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^{18}F-rhPSMA-7 positron emission tomography for the detection of biochemical recurrence of prostate cancer following radical prostatectomy

Matthias Eiber[1], Markus Kroenke[1], Alexander Wurzer[2], Lena Ulbrich[1], Lena Jooß[1], Tobias Maurer[3], Thomas Horn[4], Kilian Schiller[5], Thomas Langbein[1], Gabriel Buschner[1], Hans-Jürgen Wester[2], Wolfgang Weber[1]

1 Department of Nuclear Medicine, Klinikum rechts der Isar, TUM

2 Chair of Radiopharmacy, TUM

3 Department of Urology and Martini-Klinik, UKE

4 Department of Urology, Klinikum rechts der Isar, TUM

5 Department of Radiation Oncology, Klinikum rechts der Isar, TUM

First and corresponding author:

Matthias Eiber, Klinikum rechts der Isar, Ismaninger Straße 22, 81675 Munich, GERMANY,

Phone +49.89.4140.4549, Fax +49.89.4140.7431, Email matthias.eiber@tum.de

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ABSTRACT

Purpose: ^{18}F-labelled prostate-specific membrane antigen (PSMA) positron emission tomography (PET) tracers are increasingly used in preference to ^{68}Ga-PSMA-11 for restaging biochemical recurrence (BCR) of prostate cancer. They are associated with longer half-lives, larger scale production and lower positron range compared with their ^{68}Ga-labelled counterparts. Here we describe the efficacy of ^{18}F-labelled radiohybrid PSMA, rhPSMA-7, a novel theranostic PSMA-targeting agent for imaging BCR of prostate cancer. **Methods and Materials:** Datasets from 261 consecutive patients with non-castrate BCR after radical prostatectomy who underwent ^{18}F-rhPSMA-7 PET/CT at our institution between June 2017 and March 2018 were reviewed retrospectively. All lesions suspicious for recurrent prostate cancer were recorded. The detection rate of presumed recurrence sites was correlated with patients' PSA level, primary Gleason score, and prior therapy (androgen deprivation therapy [ADT)] and external beam radiation therapy [EBRT]). **Results:** The 261 patients had a median PSA level of 0.96 (range, 0.01–400) ng/mL. The median injected activity of ^{18}F-rhPSMA-7 was 336 MBq, with a median uptake time of 76 min. In total, 211 patients (81%) patients showed pathological findings on ^{18}F-rhPSMA-7 PET/CT. The detection rates were 71% (42/59), 86% (44/51), 86% (42/49) and 95% (76/80) at PSA levels of 0.2 to <0.5 ng/mL, 0.5 to <1 ng/mL, 1 to <2 ng/mL and ≥2 ng/mL, respectively. In 32% (7/22) patients with a PSA <0.2 ng/ml suspicious lesions were present. ^{18}F-rhPSMA-7 PET/CT revealed local recurrence in 43% (113) patients. Lymph node metastases were present in the pelvis in 42% (110), in the retroperitoneum in 17% (45) and in a supradiaphragmatic location in 8.0% (21) patients. Bone and visceral metastases were detected in 21% (54) and 3.8% (10) patients, respectively. Detection efficacy was not influenced by prior EBRT (79.1% vs. 82.1%, p = 0.55), ADT

within the 6 months preceding imaging (80.6% vs. 80.9%, p = 0.54), nor by primary Gleason score (77.9% for Gleason Score ≤7 vs. 82.6% for Gleason Score ≥ 8, p = 0.38).**Conclusion:** ^{18}F-rhPSMA-7 PET/CT offers high detection rates in early BCR after radical prostatectomy, especially among patients with low PSA values.

Keywords

Biochemical recurrence; hybrid imaging; positron emission tomography; prostate cancer; prostate-specific membrane antigen.

INTRODUCTION

Prostate cancer relapse following curative intent primary treatment remains a considerable clinical burden. Up to approximately one-third of patients experience biochemical recurrence (BCR) of prostate cancer in the 10 years following initial treatment (*1,2*). The utility of standard imaging for the localization of recurrence is limited, especially in patients with low prostate-specific antigen (PSA) levels (*3*). In recent years, investigational prostate-specific membrane antigen (PSMA)-based radiotracers have demonstrated encouraging results in the early detection of prostate cancer recurrence. The expression of membrane-bound enzyme PSMA is significantly elevated in prostate cancer cells compared with in healthy tissue (*4*) and the extracellular location of its catalytic site permits easy targeting with specific inhibitors that become internalized after ligand binding (*5*).

The PSMA-based radiotracer, ^{68}Ga-PSMA-11, compares favorably to existing agent, choline, in terms of image contrast and detection rate (*6*). A recent, large retrospective study revealed ^{68}Ga-PSMA-11 to detect recurrent prostate cancer with high specificity and a meta-analysis of data from over 1300 patients reported a pooled, subject-level ^{68}Ga-PSMA detection rate for BCR of prostate cancer of 76% (*7,8*). Most recently, a prospective bicentric study confirmed the high sensitivity of ^{68}Ga-PSMA-11 in patients with low PSA values and reported a high positive predictive value for ^{68}Ga-PSMA-11-positive lesions (*9*). ^{18}F-labelled PSMA radiotracers are also under clinical evaluation and offer a number of potential advantages such as a longer half-life, larger batch production and lower positron range compared with their ^{68}Ga-labelled counterparts. ^{18}F-DCFPyL is a second-generation small-molecule PSMA inhibitor that is

currently under investigation in a phase III study (NCT03739684), and a further example, ^{18}F-PSMA-1007, shows a favorable profile, with low bladder excretion (*10*).

Radiohybrid PSMA (rhPSMA) ligands are a new class of theranostic PSMA-targeting positron emission tomography (PET) agents with a number of favorable features including a fast process for radiolabelling with ^{18}F and radiometals (reference to co-submitted manuscript JNUMED/2019/234922). The lead compound in this class, ^{18}F-rhPSMA-7, has shown promising initial data for the detection and localization of recurrent prostate cancer, as well as rapid blood clearance (reference to co-submitted manuscript JNUMED/2019/234922). Given that accumulation of PET agents in the bladder and ureter can interfere with the diagnosis of recurrent disease and hamper assessment of primary disease (*11-13*), ^{18}F-rhPSMA-7 has notably low bladder retention when imaging 1-hour post injection (reference to co-submitted manuscript JNUMED/2019/234922).

Here, we present results of a retrospective study investigating the efficacy of ^{18}F-rhPSMA-7 for detection and localization of recurrent disease in a large homogenous series of non-castrate patients with BCR after radical prostatectomy.

MATERIALS AND METHODS

Patients

Data from patients with BCR of prostate cancer who underwent clinically indicated ^{18}F-rhPSMA-7 PET/computed tomography (CT) between June 2017 and March 2018 at our institution were reviewed retrospectively. Only patients who had undergone primary radical prostatectomy

with curative intent or salvage radical prostatectomy after external beam radiation therapy (EBRT) were included. Patients with documented castrate-resistant disease were excluded from the analysis. The patients' serum PSA level at the time of the PET/CT was recorded along with details of prior therapy.

All patients gave written informed consent for the procedure. 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). 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).

Synthesis and Administration of ^{18}F-rhPSMA-7

^{18}F-rhPSMA-7 was synthesized as described previously (reference to co-submitted manuscript JNUMED/2019/234948). A median activity of 336 MBq of ^{18}F-rhPSMA-7 (mean 333 ±44, range 191–417 MBq) was administered by intravenous bolus a median of 76 (mean 82 ±22, range 50–220) minutes prior to scanning. Please note that based on an additional investigation of biodistribution at different time points an uptake time of around 1h (50–70 min) is recommended for future use (reference to co-submitted manuscript JNUMED/2019/234922).

Imaging Protocol

All patients underwent ^{18}F-rhPSMA-7 PET/CT on a Biograph mCT flow scanner (Siemens Medical Solutions, Erlangen, Germany). A diagnostic CT scan was performed in the portal venous phase 80 seconds after intravenous injection of contrast agent (Imeron 300) followed by the PET

scan. All patients received diluted oral contrast (300 mg Telebrix). All PET scans were acquired in 3D mode with an acquisition time of 1.1 mm/second. Emission data were corrected for randoms, dead time, scatter, and attenuation and were reconstructed iteratively by an ordered-subsets expectation maximization algorithm (four iterations, eight subsets) followed by a post-reconstruction smoothing Gaussian filter (5 mm full width at one-half maximum).

Image Analysis

Images were reviewed by an experienced, board-certified nuclear medicine physician and a board-certified radiologist. All lesions suspicious for recurrent prostate cancer were noted. Any focal tracer uptake higher than the surrounding background and not associated with physiological uptake was considered suspicious for malignancy. Typical pitfalls in PSMA-ligand PET-imaging such as low-to-moderate PSMA expression associated with osteoblastic changes (i.e. with fractures or degenerative changes) or the low uptake associated with celiac and other ganglia were taken into account (*14*). All lesions suspicious for recurrent prostate cancer were noted and grouped into: (a) local recurrence (prostate bed), (b) lymph node metastases (stratified further by location into pelvic, retroperitoneal and supradiaphragmatic locations), (c) bone metastases and (d) other metastases (e.g. lung, liver).

Statistical Analysis

The detection rate of presumed recurrence sites was plotted against the baseline PSA value for both the patient-level recurrence (number of patients with at least one positive finding)

and for regional levels (local recurrence, lymph node metastases, bone metastases and other metastases as detailed above). The patient-level detection rate was correlated with primary Gleason score and prior therapy (androgen-deprivation therapy [ADT] and EBRT).

Two-sample t-tests were used to evaluate differences between single groups (Gleason Score, ADT) and Mann–Whitney U tests to evaluate differences concerning PSA values between groups with and without pathological uptakes. All tests were two-sided and used a significance level of α=5%. Statistical analyses were conducted with MedCalc software (version 13.2.0, 2014; MedCalc, Ostend, Belgium).

RESULTS

In total, 261 patients were included in this retrospective study. Patients had a median age of 72 years, a median pre-scan PSA level of 0.961 ng/mL, and 67 (26%) patients had received ADT within the six months preceding the scan (Table 1).

^{18}F-rhPSMA-7 Detection Efficacy

Detection Rate. Of the 261 patients, 211 (81%) showed one or more localized area suspicious for recurrent prostate cancer. The detection efficacy of ^{18}F-rhPSMA-7 PET/CT positively correlated with PSA levels and was 95.% (76/80; 95% CI: 0.88–0.99) for a PSA value ≥2 ng/mL, 86% (42/49; 95% CI: 0.73–0.95) for a PSA value 1–<2 ng/mL, 86% (44/51; 95% CI: 0.74–0.94) for a PSA value 0.5–<1 ng/mL, 71% (42/59; 95% CI: 0.58–0.82) for a PSA value 0.2–<0.5 ng/ml and 32% (7/22; 95% CI: 13.7–54.9) for a PSA value <0.2 ng/mL (Fig. 1). The mean PSA level

was significantly lower among patients with negative ^{18}F-rhPSMA-7 PET/CT compared with those with positive results (p=0.004; Table 2).

Lesion Location. ^{18}F-rhPSMA-7-avid lesions were detected in both prostatic and extraprostatic regions as shown in Table 3. Regional positivity also broadly increased with increasing PSA levels (Fig. 2). Local recurrence in the prostate bed ranged from 18% at PSA <0.2 ng/mL to 49% at PSA ≥2 ng/mL, while pelvic lymph node metastases were present in 14% at PSA < 0.2 ng/mL to 64% of cases at PSA ≥ 2 ng/mL. While retroperitoneal lymph node metastases were rare at lower PSA levels, 36% of patients with a PSA ≥2 ng/mL had positive retroperitoneal lymph nodes. Distant lymph node metastases were rare in very early BCR, with no supradiaphragmal lymph node metastases observed at PSA below 0.5 ng/mL. However, 20% of patients with a PSA ≥2 ng/mL were found to have positive supradiaphragmal lymph nodes. Bone metastases were visible early in the recurrence timeline. ^{18}F-rhPSMA-7-avid bone lesions were present in 9% of patients with a PSA <0.2 ng/mL and 33% of patients with PSA levels ≥2 ng/mL. Visceral metastases were absent or low across all PSA levels. Only 7.5% of patients with a PSA ≥2 ng/mL were found to have visceral metastases. Fig. 3, and Supplemental Figs. 1 and 2 present example images from the study.

Influence Of Prior Therapy and Primary Histological Differentiation

We observed no significant difference between the detection rate among patients who had previously received EBRT (79% [83/105]) compared to the rate in those who had not (82% [128/156]; p=0.55). Receiving ADT in the 6 months preceding the scan also did not appear to affect results (81% [54/67] for prior ADT compared to 81% [157/194] with no prior ADT, p=0.54).

When considering the histological differentiation at the primary diagnosis, ^{18}F-rhPSMA-7 PET/CT was positive in 78% (95/122) of patients with a Gleason score ≤7 and in 83% (72/87) of patients with a Gleason score ≥8 (p=0.38).

DISCUSSION

A PSA level greater than 0.2 ng/mL is the current definition of BCR of prostate cancer after radical prostatectomy (*15-17*). A rising PSA level following radical prostatectomy usually precedes a clinically detectable recurrence by years (*18*). However, as it cannot differentiate between local, regional or systemic disease, precise imaging techniques are required to identify areas of involvement in order to facilitate the delivery of optimized therapy.

The performance of conventional imaging techniques, such as ^{11}C-choline PET, is limited at low PSA values and its use is not recommended for patients with a PSA level below 1 ng/mL (*3,19,20*). PSMA-targeting tracers, particularly ^{68}Ga-PSMA-11 have shown more effective determination of the site of disease and as a result have demonstrated a major impact on patient management (*7,21*). Although not currently approved by the European Medicines Agency or the United States Food and Drug Administration, ^{68}Ga-PSMA-11 PET is increasingly used in research studies where it shows encouraging results.

In the present retrospective analysis investigating a large homologous cohort of patients with BCR after prostatectomy, the novel PSMA-targeting radiotracer, ^{18}F-rhPSMA-7, shows highly effective prostate cancer restaging with the site of disease recurrence located in 81% of patients and 95% of those with a PSA level of 2 ng/mL or greater. Common with other PET tracers, the detection rate of ^{18}F-rhPSMA-7 increases with increasing PSA levels (*22-24*).

Previous data suggest ^{18}F-labelled PSMA tracers can achieve higher detection rates than reported for ^{68}Ga-labelled PSMA, especially at low PSA values and the present data, notably for

PSA levels <0.5 ng/mL corroborate this (*25*). The different energy profiles of ^{18}F and ^{68}Ga may play a role in the enhanced detection of ^{18}F-labelled PSMA tracers; theoretically, the achievable resolution of ^{18}F is higher than that of ^{68}Ga (*25,26*). Our data indicate that in general, ^{18}F-rhPSMA-7 provides detection of suspected BCR at an equivalent rate to that reported for ^{68}Ga-PSMA-11, but in patients with very low PSA values (especially below 0.5 ng/mL) higher rates have been observed than reported for ^{68}Ga-PSMA-11 (*8,22*). However, it has to be emphasized that from comparisons with literature only limited conclusions can be drawn. Patient cohorts can vary substantially between different reports and sophisticated protocols (e.g. forced diuresis or additional delayed imaging) might further influence performance of ^{68}Ga-PSMA-11 by allowing for better assessment of local disease (*27*). The ^{18}F-rhPSMA-7 detection rate in our retrospective analysis is similar to that recently published for ^{18}F-PSMA-1007 (*25*).

The previously described low urinary retention of ^{18}F-rhPSMA-7 at 1h post-injection might have an ancillary effect on the enhanced detection efficacy (reference to co-submitted manuscript JNUMED/2019/234922). High accumulation of ^{68}Ga-PSMA-11 in the bladder during imaging is known to impair detection of small local recurrence especially if located in close proximity to the bladder (*13*). In a recent study of a large cohort undergoing ^{68}Ga-PSMA-11-imaging, local recurrence was present in 20% and 30% at PSA ranges of 0.2–0.5 and 0.5–1.0 ng/ml, respectively (*28*) compared with 46% and 41%, respectively in the present study (Table 3). Please note that differences in the patient cohorts may also have influenced results and that based on different protocols ^{68}Ga-PSMA-11 retention in the bladder can be reduced (*27*).

Improved detection during very early recurrence is of great clinical importance in terms of tailoring the salvage therapy approach. Salvage radiotherapy for patients with increasing PSA following prostatectomy provides the best chance of cure when delivered early (*3,29,30*). When salvage radiotherapy is delivered before the patient's PSA reaches 0.5 ng/mL, more than 60% of patients will achieve an undetectable PSA level, and there is an approximately 80% chance of being progression-free at five years (*31-35*). Owing to their ability to identify disease foci early in the recurrence timeline, multiple PET agents have been shown by recent studies to have clinical utility in influencing the future management of a patient (*23,36,37*). It was further shown that detection of lymph nodes and distant metastases has the highest impact on patient management (*21*).

Despite a largely homologous cohort, we evaluated the impact of primary histological classification and prior treatment on the detection rate of ^{18}F-rhPSMA-7. In our patient cohort the detection rate of ^{18}F-rhPSMA-7 is broadly consistent across a range of Gleason scores. Despite data indicating that PSMA-overexpression is increasing with Gleason Score (*38*), these reports mainly focus on the Gleason Score of the primary tumor. In fact, a patient cohort presenting with biochemical recurrence might already imply selection of more aggressive phenotypes of prostate cancer so that the initial primary Gleason Score might be less relevant.

Some preliminary studies also suggest that the use of ADT may evoke overexpression of PSMA (*39*), but this may be a temporal relationship that requires further study. The use of ADT at the time of the scanning has been shown to more frequently be associated with positive ^{68}Ga-PSMA-11 PET results than among those not receiving ADT (*8*) and a recent case study

demonstrated an increased number of lesions after 4 weeks' treatment with ADT despite a lower PSA level (*39*). However, similar to our previous study with ^{68}Ga-PSMA-11, here, we show that the use of ADT within the 6 months preceding the scan did not significantly influence the detection rate with ^{18}F-rhPSMA-7 (*22*). In addition, it should be considered that patients with prior ADT exposure are likely to have more advanced disease than those who have not received ADT, thus potentially highlighting a substantial confounding factor for such data in literature. In general, the role of ADT in the uptake of PSMA-based tracers is highly controversial. At a cellular level, ADT appears to moderately increase PSMA expression, but the treatment may also cause a decrease in the number of the tumor cells, constituting an effect in the opposite direction (*39*).

Please note that similar to recently published data for ^{18}F-PSMA1007 (*40*) we observed PSMA-ligand uptake in the bones which could partly be attributed to non-prostate cancer specific uptake. PSMA-ligand uptake in healing bone fractures, degenerative changes or fibrocartilage lesions has been described previously (*14,41,42*). In this scenario CT plays an important role and its respective findings are essential for the correct differential diagnosis. The assessment of non-prostate cancer related uptake using ^{18}F-rhPSMA-7 is currently under investigation by our group.

Finally, it has to be emphasized that ^{18}F-rhPSMA-7 yields a substantial logistical advantage over ^{68}Ga-labelled counterparts, as it can be produced with high yield (50–70%) using automated radiosynthesizers within a short time frame (< 1000 seconds) at room temperature (reference to co-submitted manuscript JNUMED/2019/234948). The simple radiosynthesis is easily conducted in a GMP-compliant manner, resulting in production of batches with activity suitable for distribution to offsite PET centers. In addition to logistical advantages, the true theranostic

approach with rhPSMA-ligands including ^{18}F labelling is potentially beneficial for applications outside the early biochemical recurrence. In the field of prostate cancer, a highly prevalent disease, pre-therapeutic dosimetry using PET-imaging with ^{18}F might become a relevant application of PSMA-targeted radioligand therapy.

Our retrospective analysis is subject to limitations. First, in common with most studies investigating PSMA-ligand PET imaging we lack histopathological confirmation of the detected lesions. As known from other investigations many recurrent lesions in prostate cancer are small and difficult to biopsy. However, where histopathological validation has been used, results confirm the high positive predictive value of PSMA-based PET agents (*43*). Second, we acknowledge that our study is retrospective in nature with its inherent limitations. Nevertheless, it provides substantial evidence for designing future prospective trials.

CONCLUSIONS

In this large population of patients with recurrent prostate cancer following radical prostatectomy, novel PSMA-based PET tracer, ^{18}F-rhPSMA-7, offers high detection rates that are at least equal to data reported for ^{68}Ga-PSMA-11, especially at low PSA values. Such detection early in the recurrence timeline indicates the potential for ^{18}F-rhPSMA-7 PET to guide future salvage therapy.

KEY POINTS:

Question: What is the detection efficacy of novel ^{18}F-rhPSMA7 PET/CT in non-castrate patients with biochemical recurrent prostate cancer?

Pertinent findings: ^{18}F-rhPSMA7 PET/CT offer high detection efficacy in biochemical recurrent prostate cancer at least equal to data published for ^{68}Ga-PSMA-11.

Implication for patient care: ^{18}F-rhPSMA7 is a novel and effective PET agent for imaging of recurrent prostate cancer which might be approved in the future to allow easier and wider access for patients to PSMA-ligand PET-imaging.

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Fig. 1 Overall detection rate of ^{18}F-rhPSMA-7 PET stratified by PSA value

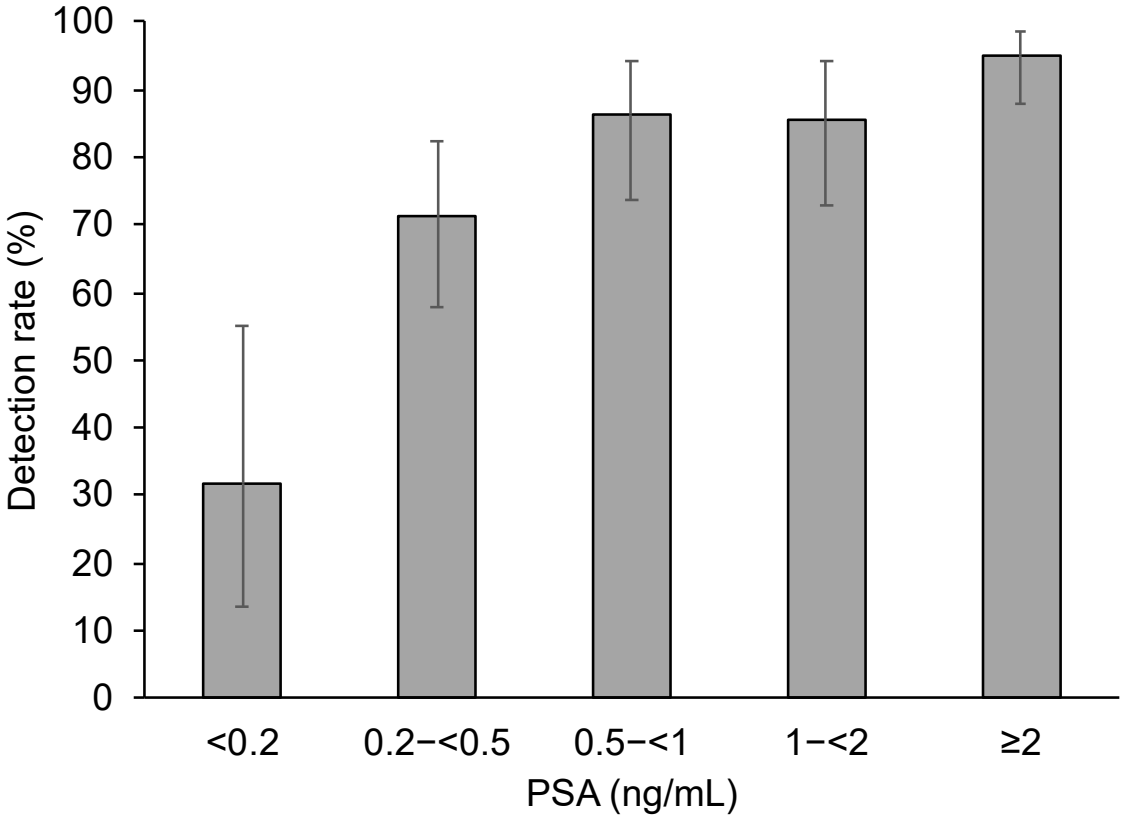


Fig. 2 Presence of ^{18}F-rhPSMA-7-avid lesions stratified by PSA value

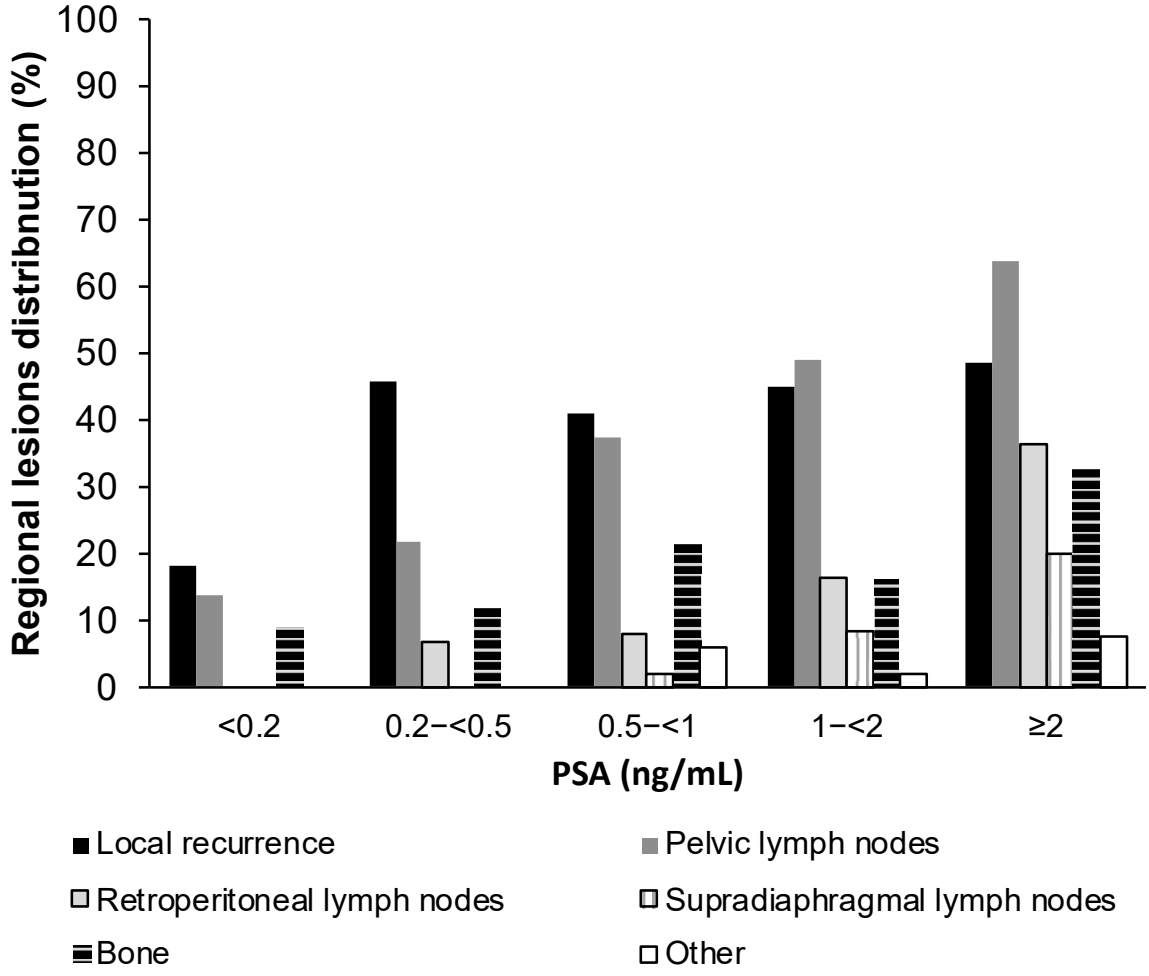


Fig. 3

Set of images from a 77-year old patient who underwent radical prostatectomy in 2015 (Gleason Score 9, pT3b, pN1) and was experiencing a rising PSA (0.15 ng/mL).
The whole-body maximum intensity projection (MIP; A) shows four sites with focal PSMA-ligand uptake in the pelvis (continuous and dotted line arrows). Axial fused PET/CT and CT images demonstrate local recurrence at the anastomosis (continuous line arrows in B and C) and an additional local recurrence at the dorsal bladder wall (continuous line arrows in D and E). In addition, a tiny lymph node metastasis is present in the right pelvis (dotted line arrows in F and G). Targeted external beam radiation treatment lead to a subsequent PSA-drop.

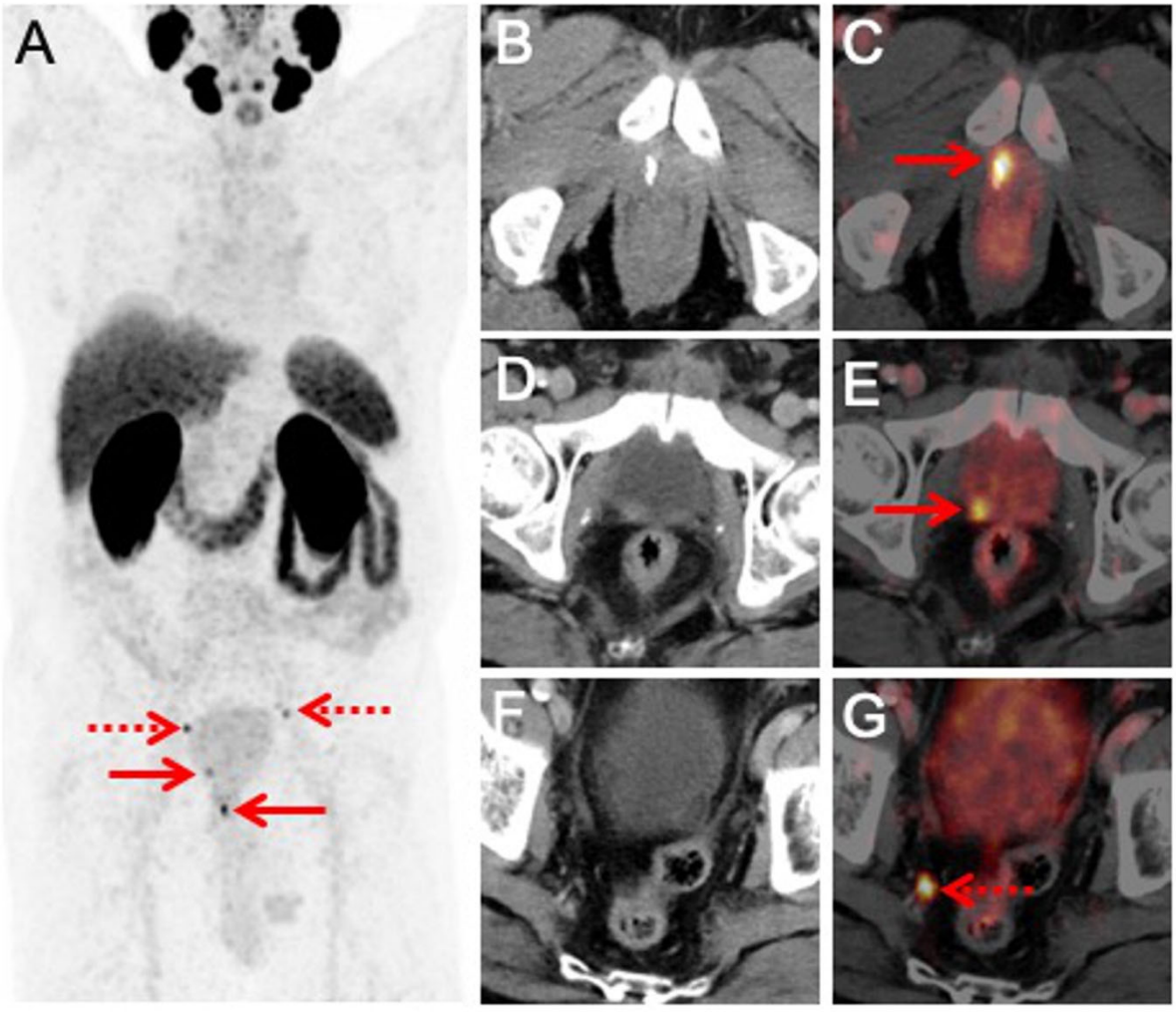


Table 1. Patient characteristics

Characteristic	***Patients,*** N = 261
Age at time of scan, years	
median (range)	72 (49–88)
Further treatment, n (%)	
External radiation after RP	105 (40)
Antihormonal treatment	97 (3)
ADT in the 6 months preceding the scan, n (%)	67 (26)
Gleason Score, n (%)	
≤ 6	12 (4.6)
7	110 (42)
≥ 8	87 (33)
Unknown	52 (20)
Pathologic Primary Tumour Staging (pT) at RP, n (%)	
pT2	76 (29)
pT3	138 (53)
pT4	6 (2.3)
Unknown	41 (15)
Pathologic regional lymph node staging (pN) at RP, n (%)	146 (56)
pN0	66 (25)
pN1	49 (19)
pNx	
Positive Margin at RP, n (%)	
R0	94 (36)
R1	73 (28)
Unknown	94 (36)
Initial PSA value, ng/mL	
Median (range)	10.5 (0.09–290)
Time between surgery and PET, months	
Median (range)	56 (0–336)
Last PSA value prior to PET, ng/mL *	
Median (range)	0.961 (0.01–400.0)
Injected activity, MBq	
Median (range)	336 (191–417)
Uptake time, min	
Median (range)	76 (50–220)

* PSA value obtained within 4 weeks prior to ^{18}F-rhPSMA-7 PET exam

Table 2. PSA levels in patients with positive vs negative ^{18}F-rhPSMA-7 PET/CT results

	Positive ^{18}F-rhPSMA-7 PET/CT	Negative ^{18}F-rhPSMA-7 PET/CT	p
Mean ± standard deviation PSA, ng/mL	8.18 ± 39.12 (n = 211)	0.91223 ±2.06 (n = 50)	0.004

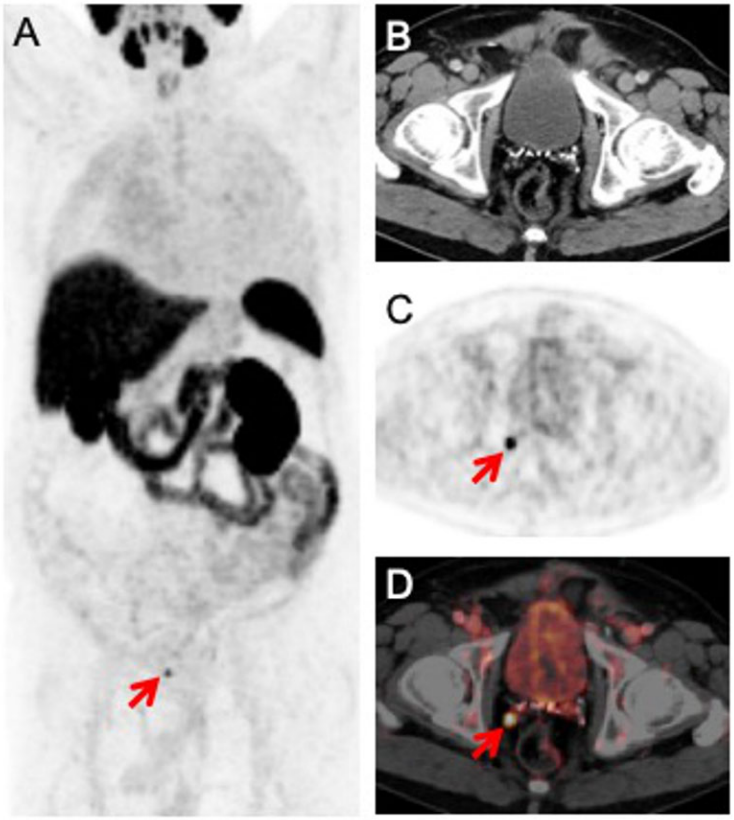
Table 3. Distribution of ^{18}F-rhPSMA-7 -avid lesions stratified by PSA values

PSA value, ng/mL		local recurrence	pelvic lymph node metastases	retroperitoneal lymph node metastases	supradiaphragmal lymph node metastases	bone metastases	visceral metastases
< 0.2	%	18	13.6	0	0	9.1	0
	n, +/all	4/22	3/22	0/22	0/22	2/22	0/22
0.2 – < 0.5	%	46	22.0	6.8	0	12	0
	n, +/all	27/59	13/59	4/59	0/59	7/59	0/59
0.5 – < 1	%	41	37.3	7.8	2.0	22	5.9
	n, +/all	21/51	19/51	4/51	1/51	11/51	3/51
1 – < 2	%	45	49.0	16	8.2	16	2.0
	n, +/all	22/49	24/49	8/49	4/49	8/49	1/49
≥ 2	%	49	63.8	36	20.0	33	7.5
	n, +/all	39/80	51/80	29/80	16/80	26/80	6/80
All patients	%	43	42	17	8	21	4
	n, +/all	113/261	110/261	45/261	21/261	54/261	10/261

Supplemental Fig. 1

Images from a 78-year old patient who underwent radical prostatectomy in 2016 (Gleason Score 8, pT3a, pN0) and had a rising PSA (0.35 ng/mL).

The whole-body MIP (A) and axial PET image (C) show intense ^{18}F-rhPSMA-7 local uptake. The corresponding CT (B) shows no specific abnormality, but the uptake projects in the fused PET/CT image (D) in the region of the right seminal vesicle suggestive of local recurrence.



Supplemental Fig. 2

Images from a 67-year old patient who underwent radical prostatectomy in 2013 (Gleason Score 8, pT2a, pN0), salvage radiation therapy (2016), stereotactic body radiation of two bone lesions (iliac bone, chest; 2017), but who was experiencing a rising PSA (1.94 ng/mL). The whole-body MIP (A) and axial PET image (C) show one intense focal PSMA expression in the region of the left hip. The corresponding CT (B) shows no specific abnormality but the uptake projects in the fused PET/CT image (D) on the left femur neck indicating a new bone metastasis.