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# Positive predictive value and correct detection rate of $^{18}$F-rhPSMA-7 PET in biochemically recurrent prostate cancer validated by composite reference standard

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**Running title:** Correct Detection Rate of $^{18}$F-rhPSMA-7 for BCR

**Conflicts of interest:** Patent application for rhPSMA (ME, HJW, AW). ME and WW are consultants for Blue Earth Diagnostics (licensee for rhPSMA). HJW is founder, shareholder and advisor board member of Scintomics GmbH, Fuerstenfeldbruck, Germany.

**Abstract**

The objective of this retrospective study was to assess the detection rate (DR), positive predictive value (PPV) and correct detection rate (CDR) of $^{18}$F-rhPSMA-7 PET/CT in biochemical recurrence (BCR) of prostate cancer (PCa) after radical prostatectomy (RP) using composite validation.

**Methods:** $^{18}$F-rhPSMA-7 PET/CT scans of patients with BCR between July 2017 and June 2018 were retrospectively reviewed. All suspicious lesions were recorded. Reference standard was histopathology or combinations of histopathology, imaging or prostate-specific antigen (PSA) follow up, defined as composite reference standard. DR was calculated as the proportion of PSMA PET positive patients to all patients independent of the reference standard, while the CDR was the percentage of patients who had at least one true positive PSMA PET lesion localized that corresponded with the reference standard. The PPV was defined as the proportion of patients who had true positive to all positive findings. The correlation between DR and patient characteristics was evaluated.

**Results:** A total of 532 patients with a median PSA level of 0.97 ng/mL (IQR: 0.41-2.46 ng/mL) were included. Out of these, 162 patients had composite follow-up at a median duration of 5.6 months (range 1.1-14.2 months). The proportion of patients who had no lesion visualized on PET/CT, localized disease, and any distant metastases (M1) were 20%, 43% and 37%, respectively. PET DR among all patients was 80%. On per-patient basis, the PPV of $^{18}$F-rhPSMA-7 PET/CT in the composite cohort was 88%, and the CDR was 70%. The PPV in the histopathology-proven cohort was 91%, and the CDR in this subgroup was 73%.

In patients with PSA levels ≥1 ng/mL the DR and PPV were 90% and 91%, respectively resulting in a CDR of 82%. In patients with PSA levels <1 ng/mL the DR and PPV were 69% and 85%, respectively resulting in a CDR of 59%. There was a significant positive correlation between $^{18}$F-rhPSMA-7 PET/CT detection efficacy and stratified PSA levels (P=0.005), as well as PSA nadir after prostatectomy (P<0.001).

**Conclusion:** $^{18}$F-rhPSMA-7 PET/CT offers high PPV in BCR after RP. Its CDR is dependent on the pre-scan PSA value with excellent CDR in patients with PSA ≥1 ng/mL.

**Keywords**

Biochemical recurrence; positron emission tomography; prostate-specific membrane antigen; correct detection rate; positive predictive value

## INTRODUCTION

Biochemical recurrence (BCR) of prostate cancer (PCa) after initial curative treatment is frequent, especially in patients with high-risk disease. Early and localized detection of recurrent PCa is essential to plan further local or systemic treatment. Early initiation of localized salvage therapy in localized disease lowers the risk of metastasis and decreases prostate cancer–specific mortality (*1,2*). Failure of salvage treatments is known to be related to incomplete tumor localization and therefore inadequate treatment strategies (*1*).

Radiolabelled-prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/ computed tomography (CT) imaging is currently regarded as the most sensitive and precise imaging modality for localization of BCR of PCa (*3,4*). Multiple prospective and retrospective studies and recent meta-analyses indicate a high accuracy of $^{68}$Ga-PSMA-11 (*5-8*). Currently, $^{18}$F-labelled PSMA-ligands are increasingly being evaluated given their advantages such as longer half-life and with this facilitated large-scale production for broad distribution. Further they offer a potentially higher image resolution due to lower positron range when compared with $^{68}$Ga-labelled agents. They showed excellent diagnostic performance in men with BCR of PCa (*9-11*), but the clinical impact is yet to be explored (*12*). $^{18}$F-rhPSMA-7 is one of a new class of radiohybrid (rh) PSMA-ligands that provides the unique opportunity of both fluorination and chelation using radiometals ($^{68}$Ga, $^{177}$Lu-177).

Data on detection rate (DR) of $^{18}$F-rhPSMA-7 in BCR after radical prostatectomy (RP) have recently been published (*11*). However, the report is lacking information on the validation of positive lesions which is important to assess the diagnostic accuracy.

Our aim was to establish the positive predictive value (PPV) and the correct detection rate (CDR) validated by a standard of truth for $^{18}$F-rhPSMA-7 PET/CT in an expanded cohort of patients with BCR after radical prostatectomy.

## MATERIALS AND METHODS

### Patients

A total number of 532 patients who underwent a clinically indicated $^{18}$F-rhPSMA-7 PET/CT for BCR between July 2017 and June 2018 were retrospectively evaluated. A subcohort of the patients in this work was already included in a prior analysis (*11*). Patients who have undergone RP either as a primary treatment or a salvage treatment after external beam radiation therapy with curative intent were included. Clinical data are presented in table 1. The median PSA-level at the time of $^{18}$F-rhPSMA-7 PET/CT was 0.97 ng/mL (IQR: 0.41-2.46 ng/mL).

All patients gave written informed consent before the $^{18}$F-rhPSMA-7 PET/CT imaging. All reported investigations were conducted in accordance with the Helsinki Declaration and with national regulations. The retrospective analysis was approved by the local Ethics Committee (permit 290/18S) and the requirement to obtain informed consent for data collection was waived. The administration of $^{18}$F-rhPSMA-7 complied with The German Medicinal Products Act, AMG §13 2b, and the responsible regulatory body (Government of Oberbayern).

### $^{18}$F-rhPSMA-7 PET/CT imaging and image interpretation

$^{18}$F-rhPSMA-7 was synthesized and PET/CT scans were performed as described previously (*11*). Shortly, PET scans were acquired in 3D mode, together with intravenous and oral contrast-enhanced CT. The mean activity of $^{18}$F-rhPSMA-7 was 331 MBq (IQR 296-364 MBq) and the mean uptake time was 80 minutes (IQR 67-89 minutes). Images were reviewed by an

experienced, board-certified nuclear medicine physician and a board-certified radiologist. The Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria were used for lesion assessment (*13*). All suspicious lesions were categorized into four regions (prostate bed, pelvic nodes, extrapelvic nodes/non-bone metastases, and bone metastasis) with a total of 21 subregions using the miTNM framework (*13*).

**Lesion detection and validation**

DR was defined as the proportion of PSMA PET positive patients to all patients independent of the reference standard, while the CDR was the percentage of patients who had at least one true PSMA PET positive lesion localized that corresponded with a reference standard. The PPV was the proportion of patients who had true positive findings divided by any positive.

The follow up data, including proven histopathology (either by biopsy or surgery), imaging and/or PSA follow up after local/focal therapy, of all patients was reviewed. The combinations of above-mentioned follow up data (priority in descending order) were defined as composite reference standard. The validated positive lesions in $^{18}$F-rhPSMA-7 PET were recorded as true or false positive. True negative was not defined.

**Statistical analysis**

DRs were compared in each stratified PSA value subgroups using Pearson's chi-squared test with a two-sided significance level of 0.05. True and false negative regions could not be determined since PET-negative regions were not be biopsied or followed up upon, thus the

specificity of the test could not be calculated. Statistical analysis was performed with MedCalc software (version 13.2.0, 2014; MedCalc, Ostend, Belgium).

## RESULTS

### Positive predictive value and correct detection rate

The DR of $^{18}$F-rhPSMA-7 PET in the entire cohort was 80% (423/532 patients, figure 1). From all patients, 162 of 532 patients (30%) had follow-up after PET with a median duration of 5.6 months (range 1.1-14.2 months). Most of these patients had follow up based on imaging (115 patients, 71%), while 22 patients (14%) and 25 patients (15%) had histopathologic and PSA follow-up after targeted treatment, respectively. PSA follow up was used as a part of the lesion validation in patients who received external beam radiation as focal salvage therapy without systemic therapy. The detailed patients' characteristics and PSA response in this subgroup are shown in the supplementary table 1 and supplementary figure 1, respectively. A patient example is shown in figure 2.

In the composite-validated cohort, 143 of 162 patients (88%) had been validated as true positive, resulting in per-patient PPV of 88% (95%CI 82-92%). An example is shown in supplementary figure 2. Based on a DR of 80%, the estimated CDR in the composite-validated cohort was 70%. For the histopathologic-validated subgroup, the per-patient PPV was 91% (95%CI: 72-97%), and the estimated CDR was 73%. PPVs according to a region-based analysis in both validated subgroups are demonstrated in table 2.

In patients with PSA level ≥1 ng/mL DR and PPV were 90% and 91%, respectively resulting in a CDR of 82%. In patients with PSA level <1ng/mL DR and PPV were 69% and 85%, respectively resulting in a CDR of 59% (table 3).

### Discordant results between $^{18}$F-rhPSMA-7 PET positivity and validation

From a total of 23 PET positive lesions in histopathology-validated cohort, 3 lesions (13%) were confirmed as non-prostate cancer-related. These comprised 1 lesion in the prostatic bed and 2 bone lesions. A $^{18}$F-rhPSMA-7 PET-positive, but biopsy-proved negative bone lesion is shown in figure 3. Eleven lesions were false positive lesions by imaging follow up. These lesions were found in pelvic lymph nodes (6/11 regions, 55%), bone (1/11 regions, 9%), prostate bed (2/11 regions, 18%), and visceral organs (2/11 regions, 18%) as detailed in supplemental tables 2, 3 and 4. Eight lesions were non-evaluable (neither true nor false positive) and were excluded from the analysis (details in supplemental tables 5 and 6).

**PET disease extent according to miTNM staging**

The miTNM stage by $^{18}$F-rhPSMA-7 PET/CT is shown in table 4. Localized disease (TrN0M0, T0N1M0, TrN1M0) was present in 43% of patients, which could be possible candidates for salvage treatment. M1-disease was present in 37% of patients. These patients evenly presented with or without loco-regional disease (Tr / N1). Only a minority of these patients had a single type of distant metastases (M1a vs. M1b vs. M1c). Distribution of different miTNM stages was substantially different in the composite cohort (less Tr, more any M1 disease) given the approach how lesions were validated.

**Correlation of lesion detection efficacy with clinical parameters**

Detection rate significantly increased with PSA value with a DR of 58%, 87%, 85%, 93%, and 95% for PSA value <0.5 ng/mL, 0.5 - <1.0 ng/mL, 1.0 - <2.0 ng/mL, 2.0 - <5.0 ng/mL, and ≥5.0 ng/mL, respectively (figure 4). $^{18}$F-rhPSMA-7 PET/CT positivity significantly correlated with

a post RP PSA-nadir of ≥0.1 ng/mL (P=0.005). In contrast, PSA doubling time (dtPSA), Gleason score, TNM staging, and time from initial therapy to PSMA PET did not significantly correlate with PET DR as shown in table 5.

In the subgroup of patients (n=166) with very low PSA (<0.5 ng/mL), 42% of the patients had a negative scan. PSMA PET-positive lesions in this subgroup were mainly located exclusively in the prostatic bed (45%). In the subgroup of patients (n=206) with low PSA (PSA value from 0.5 to <2.0 ng/mL), 47% of these patients had either local or regional pelvic node recurrence, while about one-third of them (26% for PSA 0.5 to <1.0 ng/mL, and 31% for PSA 1.0 to <2.0 ng/mL) had recurrence in multiple regions.

The proportion of patients, who had recurrence in multiple regions, increased with rising PSA value, and notably when the PSA value increased above 2 ng/mL. The percentage of recurrence in multiple regions was 13%, 26%, 31%, 62%, and 69% for PSA values <0.5 ng/mL, 0.5 - <1.0 ng/mL, 1.0 - <2.0 ng/mL, 2.0 - <5.0 ng/mL, and ≥5.0 ng/mL, accordingly.

**DISCUSSION**

Our retrospective study aimed at exploring the PPV and CDR of $^{18}$F-rhPSMA-7 PET/CT for the detection and localization of BCR in a large homogenous population of patients after RP with a focus on lesion validation by histopathology or a composite standard of truth. Our results indicate that – similar to other PSMA-ligands for PET imaging – $^{18}$F-rhPSMA-7 is effective in detecting tumor lesions even at a low PSA value (*14*). In more than half of the patients, lesions could be detected even at low PSA values < 0.5 ng/mL.

The PPV of $^{18}$F-rhPSMA-7 in a histopathology-validated cohort was similarly high (91%) when compared to other PSMA PET studies (ranges from 79% to 100%) summarized in a meta-analysis (*6*). However, composite validation delivered lower rates indicating specific challenges especially for validation by follow-up imaging (e.g. insufficient size changes, lack of morphological correlates from PSMA-ligand positive lesions). The PPV of 88% confirmed by composite validation in our analysis was similar to data from a recent prospective phase III bicentric trial for $^{68}$Ga-PSMA-11 (*15*) and early data reported for the CONDOR trial using $^{18}$F-DCFPyL (84.8% to 87.0% for three blinded independent readers) (*12,16*). In principle it is difficult to compare the PPV across different studies because of the different approaches used to validate lesions in the absence of histopathological validation.

The CDR is a new term aims to represent the detection efficacy of $^{18}$F-rhPSMA-7 PET that was proven as true positive by composite validation. This retrospective study represents the first work to uses CDR as an outcome parameter. The estimated CDR varied according to patients' PSA levels, ranging from 59% in patients with low PSA (<1 ng/mL), to 82% in patients with PSA ≥1 ng/mL. The results  demonstrate that with both a lower DR and PPV in lower PSA

values, CDR as an outcome measurement currently investigated in phase III trials needs to clearly be adjusted to the patient population (CONDOR trial NCT03739684, and SPOTLIGHT trial NCT04186845).

Of note, the criteria and method of lesion validation plays an important role in the CDR evaluation. In our study, the majority of false positive lesions validated by imaging follow-up were pelvic lymph nodes. Misinterpretation during imaging follow-up could occur for several reasons – most likely slow growth of recurrent tumor not fulfilling the pre-specified validation criteria. False positive lesions could be related to ganglia mimicking lymph nodes or PSMA-ligand uptake in reactive nodes (*17,18*). PSMA-PET positive bone lesions (designated as non-evaluable lesion based on the applied criteria) are another source of difficult validation.

The DR of $^{18}$F-rhPSMA-7 PET/CT increases with higher strata of PSA similar to other PSMA PET tracers (*6,8-10*). $^{18}$F-rhPSMA-7 has potential benefit over $^{68}$Ga-PSMA tracers for restaging in patients with low PSA range (0.5 to <1.0 ng/mL) as shown by the higher DR of $^{18}$F-rhPSMA-7 compared to $^{68}$Ga-PSMA studies (87% vs. 53% to 73%) (*5,6,8,19-21*), with comparably excellent results in patients with PSA values >2 ng/mL. In our study, the PSA-nadir significantly correlated with PSMA positivity, while the PSA doubling time did not. This is e.g. contrary to recent results for $^{68}$Ga-PSMA-11 reported by Ceci et al (*22*). Nevertheless, comparison between studies has several limitations such as the differing protocol, and injected tracer activity. Thus, limited conclusions can be drawn.

A major limitation of the present work is related to the fact that no all-embracing composition validation was possible for all patients given its retrospective nature. Thus, we can

only report an estimate of the CDR. A future prospective study with at least one lesion validation method for all patients is recommended.

## CONCLUSION

$^{18}$F-rhPSMA-7 PET/CT offers high PPV in BCR after RP even in low-PSA values. Its CDR is dependent on the pre-scan PSA-value with excellent CDR in patients with PSA ≥1 ng/mL which is also related to limitations validating lesions in early recurrence.

## KEY POINTS

**QUESTION:** What is the overall detection rate (DR), correct detection rate (CDR), and positive predictive value (PPV) of $^{18}$F-rhPSMA-7 PET/CT in biochemical recurrence of prostate cancer validated by composite reference standard?

**PERTINENT FINDINGS:** This large cohort study revealed the overall DR of 80%. The PPV of $^{18}$F-rhPSMA-7 PET/CT in composite and histopathology-proven cohort was 88%, and 91%, respectively. Thus, the CDRs in both subgroups were 70%, and 73%, accordingly. There were higher DR (90% vs. 69%), PPV (91% vs.85%), and CDR (82% vs. 59%) in subgroup of patients with PSA level ≥1 ng/mL compared with patients with PSA <1 ng/mL. There was a significant positive correlation between $^{18}$F-rhPSMA-7 PET/CT detection efficacy and stratified PSA levels (P=0.005), as well as PSA nadir after prostatectomy (P=0.000). #

**IMPLICATIONS FOR PATIENT CARE:**

$^{18}$F-rhPSMA-7 PET/CT offers high PPV in BCR after RP. Its CDR is dependent on the pre-scan PSA value with excellent CDR in patients with PSA level ≥1 ng/mL.

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**TABLES - TABLE 1.** Patient characteristics

| Characteristic | | Efficacy cohort No. (%) | |
|---|---|---|---|
| | All Patients (N=532) No. (%) | Composite cohort (N=162) No. (%) | Histopathologic cohort (N=22) No. (%) |
| **Age, median (range), years** | 71 (48-89) | 71 (51-90) | 68 (56-82) |
| **Prostate cancer therapy** | | | |
| **Local salvage therapy** | 121 (23) | 29 (18) | 7 (32) |
| **ADT** | 58 (11) | 27 (17) | 0 (0) |
| **Multiple treatment** | 115 (22) | 53 (33) | 8 (36) |
| **Others** | 2 (0) | 2 (1) | 0 (0) |
| **Not available / no prior treatment** | 236 (44) | 51 (31) | 7 (32) |
| **Time between surgery and PSMA PET, years** | | | |
| **Median (range)** | 4.7 (0-28) | 4.0 (0-23) | 3 (1-23) |
| **<4.7** | 264 (50) | 86 (53) | 12 (55) |
| **≥4.7** | 267 (50) | 74 (46) | 9 (41) |
| **Not available** | 1 (0) | 2 (1) | 1 (5) |
| **Primary T stage** | | | |
| **≤T2** | 152 (29) | 41 (25) | 11 (50) |
| **≥T3** | 288 (54) | 99 (61) | 7 (32) |
| **Not available** | 92 (17) | 22 (14) | 4 (18) |
| **Pathologic regional LN staging (pN)** | | | |
| **pN0** | 296 (56) | 86 (53) | 11 (50) |
| **pN1** | 118 (22) | 46 (28) | 6 (27) |
| **pNx** | 118 (22) | 30 (19) | 5 (23) |
| **Gleason Score / ISUP – Grade group** | | | |
| **≤7 / ≤3** | 155 (29) | 56 (35) | 11 (50) |
| **≥8 / ≥4** | 116 (22) | 46 (28) | 8 (36) |
| **Not available** | 261 (49) | 60 (37) | 3 (14) |
| **PSA nadir after prostatectomy*, ng/mL** | | | |
| **Median (range)** | 0.1 (0-200) | 0.01 (0-19) | 1.19 (0-132) |
| **<0.1** | 135 (25) | 12 (7) | 3 (14) |
| **≥0.1** | 86 (16) | 8 (5) | 0 (0) |
| **Not available** | 311 (58) | 142 (88) | 19 (86) |
| **PSA at the time of PET/CT, median (range), ng/mL** | 0.97 (0-400) | 1.19 (0-132) | 0.84 (0.19-11.6) |
| **dtPSA**, months** | | | |
| **Median (range)** | 6.84 (1-179) | 5.02 (1-33) | 4.06 (1-9) |
| **<6.8** | 59 (11) | 27 (17) | 4 (18) |
| **≥6.8** | 62 (12) | 14 (9) | 2 (9) |
| **Not available** | 411 (77) | 121 (75) | 16 (73) |

* in accordance with Bianchi et al. EurUrol. 2016;69:1142–1148

** in accordance with Pound et al. JAMA. 1999;281:1591-1597, change in therapy not excluded.

**TABLE 2.** Positive predictive value and correct detection rate of $^{18}$F-rhPSMA-7 PET/CT

| | **Total (N)** | **Confirmed (N)** | **Ruled-out (N)** | **PPV (%) (95% CI)*** | **CDR (%)** |
|---|---|---|---|---|---|
| **A) Composite validation** | | | | | |
| **PET positive (per-patient)** | 162 | 143 | 19 | 88 (82-92) | 70 |
| **PET positive (per-region)** | 210 | 157 | 53 | 75 (68-80) | |
| **B) Histopathologic validation** | | | | | |
| **PET positive (per-patient)** | 22 | 20 | 2 | 91 (72-97) | 73 |
| **PET positive (per-region)** | 23 | 20 | 3 | 87 (68-95) | |

*Calculated using Wilson score method using asymptotic variance without continuity correction. NEWCOMBE et al. Statist. Med. 17, 857—872 (1998), Method 3

Abbreviation: PPV; Positive predictive value, CDR: Correct detection rate

**TABLE 3.** Correct detection rate stratified by PSA level in composite-validated subgroup

| Stratification | No. of patients | True Positive Results, No. (%) | False Positive Results, No. (%) | DR (%) | PPV (%) | CDR (%) |
|---|---|---|---|---|---|---|
| **PSA level, ng/mL** | | | | | | |
| **<1** | 71 | 60 (85) | 11 (15) | 69 | 85 | 59 |
| **≥1** | 91 | 83 (91) | 8 (9) | 90 | 91 | 82 |

Abbreviation: DR; Detection rate, PPV; Positive predictive value, CDR; Correct detection rate

**TABLE 4.** miTNM stage by $^{18}$F-rhPSMA-7 PET/CT

| | | All patients (N=532) | | Efficacy cohort (N=162) | |
|---|---|---|---|---|---|
| **miTNM stage*** | | **N** | **%** | N | **%** |
| **M0** | | | | | |
| | T0N0M0 | 109 | 20 | 0 | 0 |
| | TrN0M0 | 117 | 22 | 20 | 12 |
| | T0N1M0 | 67 | 13 | 18 | 11 |
| | TrN1M0 | 43 | 8 | 4 | 2 |
| **M1** | | | | | |
| | T0N0M1 | 65 | 12 | 87 | 51 |
| | T0N1M1 | 67 | 13 | 18 | 11 |
| | TrN0M1 | 21 | 4 | 8 | 5 |
| | TrN1M1 | 43 | 8 | 7 | 4 |
| **Extrapelvic disease** | | | | | |
| | Any M1 | 196 | 37 | 120 | 71 |
| | M1a/c only | 17 | 3 | 16 | 9 |
| | M1b only | 38 | 7 | 90 | 53 |
| **Multiple** | | | | | |
| | Multiple regions | 184 | 35 | 43 | 25 |

*miTNM stage in accordance with PROMISE.

Abbreviation: Tr; prostate bed, N1; pelvic nodes, M1; extrapelvic disease.

**TABLE 5.** Detection rate stratified by PSA level, and other parameters per-patient basis.

| Stratification | No. | PET-Positive Results, No. (%) | χ2 p value |
|---|---|---|---|
| **All Patients** | 532 | 423 (80) | |
| **PSA, ng/mL** | | | |
| **<0.5** | 166 | 96 (58) | |
| **0.5 - <1.0** | 104 | 90 (87) | |
| **1.0 - <2.0** | 102 | 87 (85) | 0.005 |
| **2.0 - <5.0** | 86 | 80 (93) | |
| **≥5.0** | 74 | 70 (95) | |
| **PSA doubling time, months** | | | |
| **<6.8** | 59 | 49 (83) | |
| **≥6.8** | 62 | 44 (71) | 0.449 |
| **Not available** | 411 | 330 (80) | |
| **PSA nadir after prostatectomy, ng/mL** | | | |
| **<0.1** | 135 | 103 (76) | |
| **≥0.1** | 86 | 72 (84) | <0.001 |
| **Not available** | 311 | 248 (80) | |
| **Time from initial therapy to PSMA PET, years** | | | |
| **<4.7** | 264 | 207 (78) | |
| **≥4.7** | 267 | 215 (81) | 0.785 |
| **Not available** | 1 | 1 (100) | |
| **Gleason Score** | | | |
| **≤7** | 155 | 119 (77) | |
| **≥8** | 116 | 98 (84) | 0.483 |
| **Not available** | 261 | 206 (79) | |
| **Primary T stage** | | | |
| **≤T2** | 152 | 116 (76) | |
| **≥T3** | 288 | 235 (82) | 0.555 |
| **Not available** | 92 | 72 (78) | |

Abbreviation: PSA; Prostate-specific antigen, PSMA; Prostate-specific membrane antigen

**FIGURE 1.** Flow diagram for the efficacy cohort with composite validation

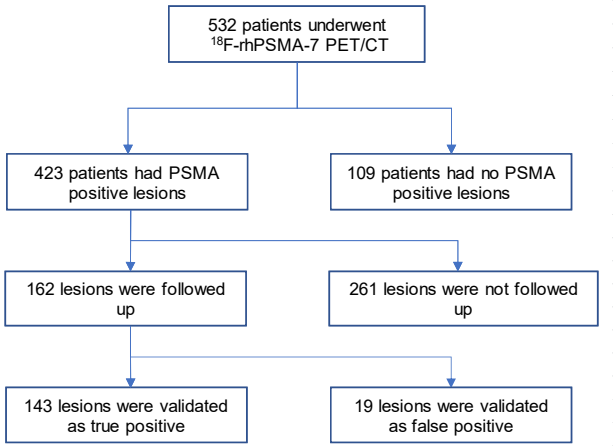
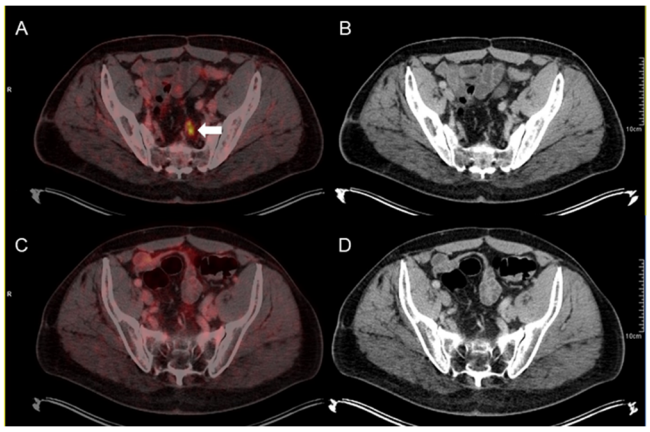
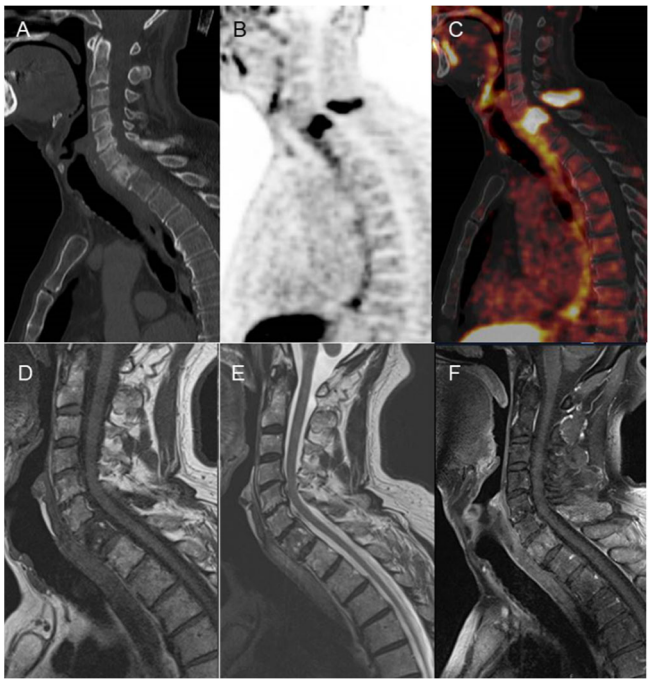


**FIGURE 2.** True positive pelvic lymph nodes metastasis




Axial fused PET/CT (A), and CT (B) revealed two subcentimeter lymph nodes with $^{18}$F-rhPSMA-7 uptake (SUVmax = 8.7) at left pre-sacral region. The largest one was measured about 6.3 mm in short axis diameter (arrow). After received external beam radiation, the follow up axial fused PET/CT (C), and CT (D) showed significantly decreased size of aforementioned lymph node, measured about 3 mm (SUVmax=3.3). This case was recorded as true positive according to size decrease >30% after targeted therapy with minimum size change of 3 mm.

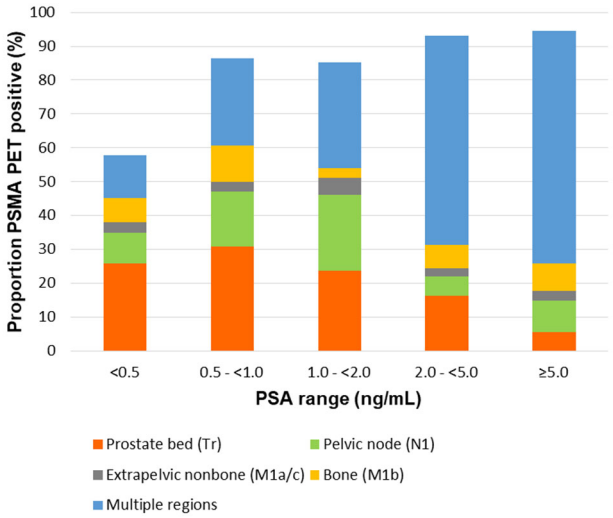
**FIGURE 3.** False positive bone lesion on $^{18}$F-rhPSMA-7 PET validated by histopathology.



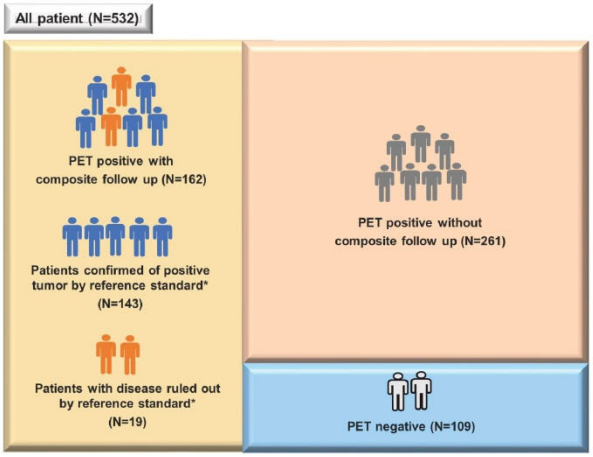

A 69-year-old male with biochemical recurrence of prostate cancer, Gleason score 7, post radical prostatectomy with follow up PSA value of 0.37 ng/mL. Sagittal CT (A) revealed sclerotic lesion at vertebral body and posterior element of C7, showing high $^{18}$F-rhPSMA-7 uptake on sagittal $^{18}$F-rhPSMA-7 PET (B), and sagittal fused PET/CT (C) with SUVmax of 22.5. This lesion showed low signal intensity (SI) on sagittal T1-weighted magnetic resonance image (MRI) (D), heterogeneous intermediate SI on sagittal T2-weighted MRI (E), with preservation of fatty marrow signal on sagittal fat-suppressed T1-weighted MRI (F). This pattern of signal intensity alteration probably corresponds to the presence of hypervascularity, and edema seen in early mixed active Paget's disease. Biopsy at C7 was performed. Histopathological specimen revealed reactive tissue without any prostate cancer cells. Thorough work-up of the biopsy sample definitely excluded a prostate cancer metastasis but a final diagnosis above the general

description of reactive tissue could not be established. Please note, that the biopsy may have the limitation in sampling errors, immunohistochemistry was not performed in this case and a re-biopsy was decided to be omitted given the unnecessary risk for the patient.

**FIGURE 4.** Detection rate stratified by PSA levels



# Graphical Abstract




**80%** **Detection rate (DR)** of $^{18}$F-rhPSMA-7 PET in the entire cohort

**88%** **Positive predictive value (PPV)**
Based on a DR of 80%, the estimated CDR in the composite-validated cohort = 70%

**82%** **CDR in patients with PSA level ≥1 ng/mL**
In this subgroup, DR and PPV were 90% and 91%, respectively resulting in a CDR of 82%.

**59%** **CDR in patients with PSA level <1 ng/mL**
In this subgroup, DR and PPV were 69% and 85%, respectively resulting in a CDR of 59%.

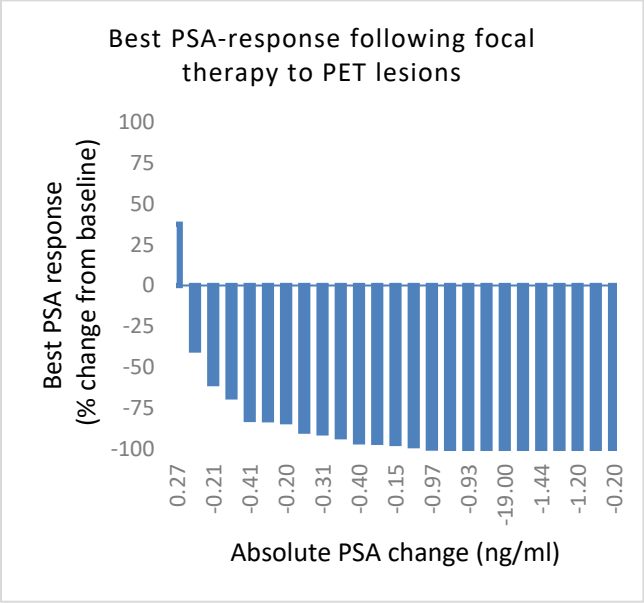
**Implication**

- $^{18}$F-rhPSMA-7 PET/CT offers high PPV in BCR prostate cancer after radical prostatectomy.
- Its CDR is dependent on the pre-scan PSA value with excellent CDR in patients with PSA ≥1 ng/mL.

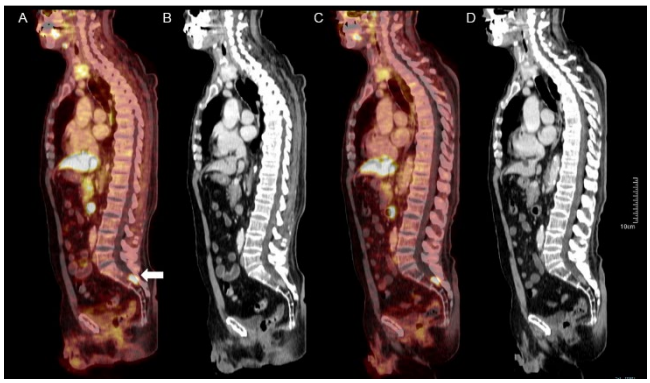
*Reference standard = histopathology, imaging or PSA follow up
CDR = Correct detection rate, BCR = Biochemical recurrent, PSA = Prostate-specific antigen

**Supplement file**

**Supplementary FIGURE 1.** Best PSA Response following focal therapy (EBRT) to $^{18}$F-rhPSMA-7 PET.



**Supplementary FIGURE 2.** True positive intraspinal metastasis




Sagittal fused PET/CT (A), and CT (B) revealed focal $^{18}$F-rhPSMA-7 uptake at a soft tissue lesion located at intraspinal sacrum level (arrow), representing intraspinal metastasis measured about 2.9 cm in long axis diameter. He received external beam radiation at this region up to a total dose of 37.5 Gy, VMAT technique supplemented by androgen-deprivation therapy, from August to September 2018. PSA was decreased from 1.44 ng/ml to 0.6 ng/ml after treatment. The follow up sagittal fused PET/CT (C), and CT (D) showed no significant change in size of aforementioned lesion, measured about 2.8 cm. This case was recorded as true positive according to significant PSA decreased (-58%) after targeted therapy.

**Supplementary TABLE 1.** Baseline characteristics of patients with PSA response following focal therapy (N = 25)

| Characteristic | No. (%) |
|---|---|
| **Age, median (range), years** | 71 (59-82) |
| **Other prior therapy** | |
| Local salvage therapy | 1 (4) |
| ADT | 1(4) |
| Multiple | 2 (8) |
| Other | 1 (4) |
| Not available / no prior treatment | 20 (80) |
| **Time between surgery and PSMA PET, median (range), years** | 2.3 (0-15) |
| <2.25 | 12 (48) |
| ≥2.25 | 13 (52) |
| **Primary T stage** | |
| <T3 | 10 (40) |
| ≥T3 | 14 (56) |
| Not available | 1 (4) |
| **Pathologic regional LN staging (pN)** | |
| pN0 | 14 (56) |
| pN1 | 6 (24) |
| pNx | 5 (20) |
| **Gleason Score** | |
| <8 | 17 (68) |
| ≥8 | 3 (12) |
| Not available | 5 (20) |
| **PSA, median (range), months** | 5.98 (4-12) |
| **dtPSA*, median (range), months** | 7.89 (2-33) |
| <6.8 | 3 (12) |
| ≥6.8 | 4 (16) |
| Not available | 18 (72) |
| **PSA nadir after prostatectomy**, median (range), ng/ml** | 0.03 (0-19) |
| <0.1 | 6 (24) |
| ≥0.1 | 4 (16) |
| Not available | 15 (60) |

**Supplementary TABLE 2.** Lesions validated as false positive by follow-up imaging per-region

| **Location** | **Per-region (N=11)** | % | Criteria of false positive† |
|---|---|---|---|
| Prostate bed | 2 | 18 | In 3-12 months follow up; all PSMA-positive lesion which do not meet the following criteria; a) size decrease >30% with systemic / focal therapy, b) size increase >20% with/without systemic / focal therapy, and c) minimum size change of 3 mm is required.<br>- Short axis diameter was used for lymph node lesion<br>- Long axis diameter was used for lesions at prostate bed and visceral organs |
| Pelvic lymph node | 6 | 55 | |
| Extrapelvic lymph nodes/ Visceral organs | 2 | 18 | |
| Bone | 1 | 9 | Negative in additional bone scan or MRI |

†According to UCLA/UCSF criteria follow up imaging / PSA response (Fendler et al. JAMA Oncol. 2019;5:856-863).

**Supplementary TABLE 3.** Lesions validated as false positive by follow-up imaging per-patient

| **Location** | **Per-patient (N=10)** | **%** |
|---|---|---|
| Prostate bed only | 1 | 10 |
| Pelvic lymph node only | 5 | 50 |
| Extrapelvic lymph nodes/ Visceral organs only | 2 | 20 |
| Bone only | 1 | 10 |
| Prostate bed, and pelvic lymph node | 1 | 10 |

**Supplementary TABLE 4.** Individual false positive lesions

| Patient number | Lesion type | Treatment after PET | Explanation | Criteria | Time to follow up study, days (months) |
|---|---|---|---|---|---|
| | **Prostate bed** | | | | |
| R233 | Soft tissue after RPE | Systemic treatment (ADT) | Decreased size: 18%; 7 mm (38mm → 31 mm) | size decrease <30% after systemic therapy | 263 (9) |
| R5 | Soft tissue after RPE | Systemic treatment (ADT) | Decreased size: 12%; 2mm (17mm → 15 mm) | size decrease <30% after systemic therapy, and minimum size change < 3 mm | 426 (14) |
| | **Pelvic lymph node** | | | | |
| R5 | Pelvic lymph node | Systemic treatment (ADT) | Decreased size: 41%; 1.5 mm (3.7 mm → 2.2. mm) | minimum size change < 3 mm | 426 (14) |
| R200 | Pelvic lymph node | No treatment | No size change: 0%; 0 mm (3.5 mm → 3.5 mm) | minimum size change < 3 mm | 105 (4) |
| R550 | Pelvic lymph node | No treatment | Increased size: 5%; 0.2 mm (4.1 mm → 4.3 mm) | size increase <20% without therapy, and minimum size change <3 mm | 185 (6) |
| R773 | Pelvic lymph node | No treatment | Increased size: 4%; 0.2 mm (4.7 mm → 4.9 mm) | size increase <20% without therapy, and minimum size change <3 mm | 159 (5) |
| R789 | Pelvic lymph node | Systemic treatment (ADT) | No size change: 0%; 0 (13 mm → 13 mm) | minimum size change <3 mm | 202 (7) |
| R1184 | Pelvic lymph node | No treatment | Decreased size: 6%; 0.5 mm | size increase <20% without | 155 (5) |

| | | | | | |
|---|---|---|---|---|---|
| | | | (8.0 mm → 7.5 mm) | therapy, and minimum size change < 3 mm | |
| | **Bone lesions** | | | | |
| R985 | Bone | Systemic treatment (ADT) | Negative in additional MRI | Negative in additional bone scan or MRI | 102 (3) |
| | **Extrapelvic lymph nodes / visceral lesions** | | | | |
| R478 | Retroperitoneal lymph node | No treatment | No size change: 0%; 0 mm (18 mm → 18 mm) | size increase <20% without therapy, and minimum size change < 3 mm | 103 (3) |
| R524 | Lung | No treatment | Increased size: 14%; 1 mm (7 mm → 8 mm) | size increase <20% without therapy, and minimum size change < 3 mm | 117 (4) |

**Supplementary TABLE 5.** Non-evaluable lesions on per-patient and per-region basis

| **Location** | **Per-patient (N=7)** | % | **Per-region (N=8)** | % |
|---|---|---|---|---|
| Prostate bed | 1 | 14 | 2 | 25 |
| Pelvic lymph node | 1 | 14 | 1 | 13 |
| Visceral organs | 0 | 0 | 0 | 0 |
| Bone | 4 | 58 | 5 | 62 |
| >1 regions | 1 | 14 | 0 | 0 |

**Supplementary TABLE 6.** Individual non-evaluable lesions

| Patient number | Lesion type | Treatment after PET | Explanation | Time to follow/up study, days (months) |
|---|---|---|---|---|
| | **Prostate bed** | | | |
| R464 | Soft tissue after RPE | Systemic treatment (ADT) | No reliably measurable lesion; lesion is adjacent to rectum | 81 (3) |
| R990 | Soft tissue after RPE | No treatment | No reliably measurable lesion; lesion is adjacent to rectum | 195 (7) |
| | **Pelvic lymph node** | | | |
| R156 | Pelvic lymph node | Systemic treatment (ADT) | No reliably measurable lesion; lesion is adjacent to iliac vein with similar density in CT | 236 (8) |
| | **Bone** | | | |
| R344 | Bone | EBRT (left 3rd rib, and pelvic region) with ADT | PSMA-positive lesion **without** corresponding sclerosis in baseline and follow up CT | 364 (12) |
| R158 | Bone | Systemic treatment (ADT) | PSMA-positive lesion **without** corresponding sclerosis in baseline and follow up CT | 329 (11) |
| R464 | Bone | Systemic treatment (ADT) | PSMA-positive lesion **without** corresponding sclerosis in baseline and follow up CT | 81 (3) |
| R582 | Bone | Systemic treatment (ADT) | PSMA-positive lesion **without** corresponding sclerosis in baseline and follow up CT | 238 (8) |
| R969 | Bone | No treatment | PSMA-positive lesion **without** corresponding sclerosis in baseline and follow up CT | 152 (5) |