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Original Article

Standardised uptake values as determined on prostate-specific membrane antigen positron emission tomography/computed tomography is associated with oncological outcomes in patients with prostate cancer

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Objectives

To investigate the association between intraprostatic, intratumoral maximum standardised uptake values (SUV_{max}) on prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) in patients with prostate cancer (PCa) prior to robot-assisted radical prostatectomy (RARP) and pathology outcomes, including pathological International Society of Urological Pathology score (pISUP) and lymph node (LN) status (pN0/pN1).

Patients and Methods

A bi-centric, secondary analysis of two previous, prospective cohort studies was performed in 318 patients with biopsy confirmed PCa and who were scheduled for RARP. Before surgery, patients received a PSMA PET/CT with either ^{68}Ga-PSMA-11 (59% of the patients) or ^{18}F-PSMA (DCFPyL; 41%) as radiotracer. PET/CT images were analysed both visually and semi-quantitatively by measuring the SUV_{max} of the most intense suspect lesion in the prostate. The association between the SUV_{max} of the primary tumour and pre- and postoperative variables was analysed.

Results

The SUV_{max} was associated with clinical and biopsy preoperative variables, as well as with pISUP score and pathological tumour stage. Patients with a pISUP of ≤2 showed significantly lower SUV_{max} compared to patients with a pISUP of >2 for both tracers (SUV_{max} ^{18}F-PSMA: median 5.1 vs 9.6, $P = 0.002$; SUV_{max} ^{68}Ga-PSMA-11: 6.6 vs 8.6, $P = 0.003$). Moreover, patients with pN1 had significantly higher median SUV_{max} than those with pN0/pNx for both tracers (SUV_{max} ^{18}F-PSMA: 7.9 vs 12.3, $P = 0.04$; SUV_{max} ^{68}Ga-PSMA-11: 7.6 vs 12.0, $P < 0.001$). On multivariable logistic regression analysis, the intraprostatic SUV_{max} was an independent predictor of pN1 for both ^{68}Ga-PSMA-11 (per doubling: odds ratio [OR] 1.96, 95% confidence interval [CI] 1.27–3.01)) and ^{18}F-PSMA (per doubling: OR 1.79, 95% CI 1.06–3.03).

Conclusion

Intraprostatic, intratumoral PSMA intensity on PET/CT, as semi-quantitatively expressed by SUV_{max}, may be a valuable innovative biomarker in patients with localised PCa, as it is highly associated with known conventional prognostic factors, such as pISUP and LN status.

Keywords

^{18}F-DCFPyL, ^{68}Ga-PSMA-11, prostate cancer, standardised uptake values, biomarkers, #uroonc, #PCSM, #ProstateCancer

Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer in men around the world [1]. Curative therapy for patients with clinically significant and localised PCa includes robot-assisted radical prostatectomy (RARP), brachytherapy, and external beam radiation therapy [2]. Along with RARP, an extended pelvic lymph node dissection (ePLND) is usually indicated for patients with intermediate- and high-risk disease stage, as a staging method for lymph node (LN) involvement [2]. The most common prognostic variables to predict the outcome of patients with PCa after treatment include the PSA level at the time of diagnosis, the biopsy International Society of Urological Pathology (bISUP) score, the percentage of positive biopsies, and the clinical tumour stage [2-4]. These variables have prognostic ability on a group level but not for the individual patient [5,6].

Besides common clinical and pathological prognostic parameters, different imaging modalities may assist clinicians to assess outcome of disease in patients with PCa. Recently, prostate-specific membrane antigen (PSMA) positron-emission tomography (PET)/CT has been introduced as a valuable alternative for conventional imaging. PSMA is usually labelled with ^{68}Gallium (e.g. ^{68}Ga-PSMA-11) or ^{18}Fluorine (e.g. ^{18}F-DCFPyL [PSMA]) and is highly overexpressed in PCa cells [7,8]. PSMA PET/CT has shown diagnostic superiority in detecting PCa metastases, compared to bone scintigraphy and CT scan, especially in the recurrent stage setting of the disease [9-11]. For primary staging purposes, PSMA PET/CT has found its place in the armamentarium of the urologist to select patients for different treatment options [12,13].

Besides visual interpretation of PSMA-PET/CT images, semi-quantitative measurements of PSMA expression, such as by the measurement of standardised uptake values (SUV), can be extracted from the PET/CT scan, conforming with the European Association of Nuclear Medicine (EANM) standardised reporting guidelines for PSMA-PET (E-PSMA) [14]. SUV represents the amount of the tracer uptake in a pre-defined anatomical region on the PET/CT, that usually normalises the lesion activity to the body weight and the injected activity of tracer [15]. Histological studies have shown that increased immunohistochemical PSMA expression is associated with higher tumour grade and disease progression [16,17]. The semi-quantitative measurement of the ^{18}F-PSMA uptake in the dominant intraprostatic lesion on PET/CT, expressed as SUV, might therefore be an alternative imaging biomarker, that, like the immunohistochemical expression of PSMA, may be associated with tumour characteristics and clinical outcome [18].

The aim of this study was to examine if intraprostatic SUV measured from both ^{68}Ga-PSMA-11 and ^{18}F-PSMA PET/CT is associated with well-established prognostic tumour markers, such as pathological ISUP score (pISUP), pathological tumour stage (pT) and pathological LN status (pN).

Patients and Methods

Study Design and Patient Population

This study was a bi-centric, secondary analysis of two previous prospective cohort studies. All consecutive patients with histologically confirmed intermediate- to high-risk PCa received a PSMA-PET/CT scan before RARP, with or without an additional ePLND. Patients were included from August 2016 until August 2020. An ePLND was performed based on a ≥8% risk of LN involvement, as predicted by the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram [19], or in the presence of high-risk features: PSA level of >20 ng/mL, ISUP score 4 and 5, or suspicion of clinical tumour stage (cT)2c or higher [2]. Patients were included in two reference centres of the Prostate Cancer Network Netherlands, the Amsterdam University Medical Center (location VUmc) and the Netherlands Cancer Institute (NCI). This study encompasses a secondary analysis based on two studies that were approved by the local medical ethical committees (review number 2017.543 [VUmc] and review number IRBdm19-348 [NCI]). All patients signed informed consent when enrolled in the original studies, explicitly allowing secondary analysis of their study data.

Preoperative and Postoperative Variables

Preoperative parameters that were assessed included age, initial PSA level, cT, European Association of Urology (EAU) risk classification [2], bISUP, and number of (positive) cores [3]. Postoperative parameters that were assessed included: pISUP as determined in the RARP specimen, pT, pN, and surgical margin status.

PSMA-PET/CT Imaging Protocol

For the VUmc patients, PSMA-PET/CT imaging was performed with ^{18}F-DCFPyL (PSMA), a second-generation fluorinated PSMA radiotracer. The scanner used was a Philips Ingenuity (Philips®, the Netherlands/USA) PET/CT system. ^{18}F-DCFPyL (PSMA) was synthesised at the on-site cyclotron facility according to Good Manufacturing Practices and was also provided to the NCI for imaging purposes. At the NCI, PSMA-PET/CT imaging was performed with both ^{68}Ga-PSMA-11 and ^{18}F-PSMA tracers, using a Philips Gemini TF-II or Vereos Digital PET/CT (Philips®, the Netherlands/USA). The ^{68}Ga-PSMA-11 was radiolabelled in-house using a fully automated system (Scintomics GmbH, Germany). All PET-images were combined with either a low-dose CT scan (120–140 kV, 40–80 mA) or a diagnostic CT scan (130 kV, 110 mA), for attenuation correction and anatomical localisation. All PET images were corrected for scatter, decay,

and random coincidences and were conducted according to EANM Research Ltd. (EARL) standards [20].

Image Interpretation of PSMA-PET/CT Imaging

At both centres, ^{18}F-PSMA and ^{68}Ga-PSMA-PET/CT scans were assessed by nuclear medicine physicians (D.O., M.D.) with ample experience of reading PSMA-PET/CT scans. The PSMA-PET/CT scan results used in this study were based on clinical reports, which were structured in line with the E-PSMA guidelines [14]. This means it included the location of the primary prostate lesion and possible secondary lesions, molecular imaging (mi)T stage and the presence of LN, bone or visceral metastases [21]. Imaging results were primarily based on visual interpretation, relating PSMA uptake to background uptake in the blood, liver, and salivary glands on a visual scale (0–3), as recently proposed [14].

Scan Assessment, SUV Assessment

For semi-quantitative analysis, the SUV_{max} was measured for the most clinically suspect prostatic lesion of each patient and was normalised for body weight. SUV_{max} was chosen because it does not require exact tumour borders as compared to SUV_{mean} [22] and therefore is clinically most used. Suspect lesions were delineated according to the available clinical reports describing the dominant intraprostatic lesion. SUV_{max} was measured according to the E-PSMA criteria and was compliant with EARL standards [14,15]. Volumes-of-interest (VOIs) were manually drawn at least 1.5 cm in diameter over the index lesion, carefully omitting physiological activity from the urethra or bladder. If no PSMA expression suspect for PCa was detected by the nuclear medicine physician, a VOI was drawn over the prostate location corresponding with a suspect lesion on multiparametric MRI (mpMRI), when available. Available clinical software of the Intellispace Portal (Philips®, the Netherlands/USA) and Osirix MD (Pixmeo SARL, Switzerland) were used to calculate the SUV_{max}. To cross-validate both measuring software programs, identical scans from four patients were analysed with both programs, with 100% agreement.

Statistical Analysis

The primary outcome of this study was to determine if intraprostatic, intratumoral SUV_{max} is a prognostic variable associated with known pathological prognosticators of PCa, such as pISUP score, pT stage, and pN stage. To compare the medians of SUV_{max} with ISUP grade, pT stage, surgical margin status, and pN stage, the Mann–Whitney-Wilcoxon test was used for two groups; and the Kruskal–Wallis test was used for multiple groups. The intraprostatic SUV_{max} was compared to initial PSA level by linear regression analysis (R^2) using Pearson's correlation coefficient. A multivariable logistic regression analysis with predefined preoperative variables was performed for both tracers to predict pN1 status after RARP and ePLND, including SUV_{max} of the dominant intraprostatic lesion. For the preoperative analysis, initial PSA level, bISUP score and cT stage were used. Numerical variables were assessed for normality using histogram analysis and were summarised with median values and interquartile ranges (IQRs), categorical variables with proportions. Significance level was set at $P < 0.05$. Statistical analysis was performed using the IBM® Statistical Package for the Social Sciences (SPSS®) for Windows®, version 26 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

A total of 318 patients were included in this study. All patients received a PSMA-PET/CT before RARP of whom 288/318 (91%) underwent ePLND. Included patients had a median (IQR) age of 68.5 (62.4–72.5) years, and a median (IQR) initial PSA-level of 10.4 (7.2–19.8) ng/mL. According to EAU guidelines, 76/318 (23.9%) patients had intermediate-risk PCa and 242/318 (76%) high-risk PCa. The median (IQR) MSKCC risk for pelvic LN metastases was 15% (9.7–34%). Preoperative characteristics of included patients are listed in Table 1.

Scan Characteristics

In total, 129/318 (40%) patients received a ^{18}F-PSMA-PET/CT scan before surgery and 189/318 (59%) patients received a ^{68}Ga-PSMA-11-PET/CT. The ^{18}F-PSMA-PET/CT images were acquired at a median (IQR) of 118 (90–123) min after intravenous injection of a median (IQR) dose of 305.4 (240.2–318.2) MBq. A median (IQR) dose of 98.7 (92.4–104.5) MBq ^{68}Ga-PSMA-11 was administered, and scanning started at a median (IQR) of 48 (44–53) min after injection.

Postoperative Tumour Features

The pathological features after RARP and ePLND are listed in Table 2. When comparing bISUP score to pISUP score, there was under grading of the bISUP in 121/318 (38%) patients, and over grading of bISUP in 59/318 (19%). A total of 112/318 (35%) patients who underwent RARP had positive surgical margins (R1), vs 203/318 (64%) who had free surgical margins (R0). In 68/288 (24%) patients undergoing ePLND, pN1 status was detected at pathological examination. An overview of the diagnostic accuracy of ^{18}F-PSMA PET/CT and ^{68}Ga-PSMA PET/CT is depicted in Table S1.

Table 1 Baseline characteristics of patients undergoing PSMA PET/CT at initial staging for 129 included patients who received a ^{18}F-PSMA PET/CT and 189 patients who received a ^{68}Ga-PSMA-11 PET/CT.

Baseline characteristics		
Median (IQR)	**^{18}F-DCFPyL (*N* = 129)**	**^{68}Ga-PSMA-11 (*N* = 189)**
Age, years	67 (62–71)	69 (65–74)
Prostate volume, mL	40 (33–60)	45 (38–61)
Initial PSA level, ng/mL	10.5 (7.2–20.0)	10.3 (7.3–19.3)
Positive biopsy cores, % of total cores	42 (25–71)	38 (13–67)
MSKCC risk of LN metastases	16 (11–31)	15 (9–36)
***N* (%)**		
EAU risk category [2], *n* (%)		
Intermediate	40 (31)	36 (19)
High	89 (69)	153 (81)
Total	129 (100)	189 (100)
bISUP score*, *n* (%)		
1	3 (2)	16 (9)
2	32 (25)	31 (16)
3	39 (30)	41 (22)
4	35 (27)	67 (35)
5	20 (16)	34 (18)
Total	129 (100)	189 (100)
cT stage, *n* (%)		
1c	46 (36)	68 (36)
2a/b	29 (23)	41 (22)
2c	21 (16)	51 (27)
3a	25 (19)	17 (9)
3b	7 (5)	12 (6)
Total	129 (100)	189 (100)
miN stage, *n* (%)		
miN0	108 (84)	164 (87)
miN1	21 (16)	25 (13)
Total	129 (100)	189 (100)

*ISUP 1 = Gleason score 3 + 3 = 6. ISUP 2 = Gleason score 3 + 4 = 7. ISUP 3 = Gleason score 4 + 3 = 7. ISUP 4 = Gleason score 4 + 4 = 8/ Gleason score 3 + 5 = 8 /Gleason score 5 + 3 = 8. ISUP 5 = Gleason score 4 + 5 = 9/Gleason score 5 + 4 = 9/Gleason score 5 + 5 = 10. *ISUP Definition.*

Associating Intraprostatic SUV_{max} with Initial PSA level and Postoperative Outcomes

Patients who received an ^{18}F-PSMA-PET/CT scan before surgery had a median (IQR) SUV_{max} of the intraprostatic dominant lesion of 7.8 (5.8–13.8). A clinical example of a patient receiving both a ^{18}F-PSMA-PET/CT and RARP with corresponding intraprostatic SUV_{max} is shown in Fig. 1. For patients who received ^{68}Ga-PSMA-11-PET/CT, the median (IQR) SUV_{max} of the intraprostatic dominant lesion was 8.1 (4.9–14.5). On univariable analysis, initial PSA level showed a statistically significant, but weak correlation with SUV_{max} for both tracers ((^{18}F-PSMA: $R^2 = 0.09$, $P < 0.001$; ^{68}Ga-PSMA-11: $R^2 = 0.02$, $P < 0.03$), as shown in Fig. 2.

When assessing pISUP, patients with pISUP ≤2 had a significantly lower SUV_{max} compared to patients with pISUP >2 for both tracers (SUV_{max} ^{18}F-PSMA: 5.1 vs 9.6, $P = 0.002$; SUV_{max} ^{68}Ga-PSMA-11: 6.6 vs 8.6, $P < 0.001$). Overall, the intraprostatic SUV_{max} scores were statistically different for pISUP for both tracers (SUV_{max} ^{18}F-PSMA, $P = 0.01$; SUV_{max} ^{68}Ga-PSMA-11, $P = 0.007$), as shown in Fig. 3A.

When assessing pT stage, patients with pT3a/b receiving ^{68}Ga-PSMA-11-PET/CT had a statistically significant higher median intraprostatic SUV_{max} than patients who had pT2 (6.9 vs 9.9, $P = 0.01$; Fig. 3B). There was no significant difference in median SUV_{max} for different pT stages for ^{18}F-PSMA-PET/CT (7.5 vs 8.6, $P = 0.1$). For patients receiving ^{68}Ga-PSMA-11-PET/CT, those with a positive surgical margin had a significantly higher median intraprostatic SUV_{max} than those who had negative surgical margins (9.6 vs 7.3, $P = 0.009$; Fig. 3C). No significant difference in median SUV_{max} for surgical margin status was found for ^{18}F-PSMA-PET/CT (7.7 vs 9.0, $P = 0.1$).

Finally, patients with PCa with pN1 in the LND specimens had significantly higher median SUV_{max} than those with pN0/pNx for both tracers (SUV_{max} ^{18}F-PSMA: 7.9 vs 12.3, $P = 0.04$; SUV_{max} ^{68}Ga-PSMA-11: 7.6 vs 12.0, $P < 0.001$; Fig. 3D).

The Prognostic Value of Intraprostatic SUV_{max} using Multivariable Analysis

When analysing preoperative parameters, including intraprostatic, intratumoral SUV_{max}, cT stage, PSA level, and bISUP grade, the only independent variables for the prediction of pN1 disease on multivariable analysis were ^{68}Ga-PSMA-11-PET/CT intraprostatic SUV_{max} (per doubling: odds ratio [OR] 1.96, 95% CI 1.27–3.01; $P = 0.002$), and ^{18}F-PSMA-PET/CT intraprostatic SUV_{max} (per doubling: OR 1.79, 95% CI 1.06–3.03; $P = 0.03$; Table 3).

Discussion

The aim of this study was to examine if intraprostatic intratumoral PSMA uptake, as determined by SUV_{max} on PSMA-PET/CT, is associated with conventional prognostic variables in patients with intermediate- to high risk primary PCa undergoing RARP. Two commonly used PSMA tracers (i.e. ^{68}Ga-PSMA-11 and ^{18}F-PSMA) were analysed. In this study, significant associations were found between PSMA-PET/CT median SUV_{max} of the dominant intraprostatic lesion and pISUP for both studied tracers, and between SUV_{max} and surgical margin status and pT stage for ^{68}Ga-PSMA-11. Additionally, a significantly higher median PET/CT lesional SUV_{max} was found for positive pelvic LN status (pN1) compared to negative pelvic LN status (pN0) for both tracers. On multivariable analysis, when multiple preoperative variables were assessed for their ability to predict LN metastatic disease after surgery, the median PET/CT SUV_{max} of the dominant intraprostatic lesion proved to be an

Table 2 Characteristics of patients undergoing RARP and EPLND for 129 included patients who received a ^{18}F-DCFPyL PET/CT and 189 patients who received a ^{68}Ga-PSMA-11 PET/CT.

Pathology results	^{18}F-PSMA *N* (%)	^{68}Ga-PSMA-11 *N* (%)
Pathological ISUP score [2]*		
1	3 (2.3)	3 (1.6)
2	44 (34)	67 (35)
3	49 (38)	68 (36)
4	7 (5.4)	20 (10)
5	24 (19)	30 (16)
n.a.†	2 (1.6)	2 (1.1)
Total	129 (100)	189 (100)
pT stage		
pT2	58 (45)	87 (46)
pT3a	43 (33)	54 (29)
pT3b	25 (19)	48 (25)
n.a.†	2 (1.6)	2 (1.1)
Total	129 (100)	189 (100)
pN stage		
N0	102 (79)	118 (62)
N1	21 (16)	47 (25)
Nx	6 (4.7)	24 (13)
Total	129 (100)	189 (100)
Surgical margin status (R)		
R0	85 (63)	119 (63)
R1	42 (31)	70 (25)
n.a.†	2 (1.6)	2 (1.1)
Total	129 (100)	189 (100)

*n.a., not available. ISUP 1 = Gleason score 3 + 3 = 6. ISUP 2 = Gleason score 3 + 4 = 7. ISUP 3 = Gleason score 4 + 3 = 7. ISUP 4 = Gleason score 4 + 4 = 8/Gleason score 3 + 5 = 8/Gleason score 5 + 3 = 8. ISUP 5 = Gleason score 4 + 5 = 9/Gleason score 5 + 4 = 9/Gleason score 5 + 5 = 10. *ISUP definition. †In two patients, ePLND was successfully performed, yet surgical removal of the prostate proved unfeasible due to extensive intraoperative bleeding.*

independent prognostic factor for pN1 disease for both tracers.

To our knowledge, we report on the first series of patients comparing SUV_{max} on ^{18}F-PSMA-PET/CT to clinical outcomes, and on the largest ^{68}Ga-PSMA-11 cohort to date [18,23,24]. Moreover, this study reports on the first large series of patients describing the association of SUV_{max} with pN status for both nuclear tracers. When the SUV_{max} on PSMA PET/CT of the intraprostatic lesion was assessed, patients with pISUP 1–2 had statistically lower values than those with pISUP 3–5, for both tracers (SUV_{max} ^{18}F-PSMA: 5.1 vs 9.6, $P = 0.002$; SUV_{max} ^{68}Ga-PSMA-11: 6.63 vs 8.63, $P < 0.001$). This outcome confirms previous immunohistochemical staining studies showing that increased PSMA protein expression is associated with higher tumour grade and disease progression [16,17]. Demirci *et al.* [23] retrospectively evaluated 141 patients with intermediate- and high-risk primary PCa, who received ^{68}Ga-PSMA-11-PET/CT imaging before RARP. In line with our results, that study group also reported a higher mean SUV_{max} for pISUP 3–5 patients compared to pISUP 1–2 patients (18.9 vs 7.2, $P < 0.001$) [23]. Unfortunately, one of the drawbacks of that study was that it had a bi-centric set-up that led to a wide range of the applied ^{68}Ga-PSMA-11 doses (113–384 MBq). This again might have caused inaccuracies of interpretation, as SUV_{max} is highly dependent on dosage [25]. Again, in a recent retrospective study by Roberts *et al.* [18] evaluating 71 patients with biopsy confirmed PCa who received ^{68}Ga-PSMA-11-PET/CT before RP, a strong association between pISUP ≥3 and PET/CT intraprostatic SUV_{max} ($P = 0.01$) was observed.

An association of SUV_{max} and pISUP is important as it is known that the bISUP is not directly comparable to pISUP due to under and over grading of the biopsy Gleason score compared to that in the RP specimen [26]. Therefore, the assessment of SUV_{max} on diagnostic PSMA-PET/CT imaging might predict the pISUP more reliably before treatment than when a prediction of pISUP is made based on the bISUP and other clinical variables alone. For instance, if SUV_{max} predicts high pISUP in those with a low bISUP and a low initial PSA level, a more aggressive approach could be followed, whereas in those with low SUV_{max}, a more conservative approach or an adaption of treatment could be made. The previous PRIMARY study by Emmett *et al.* [27] investigated the biopsy outcomes of patients with an increased risk of PCa. In that prospective trial including 296 men, patients received a ^{68}Ga-PSMA PET/CT and mpMRI before prostate biopsy. The ^{68}Ga-PSMA PET/CT and mpMRI improved the negative predictive value and sensitivity for detecting clinically significant (cs)PCa in a mpMRI-triaged population. In that study, SUV_{max} was associated with higher bISUP ($P < 0.001$). In fact, all men with a SUV_{max} of ≥12 had csPCa on prostate biopsy, independent of mpMRI findings. Furthermore, in men with mpMRI Prostate Imaging-Reporting and Data System (PI-RADS) 4 or 5, a SUV_{max} of ≥9 classified csPCa with 100% specificity, meaning that patients with a positive mpMRI and high SUV_{max} on PSMA PET/CT might be omitted prostate biopsy. Although our study consisted of patients with biopsy confirmed patients undergoing RARP, like Emmett *et al.* [27], SUV_{max} was highly associated with pISUP. Future randomised studies will determine whether biopsy can safely be omitted in men with a high clinical suspicion of csPCa but with low SUV_{max} on diagnostic PSMA PET/CT.

In the present study, significantly higher median PET/CT SUV_{max} of the intraprostatic lesions was found in patients with pT3a/b disease, compared to patients with pT2 disease for the ^{68}Ga-PSMA-11-PET/CT cohort (9.9 vs 6.9, $P = 0.01$). Again, an adaption of the treatment plan could be made if a higher-than-expected median SUV_{max} of the dominant lesion was reported on diagnostic PSMA-PET/CT. For example, the surgical plan could be changed to perform non-nerve sparing surgery or an ePLND in those with suspicion of capsular penetration or invasion of the seminal vesicles on PSMA

Fig. 1 A 70-year-old man with cT2a, ISUP 2 (systematic TRUS biopsy) PCa and initial PSA level of 11 ng/mL was considered a candidate for RP with ePLND. The MSKCC nomogram showed an 8% risk of LN involvement. Fused ^{18}F-PSMA PET/CT transversal view of the pelvic region (**A**) revealed high local PSMA expression mostly in the left side of the prostate from the apex to base, without seminal vesicle involvement. The SUV_{max} of this index lesion was 36.5. Transversal view CT only (**B**), fused PET/CT coronal view (**C**), and maximum intensity projection image (**D**) show a right sided para-iliacal LN measuring 7 mm, suspicious for a PCa metastasis. No suspicion of a PCa-LN metastasis on the left side existed. Histopathological analysis showed a pT3a, pISUP 5 PCa in the RP specimen. Two LN metastases were found after histopathological analysis of 26 resected LNs, one left-sided in the iliac region and one right-sided iliac LN.

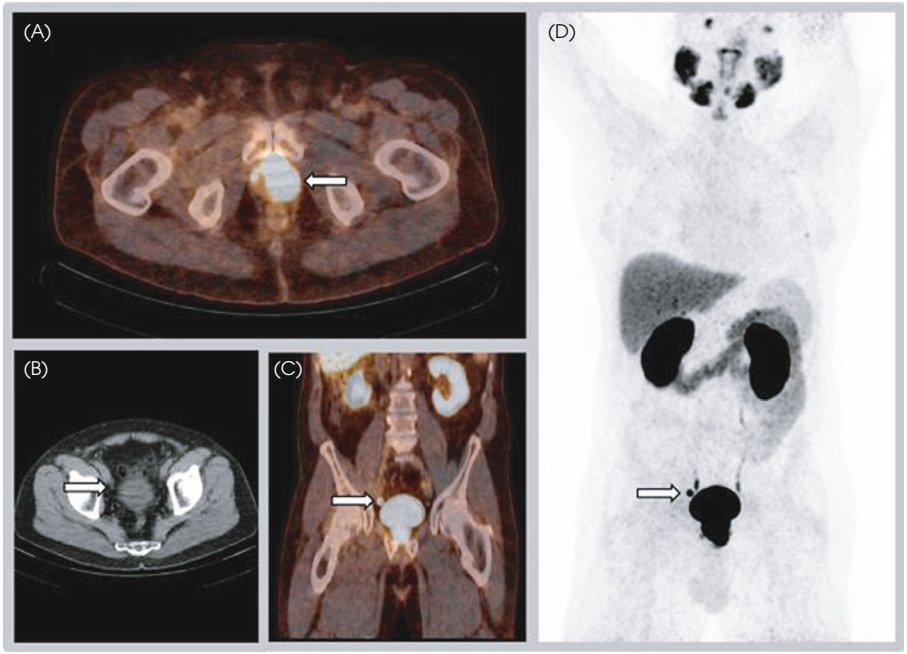
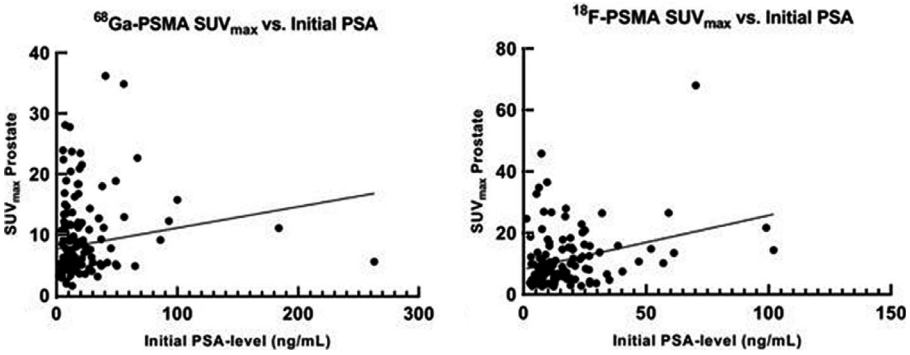


Fig. 2 Association between initial PSA-level and both ^{68}Ga-PSMA-11 and ^{18}F-PSMA SUV_{max}. The scatter plots show the correlation between PSA level and SUV_{max} value of the prostate, which shows low correlation for both tracers (^{18}F-DCFPyL, $R^2 = 0.09$, $P < 0.001$; ^{68}Ga-PSMA-11, $R^2 = 0.02$; $P < 0.03$).



PET/CT and who also have a high SUV_{max} of the dominant lesion.

Moreover, higher intraprostatic SUV_{max} on ^{68}Ga-PSMA-11-PET/CT was found in patients with positive surgical margins (R1). This association was confirmed by the study of Roberts *et al.* [18] who showed an independent prognostic association between SUV_{max} and margin status on multivariable analysis ($P < 0.001$). In a study by Wang *et al.* [28], that studied 195 patients receiving a ^{68}Ga-PSMA-11-PET/CT for initial staging before RARP, an association was reported between SUV_{max} and surgical margin status on univariate analysis ($P = 0.04$). The SUV_{max} was not found to be an independent variable for surgical margin status when assessed along other imaging parameters such as tumour volume, miN status, miT stage. In a multivariate analysis, only miN status was found to be an independent predictive parameter. In the present study, no

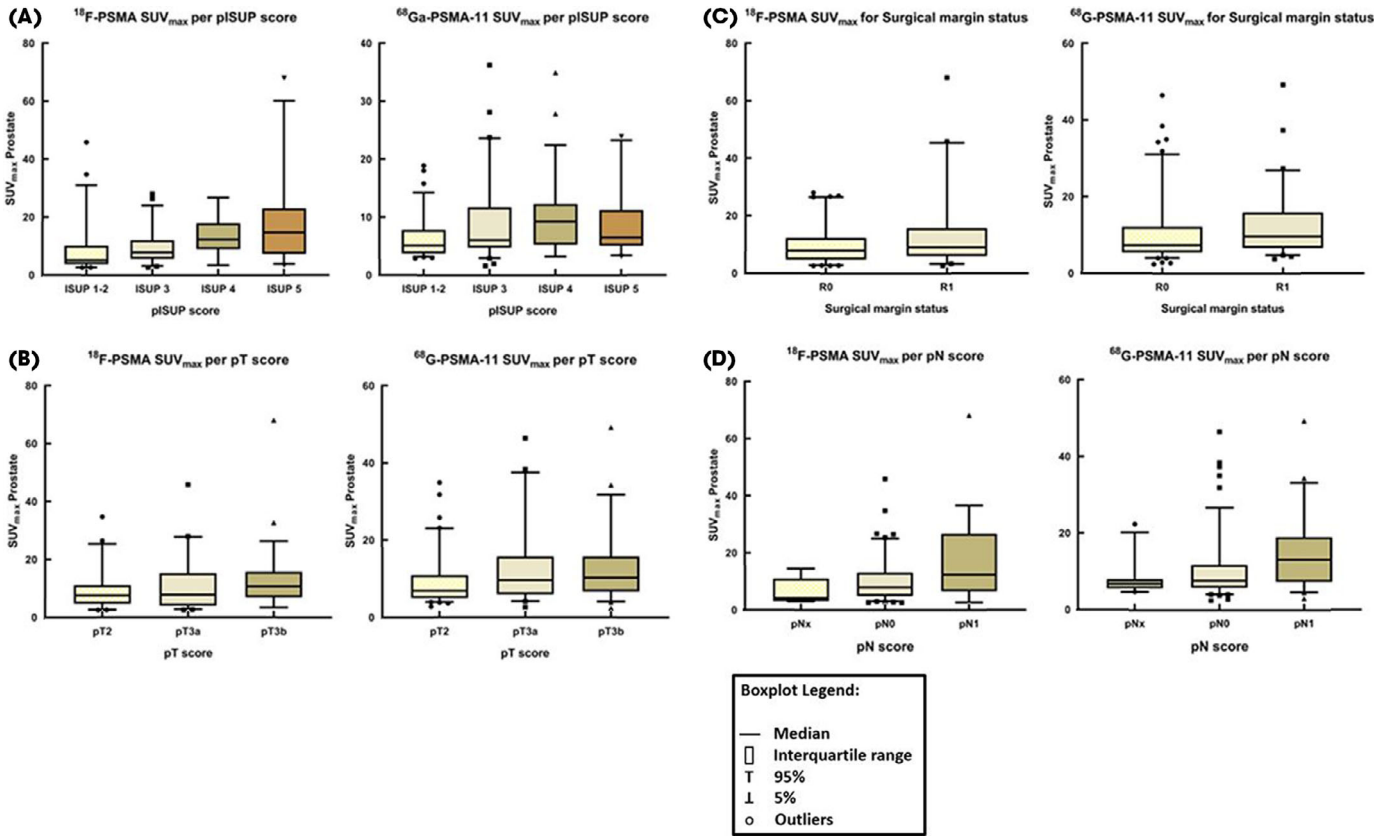


Fig. 3 Box plots of SUV_{max} scores of the dominant intraprostatic lesion for both ^{18}F-PSMA PET/CT and ^{68}Ga-PSMA-11 PET/CT, stratified by pathological ISUP scores (**A**), pT stage (**B**), surgical margin status (**C**), and pN stage (**D**).

Table 3 Multivariable logistic regression analysis to predict pN1 after RARP with ePLND in 318 patients with intermediate- and high-risk PCa using predefined preoperative variables, including intraprostatic, intratumoral SUV_{max}, cT stage, PSA level, and bISUP grade. Effect sizes are presented as ORs with 95% CIs.

	^{18}F-PSMA		^{68}Ga-PSMA-11	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
log_2 (Initial PSA value)	0.76 (0.47–1.23)	0.3	1.02 (0.74–1.41)	0.9
log_2 (SUV_{max} prostate)	1.79 (1.06–3.03)	0.03	1.96 (1.27–3.01)	0.002
Prostate biopsy grade group according to ISUP*				
1–2				
3	1.10 (0.26–4.68)	0.9	1.07 (0.33–3.53)	0.9
≥4	1.57 (0.43–5.77)	0.5	1.63 (0.62–4.28)	0.3
cT stage				
cT1				
cT2 (a,b,c)	0.56 (0.20–1.59)	0.3	1.74 (0.73–4.13)	0.2
cT3(a,b)	0.71 (0.06–8.50)	0.8	1.77 (0.59–5.35)	0.3

*ISUP 1 = Gleason score 3 + 3 = 6. ISUP 2 = Gleason score 3 + 4 = 7. ISUP 3 = Gleason score 4 + 3 = 7. ISUP 4 = Gleason score 4 + 4 = 8/Gleason score 3 + 5 = 8/Gleason score 5 + 3 = 8. ISUP 5 = Gleason score 4 + 5 = 9/Gleason score 5 + 4 = 9/Gleason score 5 + 5 = 10. *ISUP definition.*

significant association was found between SUV_{max} in the ^{18}F-PSMA cohort for both pT stage and surgical margin status. These findings cannot be explained by a difference in demographical or surgical characteristics between the cohorts studied with the different tracers. Possibly, the smaller sample size could have been responsible for this lack of association. When analysing the difference between the two tracers in terms of outcomes based on visual interpretation, previous studies have shown no significant differences between ^{18}F-PSMA and ^{68}Ga-PSMA-11 [11,29,30].

The multivariable analysis comparing preoperative parameters to LN status showed that SUV_{max} remained an independent predictor for pN1 disease for both tracers

(^{18}F PET/CT per doubling: OR 1.96, 95% CI 1.27–3.01; and ^{68}Ga PET/CT per doubling: OR 1.79, 95% CI 1.06–3.03). Preoperative parameters such as initial PSA and bISUP score were not prognostic of pN status. These findings seem to contrast with previous reports [19,31]. The multivariable result that PSA was not a prognostic factor for positive LN status in the presence of SUV_{max} seems intuitive as the association between PSA values and SUV_{max} was only weak on univariate analysis for both tracers. This is in contrast with a study by Uprimny *et al.* [24], who studied 90 patients receiving a ^{68}Ga-PSMA-11-PET/CT for initial staging, and who found a stronger association between PET/CT intraprostatic SUV_{max} and the initial PSA level ($R = 0.506$, $P < 0.001$). When analysing the postoperative variables in the multivariable analysis in our study to predict pN1 status, significant predictors in the ^{68}Ga-PSMA-11-PET/CT cohort included the intraprostatic SUV_{max} as well as the known predictors such as positive surgical margin status, pISUP >3, and the presence of pT3. For the ^{18}F-PSMA-PET/CT cohort, only pT3 stage was a significant predictor for the pN1 status, which can be explained by the discrepancies displayed in the cohort before.

As a limitation, the histopathological LN metastasis rate might have been underreported due to unresected LN metastases on surgical excision or due to undetected LNs on pathological examination. However, this is not a study-specific limitation, but rather a general limitation that is inherent to the ePLND template and pathological examination. As a final point, the delineation of VOIs by two observers can result in inter-observer variability, due to the manually drawn in mask around the PSMA-avid dominant intraprostatic lesion to rule out bladder activity interference. The validation of the mask by a second observer was deployed to reduce inter-observer variability. Also, as a validation of the method, the delineations were performed by both observers in four cases, which resulted in a 100% agreement of SUV_{max} level.

Based on present results, SUV_{max} could have a role in predicting pathological tumour characteristics and clinical outcomes in patients with intermediate- to high risk primary PCa undergoing PSMA-PET/CT imaging before radical surgery. For future studies, intraprostatic SUV_{max}, as measured on PSMA-PET/CT, could be an addition to future initial staging nomograms, thereby helping the clinician in treatment selection and shared decision-making [19,32].

Conclusion

This study evaluated the prognostic value of intraprostatic, intratumoral SUV_{max} for ^{68}Ga-PSMA-11 and ^{18}F-PSMA-PET/CT before RARP. An association was found between median intraprostatic SUV_{max} on PET/CT and conventional prognostic tumour characteristics, such as pISUP and pN stage in patients with primary intermediate- to high-risk PCa. The SUV_{max} remained an independent predictive factor for pN1 status on multivariable analysis. Therefore, PSMA-PET/CT has the potential to be of value for the preoperative prediction of intraprostatic tumour aggressiveness features. Further research is needed to examine the prognostic value of SUV_{max} by PSMA PET/CT as a future biomarker in the primary staging of intermediate- to high-risk PCa.

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Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Abbreviations: bISUP, biopsy ISUP score; cT, clinical tumour stage; EANM, European Association of Nuclear Medicine; EARL, EANM Research Ltd; EAU, European Association of Urology; E-PSMA, EANM standardised reporting guidelines for PSMA-PET; IQR, interquartile range; ISUP, International Society of Urological Pathology: LN, lymph node; (eP)LND, (extended pelvic) LN dissection; mi, molecular imaging; mpMRI, multiparametric MRI; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, Netherlands Cancer Institute; (cs)PCa, (clinically significant) prostate cancer; PET, positron emission tomography; pISUP, pathological ISUP score; pN, pathological LN status; PSMA, prostate-specific membrane antigen; pT, pathological tumour stage; (RA)RP, robot-assisted radical prostatectomy; $SUV_{(max)}$, (maximum) standardised uptake values; VOI, volume of interest; VUmc, Amsterdam University Medical Center.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. The diagnostic value of (**A**) ^{18}F-PSMA PET/CT and (**B**) ^{68}Ga-PSMA PET/CT for detecting lymph-node metastatic disease, and (**C**) the size of PET/CT detected and missed LN metastases after PLND.