evaluation (i.e. no assessment of the blood activity is needed). (*16,31*) **-Less variability given the radiotracers clearance. (*13*)** Therefore providing better repeatability and a better response assessment when analyzing the effect of PSMA targeted radioligand therapies.(*14*)	-Susceptibility to errors in scanner and dose calibration, insufficient correlation between systemic distribution volume and body weight and inter-study variability of arterial input function. (*12*) -No reproducible relation exists between SUV and K_i (*16*)	-Validated surrogate of metabolic uptake rate K_i (*16,32*) -Is a SUV normalized to the radiotracer concentration in blood plasma available for influx in tissue. (*31*) This immediately poses a con as the blood plasma should be normal tissue with a constant and stable radiotracer volume. (*12*)	-Needs a second Region of Interest (ROI) to derive the blood activity concentration. (*12*) - More dependent on uptake time compared to SUV. (*12*) -Worse repeatability than SUVs, potentially hampering response assessment. In addition, image reconstruction via point-spread-function (PSF) worsened the repeatability significantly for TBR. SUV_{Peak} however was not affected (*14*)

Table 2. Baseline patient characteristics (A) and baseline scan characteristics (B)

(A)

Patient Characteristics		Median (Range)
N		116
Age (median + range, in yrs.)		68.0 (49.0-84.0)
Weight (Kg)		82.5 (50.0-122.0)
Height (cm)		180.0 (155.0-198.0)
PSA level (median + range, ng/mL)		9.7 (0.5-2790.0)
Gleason score (cuml)		7 (6-9)
Scan indication (N + % of total)	*Staging*	81/116 (69.8%)
	Recurrent PCa	25/116 (21.6%)
	mCRPC	10/116 (8.6%)
Therapy prior to PET (N + % of total)		34/116 (29.3%)

N= Number Yrs = Years; Kg = Kilograms; cm = centimeter; ng/mL = nanogram per milliliter; cuml = cumulative

(B)

Scan characteristics	**Primary**	**Recurrent PCa**	**mCRPC**
administered radiotracer (median + range, in MBq)	314.1 (250.4-329.3)	311.4 (289.6-328.2)	314.9 (280.0-330.9)
Net time between inj. and scan start (min)	118.5 (57.1-163.7)	119.6 (75.8-149.4)	119.9 (118.0-141.2)
Max SUV Peak per patient	6.7 (2.0-58.7)	11.8 (1.8-62.3)	17.4 (2.8-53.7)
TTV (CC)	8.1 (1.4-79.2)	24.4 (2.9-173.4)	21.5 (5.4-473.1)
TLU prostate (%ID)	0.042 (0.004-0.695)	0.026 (0.003-0.457)	0.069 (0.015-0.288)
TLU Whole Body (%ID)	0.042 (0.004-0.704)	0.108 (0.007-1.268)	0.123 (0.011-0.549)

MBq = Mega Bequerell, TTV = Total Tumor Volume, CC = Milliliters, min = Minutes, TLU = Total Lesion Uptake, %ID = Percentage of Injected Dose

Supplemental table 1. Patient characteristics stratified for disease setting

Patient characteristics		*Primary PCa*	*Recurrent PCa*	*mCRPC*
N (% of total)		81/116 (70.0%)	25/116 (22.0%)	10/116 (8.0%)
Age (median + range, in yrs.)		67.0 (49.0-77.0)	70.0 (51.0-84.0)	72.5 (61.0-79.0)
Weight (Kg)		84.0 (65.0-122.0)	82.0 (50.0-115.0)	83.5 (68.0-94.0)
Height (cm)		181.0 (155.0-194.0)	178.0 (167.0-198.0)	177.5 (168.0-185.0)
PSA (ng/mL)		11.1 (1.2-99.0)	5.0 (0.5-120.0)	7.7 (0.5-2790.0)
Gleason score (cum)		7 (6-9)	8 (6-9)	8 (6-9)
Treatment prior to PET/CT (N + % of total)		0/81 (0.0%)	25/25 (100.0%)	10/10 (100.0%)
RALP (N + % of total)		-	14/25 (56.0%)	0/10 (0.0%)
Chemotherapy and ADT (N + % of total)	ADT	-	0/25 (0.0%)	7/10 (70.0%)
	ADT + chemotherapy	-	3/25 (12.0%)	3/10 (30.0%)
Radiotherapy (N + % of total)		-	8/25 (32.0%)	0/10 (0.0%)

% of total = percentage of total patients; yrs = years; Kg = Kilograms; cm = centimeters; ng/mL = nanogram per milliliter; cum = cumulative; RALP = Robot Assisted Laparoscopic Prostatectomy; ADT = Androgen Deprivation Therapy

Graphical abstract