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^{18}F-rhPSMA-7 PET for the Detection of Biochemical Recurrence of Prostate Cancer after Curative-intent Radiation Therapy: A Bicentric Retrospective Study

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Running title: ^{18}F-rhPSMA-7 PET for BCR after radiotherapy

ABSTRACT

This bi-centric, retrospective analysis investigates the efficacy of PET/CT with novel theranostic PSMA-targeting ligand, ^{18}F-rhPSMA-7, in patients with biochemical recurrence (BCR) of prostate cancer following curative-intent primary radiotherapy. **Methods:** Datasets from patients with BCR of prostate cancer following EBRT or brachytherapy who underwent ^{18}F-rhPSMA-7 PET/CT at either the Technical University Munich (TUM) or Ludwig-Maximilians-University Munich (LMU) were retrospectively reviewed by experienced nuclear medicine physicians and radiologists in both centers. Median (range) injected activity was 299 (204–420) MBq and median (range) uptake time was 77 (46–120) minutes. All lesions suspicious for recurrent prostate cancer were noted. Detection rates were correlated with patients' PSA level, primary Gleason score (GS), and prior use of androgen-deprivation therapy (ADT). **Results:** 97 patients were included (n=65 TUM and n=32 LMU). Median (range) pre-scan PSA was 4.19 (0.1–159) ng/mL. Primary GS was ≤6 in 19, 7 in 25, ≥8 in 33 and unknown in 20 patients. 30 patients received ADT in the 6 months preceding PET/CT. ^{18}F-rhPSMA-7 identified lesions in 91/97 (94%) patients. Detection rates stratified by PSA were 88% (22/25), 97% (30/31), 90% (19/21), and 100% (20/20) for PSA <2, 2–<5, 5–<10, and ≥10 ng/mL, respectively. Detection rates in the subgroup of patients not meeting the Phoenix criteria for BCR were 80% (4/5), 90% (9/10), 100% (4/4), and 83% (5/6) for PSA <0.5, 0.5–<1, 1–<1.5, and 1.5–2 ng/mL, respectively. There were no significant differences between detection rates among patients with prior ADT and without (100% vs. 91%; p=0.173) or patients with GS ≤7 vs. ≥8 (98% vs. 91%, p=0.316).^{18}F-rhPSMA-7 revealed local recurrence in 80% (78/97), pelvic lymph node metastases in 38% (37/97), retroperitoneal and supra-diaphragmatic lymph nodes in 9% (9/97) and 4% (4/97) respectively, bone metastases in 27% (26/97), and visceral metastases in 3% (3/97). In the subgroup of patients with PSA <2 ng/mL above nadir, local recurrence occurred in 76% (19/25) and pelvic lymph node metastases in 36% (9/25). **Conclusions:** ^{18}F-rhPSMA-7 PET/CT demonstrates high detection rates in prostate cancer patients

with BCR after primary RT, even at low PSA-values. Its diagnostic efficacy is comparable to published data for other PSMA-ligands.

Key Words: prostate specific membrane antigen (PSMA); PET imaging; biochemical recurrence (BCR); radiation therapy

INTRODUCTION

Biochemical recurrence (BCR) of prostate cancer (PC) with rising prostate specific antigen (PSA) levels is observed in up to half of patients after radical prostatectomy (RP) or primary radiotherapy with curative intent and represents the first sign of treatment failure (*1*). The definition of BCR, however, depends on the applied primary therapy option. BCR following RP is defined by two consecutive PSA rises >0.2 ng/mL (*2*), whereas BCR after radiotherapy is defined by a PSA rise of ≥2 ng/mL above the nadir (*3*). This PSA threshold defined by the Phoenix criteria was presented in 2006, when detection of PC recurrence was based on conventional imaging and highly sensitive molecular imaging methods, such as positron emission tomography (PET) with prostate-specific membrane antigen (PSMA)-targeting ligands was not yet available.

^{68}Ga-labeled PSMA-ligands provide high sensitivity for the detection of BCR with increasing pooled detection rates of 42%, 58%, 76%, and 95% at rising PSA categories of 0–0.2, 0.2–1.0, 1–2, and >2 ng/ml (*4*). Thus PSMA-PET might also be of high value in patients after primary curative intent radiotherapy even those at earlier stages of BCR with low PSA values. While ^{68}Ga-labeled compounds are currently the most used tracers for PSMA-targeted PET imaging, ^{18}F-labeled labeled PSMA ligands offer advantages regarding half-life and image resolution.

Several ^{18}F-labeled PSMA ligands (e.g. DCFPyL, PSMA-1007) have been introduced and are currently evaluated in phase III clinical studies, with DCFPyL being recently approved. First data indicate similar diagnostic performance with pooled BCR detection rates of 49%, 73%, 88% and 92% for PSA categories of 0–0.5, 0.5–1.0, 1–2, and ≥2 ng/mL, respectively (*5*). Furthermore, hepato-biliary excretion of ^{18}F-PSMA-1007 reduces tracer accumulation in the urinary bladder, which might be of particular value in cases of BCR after primary radiotherapy, where local recurrence and pelvic lymph node metastases represent common localizations of prostate cancer recurrence (*6,7*). Detection rates for BCR are mainly reported in patients after primary RP and data on the diagnostic efficacy of ^{18}F-labeled PSMA-ligands have

only been presented within mixed cohorts of RP and radiotherapy patients, and so, specific information on the diagnostic performance in patients with BCR after curative intent radiotherapy is rare (*5*).

Recently, radiohybrid PSMA (rhPSMA) ligands have been introduced as novel theranostic PSMA agents enabling radiolabeling with radiometals (e.g. ^{68}Ga and ^{177}Lu) and ^{18}F (*8*). Initial data for its lead compound ^{18}F-rhPSMA-7 state similar diagnostic performance for primary N-staging and localization of BCR after RP as compared to other PSMA-ligands (*9,10*). Its urinary excretion is lower compared with ^{68}Ga-PSMA-11 even after an uptake time of up to 2.5 hours (*11*). Here, we present results of a bicentric, retrospective analysis evaluating the diagnostic efficacy of ^{18}F-rhPSMA-7 PET/CT in patients with BCR after primary curative intent radiotherapy.

MATERIALS AND METHODS

Patients

Data from prostate cancer patients with BCR after primary radiotherapy with curative intent who underwent PET/CT with ^{18}F-rhPSMA-7 between October 2017 and March 2019 at the Technical University Munich (TUM) or the Ludwig-Maximilians-University Munich (LMU) were retrospectively reviewed. Patients with prior salvage prostatectomy after primary radiotherapy or documented castrate-resistant disease were excluded. Finally, a total number of 97 patients were included and patients' PSA values as well as clinical information on prior therapies including prior androgen deprivation therapy (ADT) were noted. The retrospective analysis was approved by the local Ethics Committee in both centers (TUM permit: 290/18S; LMU permit: 20-178). The requirement to obtain written informed consent was waived.

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

Radiolabeling of ^{18}F-rhPSMA-7 was performed as described previously (*8*). ^{18}F-rhPSMA-7 was administered in compliance with the German Medicinal Products Act, AMG § 13 2b and the responsible

regulatory body (government of Upper Bavaria). All patients gave written informed consent. The median injected activity was 299 MBq (mean: 306 MBq, range: 204–420 MBq) and median uptake time was 77 minutes (min) (mean: 76 min, range: 46–120 min). Patients received diluted oral contrast (300 mg Telebrix) and 20 mg furosemide.

^{18}F-rhPSMA-7 PET/CT was performed on a Biograph mCT Flow scanner (Siemens Medical Solutions; n= 73 patients; n=65 at TUM and n=8 at LMU) and on a Discovery 690 scanner (General Electric, Milwaukee, MI, USA; n=24 at LMU). PET/CT scans were acquired in 3-dimensional mode with an acquisition time of 1.1 mm/s on the Biograph mCT flow and 2.5 min per bed position on the GE Discovery 690. PET images were reconstructed using ordered subset expectation maximization algorithm (mCT flow: TrueX, 4 iterations, 8 subset; GE Discovery 690: VUE point FX, 2 iterations, 26 subsets) followed by a post-reconstruction smoothing gaussian filter (5 mm in full width at half maximum). Phantom studies based on the National Electrical Manufacturers Association NU2-2001 standard were conducted at the LMU to allow valid pooling of results between Siemens and GE scanners. A diagnostic CT scan was performed prior to the PET scan in portal venous phase 80 s after intravenous injection of contrast agent.

Image Analysis

All images were interpreted during clinical rounds by a consensus reading by an experienced, board-certified nuclear medicine physician and a board-certified radiologist and centrally re-evaluated by an experienced nuclear medicine physician at each site (HI at the LMU and ME at the TUM). Any focal tracer accumulation higher than surrounding background and not associated with physiologic uptake or unspecific tracer uptake due to typical pitfalls (*12*) was considered suggestive of malignancy. All lesions suspected of representing prostate cancer recurrence were noted. Lesions were categorized as local recurrence (prostate bed), lymph node metastases (further stratified as pelvic, retroperitoneal or supradiaphragmatic), bone metastases, or other distant metastases (e.g. visceral metastases).

Statistical Analysis

Detection rates of lesions representing prostate cancer recurrence were plotted against baseline PSA values on a per patient basis and on a localization basis (local recurrence, lymph node metastases, bone metastases, and other metastases). Descriptive analysis was performed by calculating the median, mean, range, and interquartile range. Unpaired Two-sample t-tests and Mann-Whitney U tests were used to evaluate differences between single groups. Fisher's exact test was used to evaluate detection rates in patients with and without ADT and in patients with Gleason scores ≤7 and ≥8. A p-value less than 0.05 was considered significant. Statistical analyses were performed using SPSS statistics (version 26, IBM).

RESULTS

In total, 97 patients were included in this bicentric retrospective analysis. Median age was 74 years (range: 57–87). PSA value within the 4 weeks preceding ^{18}F-rhPSMA-7 PET/CT was documented for every patient; median PSA prior to PET was 4.19 ng/mL (range 0.0–159; interquartile range: 1.96–8.6 ng/mL). 25 patients (26%) had a PSA ≤2 ng/mL and did not reach the PSA threshold for BCR defined by the Phoenix criteria; median PSA in this subgroup was 0.88 ng/mL (range: 0.0–1.96; interquartile range: 0.7–1.46). 30 patients (31%) had received ADT within 6 months prior to PET/CT. Detailed patient characteristics including primary Gleason Score and initial PSA are provided in Table 1.

Detection Rate of ^{18}F-rhPSMA-7 PET/CT on Patient-base

Detection Efficacy. ^{18}F-rhPSMA-7 PET/CT showed pathologic findings suggestive for prostate cancer recurrence in 91 of 97 patients (94%). Mean PSA in patients with at least one or more localized areas suggestive of recurrent prostate cancer was 9.6 ng/mL compared to 3.1 ng/mL in PET negative patients (p=0.183). The overall detection efficacy stratified by PSA was 88% (22/25) for PSA <2 ng/mL, 97% (30/31) for PSA 2–<5 ng/mL, 90% (19/21) for PSA 5–<10 ng/mL and 100% (20/20) for PSA ≥10 ng/mL (Figure

1). After further sub-classification of patients outside the Phoenix criteria for BCR (n=25), detection rates were 80% (4/5) for PSA <0.5 ng/mL, 90% (9/10) for PSA 0.5–<1 ng/mL, 100% (4/4) for PSA 1–<1.5 ng/mL and 83% (5/6) for PSA 1.5–<2 ng/mL (Figure 2).

Effect of ADT and GS. There were no significant differences between detection rates among patients with prior ADT in the 6 months preceding ^{18}F-rhPSMA-7 PET/CT (100% [30/30]) and those without prior ADT (91% [61/67]; p=0.173; Figure 3a) or patients with GS ≤7 (98% [42/43]) and GS ≥8 (91% [31/34], p=0.316; Figure 3b).

Localization of ^{18}F-rhPSMA-7 PET-positive lesions

Detailed localization of ^{18}F-rhPSMA-7 avid lesions suggestive for recurrence of prostate cancer are shown in Table 2. A clear trend towards a higher proportion of patients with distant metastases (non-regional lymph node metastases and bone metastases) was noted with rising PSA (Figure 4). Overall local recurrence was observed in 80% (78/97), pelvic lymph node metastases in 38% (37/97), non-regional lymph nodes in 13% (13/97), bone metastases in 27% (26/97) and visceral metastases in 3% (3/97; 2 patients with penile metastases and 1 patient with lung metastasis).

In the subgroup of patients with PSA values <2 ng/mL, local recurrence occurred in 76% (19/25) and pelvic lymph node metastases in 36% (9/25) of patients. Furthermore, a low number of distant metastases including bone metastases in 20% (5/25) and visceral metastasis in 4% (1/25) were present; no non-regional retroperitoneal or supradiaphragmatic lymph nodes were detected on ^{18}F-rhPSMA-7 PET/CT.

DISCUSSION

This bicentric, retrospective analysis evaluates the diagnostic efficacy of the novel ^{18}F-labeled PSMA-ligand, ^{18}F-rhPSMA-7, for the detection of prostate cancer recurrence in patients after primary radiotherapy with curative intent. Recently, it has been shown that ^{18}F-rhPSMA-7 provides high detection

rates for BCR after RP (*9*). Of 261 patients with a median PSA of 0.91, 211 (81%) showed at least one lesion suggestive of PC recurrence. In analogy to previously described data for other ^{18}F- and ^{68}Ga-labeled PSMA ligands, increasing detection rates were observed at increasing PSA values (*9,13-15*).

The current analysis focuses on patients with BCR after primary curative-intent radiotherapy. A rising PSA after RP and curative intent radiotherapy is the first sign of primary therapy failure and salvage therapies include pelvic lymph node dissection and/or radiotherapy in case of pelvic lymph node metastases or systemic therapies including ADT and chemotherapy in case of distant metastases (*1*). However, detection and localization of PC recurrence in patients with BCR after curative intent radiotherapy can be challenging. Considering the availability of different salvage therapy options and the impact of PSMA-PET imaging on patient management, early detection of recurrence remains crucial for optimal treatment planning (*2,16,17*).

BCR rates after primary curative-intent radiotherapy range from 10% to 60% with EBRT or 7% to 35% with brachytherapy, and up to 44% despite EBRT dose escalation of 78 Gy (*18-20*). While the overall pooled diagnostic efficacy of ^{18}F-labeled PSMA ligands for the detection of BCR is 81% (95% CI, 71–88), it increases from 49% to 92% at PSA levels of <0.5 ng/mL and ≥2 ng/mL, respectively (*5*). However, data are mainly reported for patients after RP and detailed information on BCR detection rates in patients after primary radiotherapy are mainly available for small subgroups of mixed cohorts (*5*). Dietlein et al. reported overall BCR detection rates of 79% (19/24) and 92% (56/61) for ^{18}F-DCFPyL PET and ^{68}Ga-PSMA-11 PET after primary radiotherapy and 71% (27/38) and 68% (46/68) ^{18}F-DCFPyL PET and ^{68}Ga-PSMA-11 PET after RP, respectively (*21*). Surprisingly, detection rates were PSA-independent in the radiotherapy group, whereas rising PSA levels have been reported to be clearly associated with higher detection rates in patients after RP (*13-15*). This might at least partially be explained by the Phoenix criteria definition of a PSA rise of 2 ng/mL above the nadir. However, with the nadir varying substantially between patients, the

absolute PSA value at the time of imaging might be less relevant compared with patients with BCR after RP.

Similarly, detection rates were also not positively correlated with PSA in the present study. This might be partly related to the high detection efficacy in all subgroups: 88%, 97%, 90%, and 100% for PSA <2 ng/mL, 2–<5 ng/mL, 5–<10 ng/mL, and ≥10 ng/mL, respectively. PSA-independence was also observed in the subgroup of patients, who did not reach the threshold for BCR defined by the Phoenix criteria (PSA ≥2 ng/mL above the nadir) with detection rates of 80%, 90%, 100%, and 83% for PSA <0.5 ng/mL, 0.5–<1 ng/mL, 1–<1.5 ng/mL, and PSA 1.5–<2 ng/mL, respectively. Similar detection efficacies (including both ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL PET scans) in a subgroup of 63 patients not meeting the Phoenix criteria were most recently reported (*22*). The authors reported no influence of PSA-value on PET outcome and detection rates of 75.0% (12/16), 89.3% (25/28), and 84.2% (16/19) at PSA levels of <1.0 ng/mL, 1.0–1.49 ng/mL, and 1.5–1.99 ng/mL above the nadir, respectively were present. However, PSA-independence might be a consequence of the relatively small number of patients in each PSA group reported in these cohorts including the present work (*21,22*).

Notably, Meredith et al. described increasing detection rates for ^{68}Ga-PSMA-11 in 107 patients after primary radiotherapy, however, lower detection rates in patients with very low PSA values might also be attributed to the small sample sizes in these groups with detection rates of 33% at PSA 0.01–<0.5 ng/mL in 1/3 patients and 71% at PSA 0.5–<1 ng/mL in 5/7 patients, respectively (*23*). Recently, Raveenthiran et al. presented data on the diagnostic efficacy of ^{68}Ga-PSMA-11 in 276 patients after primary radiotherapy, representing the largest cohort so far (*24*). While 203 patients were above the threshold for BCR defined by the Phoenix criteria, PSA in the remaining 73 patients was <2 ng/mL. They observed a slight trend towards increasing detection rates at rising PSA levels with 66.7% (8/12) for PSA <0.5 ng/mL, 77.8% (14/18) for PSA 0.5–<1 ng/mL, 76.7% (33/43) for PSA 1–<2.0 ng/mL, and 90.6% (184/203) for PSA >2 ng/mL. Likewise, Einspieler et al. presented higher detection rates with rising PSA levels in a cohort of 118 patients

with BCR according to Phoenix criteria with 81.8% (36/44), 95.3% (41/43), 96.8% (30/31) at PSA levels of 2–<5, 5–<10, and ≥10 ng/mL, respectively (*7*).

In summary, detection efficacy of PSMA-ligand PET in patients meeting the Phoenix criteria ranges from 91–100% (Table 3) (*3,7,23,24*). With an overall detection rate of 96%, our data for ^{18}F-rhPSMA-7 PET/CT fit well into this range. Moreover, our data add to the increasing evidence in literature that indicate that PSMA-ligand PET imaging might also detect lesions indicative for recurrent disease in patients with PSA levels below the threshold set by the Phoenix criteria for BCR. In the present work, the overall detection rate for ^{18}F-rhPSMA-7 in patients with BCR at PSA levels <2 ng/mL was 88% (22/25) and highly comparable to the cohorts of Jansen et al. (84% [53/63]) (*22*), Raveenthiran et al. (75% [55/73]) (*24*), and Meredith et al. (80% [20/25]; Table 3) (*23*). These results strongly indicate that the classical definition of BCR after radiotherapy should be redefined in an era of sensitive PSMA-ligand PET-imaging. Sonni et al. presented data from a prospective single center study evaluating the impact of PSMA-PET imaging on patient management in different clinical situations (*17*). According to this trial, patients with BCR after primary radiotherapy who do not meet the Phoenix criteria seem to be those profiting most from the high sensitivity of PSMA-PET imaging. In the era of PSMA-PET, the definition of BCR according the Phoenix criteria should be revisited or PSMA-PET should be integrated in the definition of recurrence. However, larger patient groups and preferably prospective data are required to confirm this hypothesis.

Comparable to previously described data, PSMA-PET detection rates for BCR after primary radiotherapy are not clearly influenced by prior ADT therapy or primary GS (*7*). We found no significant differences in detection rates for patients who received ADT in the 6 months preceding ^{18}F-rhPSMA-7 PET vs. patients without prior ADT (100% vs. 91%; p=0.173). Similar results have been demonstrated using ^{18}F-rhPSMA-7 PET in patients with BCR following RP (detection rate of 81% for both prior ADT vs. no ADT; p=0.54) (*9*). However, the impact of ADT on PSMA-PET is still a matter of debate. Despite data indicating reduced PSMA ligand uptake after long term ADT (*25*), the need for withdrawal of ADT prior to PSMA-targeted PET

remains controversial, particularly when considering the therapeutic effects of ongoing ADT (*26*). However, concomitant use of ADT at the time of primary radiotherapy will have an impact on patterns of failure which might have impact on lesion detection. Unfortunately, due to the retrospective design of this study, detailed information on concomitant use of ADT during primary radiotherapy was not available for all patients.

Localization of PC recurrence at early stages of BCR and the impact on treatment planning represents one of the main strengths of PSMA-ligand PET. In a recent review, the impact of PSMA-ligand PET on therapy planning ranged from 30% to 76% (*17,27,28*). Patients can be guided away from systemic treatment in up to 40% and application of PSMA-directed local therapy in up to 60% of patients (*28*). PSA prior to salvage therapy represents the strongest predictor of survival after salvage RP and salvage radiotherapy (*29-31*). The majority of patients in our cohort showed localized disease with local recurrence in 80% (78/97) and pelvic lymph node metastases in 38% (37/97), however distant metastases were observed in up to 27% of patients, with bone metastases representing the main site. Please note, that this analysis lacks details on potential unspecific bone uptake. This potential pitfall has been reported for different PSMA-ligands in a large number of case reports, specific analyses and reviews (*12,32-34*). Specifically, Krönke et al., reported a total number of 120 areas of focal increased uptake being interpreted as non-prostate cancer related using 18F-rhPSMA-7 with the majority (n=45) being located in the ribs.

Likewise, in the study by Raaventhiran et al. local recurrence was the most common site of tumor recurrence. However, it was noted in only 57% (157/276) patients compared with 80% in our cohort (*24*). This might be attributed to the high accumulation of ^{68}GaPSMA-11 in the urinary bladder, which can impair detection of small local recurrences in close proximity to the bladder (*35*). Nonetheless, false positive findings in the prostate represent a further possible pitfall of PSMA-PET imaging, particularly in the post-radiotherapy setting as described in a recently published prospective multi-center trial (*36*). We

acknowledge that given the lack of histopathological validation in the present study this cannot be completely excluded. However, all scans have been re-evaluated by experienced readers.

Although the small sample size limits meaningful conclusions, distribution of tumor localization was not influenced by patients' PSA in the present study. However, whereas no non-regional lymph node metastases were observed in patients with PSA levels <2 ng/mL, bone metastases and even visceral metastases were identified in 20% (5/25) and 4% (1/25), respectively. In the overall cohort, visceral metastases were identified in the lung and in the penile shaft in two cases, both representing rare sites of tumor recurrence after BCR (*37,38*). In one patient with a PSA of 0.72 ng/mL, a penile metastasis represented the only finding on ^{18}F-rhPSMA-7 PET. Almost consistent rates of localized disease and distant metastases indicate that early identification of localized salvage therapy or systemic therapy could be delayed when strictly following Phoenix criteria thresholds in BCR patients after primary radiotherapy. Our findings warrant further investigations using PSMA-ligand PET in patients with low PSA not meeting the Phoenix criteria.

This study has several limitations. Firstly, ^{18}F-rhPSMA-7 PET findings have not been validated by histology, which represents the reference standard for definition of PC recurrence. However, many lesions are not feasible for biopsy due to difficult localization and small size. Second, the data are retrospective, and the sample size is relatively small, particularly only 25 patients below the threshold of 2 ng/mL defined by the Phoenix criteria. Currently, there are two clinical trials investigating the safety and diagnostic efficacy of an ^{18}F-labeled rhPSMA ligand in patients with PC recurrence (SPOTLIGHT trial; NCT04186845) and newly diagnosed PC (LIGHTHOUSE trial; NCT04186819). Furthermore, detailed information regarding primary radiotherapy is missing due to the retrospective design of this study (e.g. radiation field and dose, concomitant ADT), which is likely to have an impact on patterns of failure.

CONCLUSION:

^{18}F-rhPSMA-7 PET/CT demonstrates high detection rates in patients with BCR of prostate cancer after primary radiotherapy. The detection rate was not influenced by GS, prior use of ADT or PSA levels. Consistent with published data for other PSMA ligands, high detection rates were observed even in patients with PSA levels <2 ng/mL indicating that ^{18}F-rhPSMA-7 has the potential to guide salvage therapy even at early stages of BCR after primary radiotherapy.

DISCLOSURE

Hans-Jürgen Wester, Alexander Wurzer, and Matthias Eiber are named as inventors on a patent application for rhPSMA. Hans-Jürgen Wester and Matthias Eiber received funding from the SFB 824 (DFG Sonderforschungsbereich 824, project B11) from the Deutsche Forschungsgemeinschaft, Bonn, Germany, and from Blue Earth Diagnostics (licensee for rhPSMA) as part of an academic collaboration. Hans-Jürgen Wester is a founder, shareholder, and advisory board member of Scintomics GmbH, Fuerstenfeldbruck, Germany. Matthias Eiber is a consultant for Blue Earth Diagnostics. No other potential conflicts of interest relevant to this article exist. Writing support was provided by Dr C. Turnbull (Blue Earth Diagnostics, Oxford, UK).

KEY POINTS

Question

What is the detection efficacy of ^{18}F-rhPSMA-7 PET/ CT in patients with biochemical recurrence of prostate cancer after primary curative intent radiotherapy?

Pertinent findings:

^{18}F-rhPSMA-7 PET/CT offers high detection efficacy in patients with biochemically recurrent prostate cancer above and below the PSA threshold of 2 ng/mL defined by the Phoenix criteria. Efficacy is highly comparable to data published for ^{68}Ga-PSMA-11.

Implications for patient care:

^{18}F-rhPSMA-7 has the potential to guide therapy following biochemical recurrence after failure of primary radiotherapy.

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TABLES

Table 1. Patient characteristics

Characteristic	Value
Number of Patients, n	97
Age at time of ^{18}F-rhPSMA-7 PET/CT (y)	
Median (minimum - maximum)	74
Range	57–87
Previous primary therapy with curative intent	
EBRT (Photon therapy) (n)	76
EBRT (Proton therapy) (n)	4
Brachytherapy (n)	13
Brachytherapy AND Photon therapy (n)	4
Gleason Score (n)	
≤ 6	19
7	25
≥ 8	33
Unknown	20
Initial PSA (ng/mL)	
Median	10.86
Range	0.72–80.77
Interquartile range	7.5–17.6
Unknown (n)	31
PSA prior to ^{18}F-rhPSMA-7 PET/CT (ng/ml)	
Median	4.19
Range	0.1–159.0
Interquartile range	1.96 - 8.60
ADT during / within 6 mo before ^{18}F-rhPSMA-7 PET/CT (n)	30
Median time between radiotherapy and ^{18}F-rhPSMA-7 PET/CT (mo)	97

EBRT = external beam radiation therapy; PSA = prostate specific antigen; ADT = androgen deprivation therapy

Table 2. Localization of ^{18}F-rhPSMA-7 PET Positive Tumor Lesions Stratified by PSA value

PSA-value (ng/mL)	Local recurrence	Pelvic lymph node metastases (N1)	Distant metastases			
			Retroperitoneal lymph nodes (M1a)	Supra-diaphragmatic lymph nodes (M1a)	Bone metastases (M1b)	Visceral metastases (M1c)
<2 ng/ml	19/25 (76%)	9/25 (36%)	0/25 (0%)	0/25 (0%)	5/25 (20%)	1/25 (4%)
2–<5 ng/ml	26/31 (84%)	6/31 (19%)	4 /31 (13%)	1/31 (3%)	8/31 (26%)	1/31 (3%)
5–<10 ng/ml	16/21 (76%)	12/21 (57%)	1/21 (5%)	1/21 (5%)	3/21 (14%)	0/21 (0%)
≥10 ng/ml	17/20 (85%)	10/20 (50%)	4/20 (20%)	2/20 (10%)	10/20 (50%)	1/20 (5%)
All patients	78/97 (80%)	37/97 (38%)	9/97 (9%)	4/97 (4%)	26/97 (27%)	3/97 (3%)

Table 3. Detection rates in patients with biochemical recurrence after primary curative intent radiotherapy stratified by PSA level

Author	Year	Radiopharmaceutical	N	Detection rates per PSA category	
				<2 ng/mL	≥2 ng/mL
Present study	2021	^{18}F-rhPSMA-7	97	88%	95.8%
Einspieler et al. (*7*)	2017	^{68}Ga-PSMA-11	118	n.r.	90.7%
Jansen et al. (*22*)	2019	^{68}Ga-PSMA-11 and ^{18}F-DCFPyL	63	84.1%	n.r.
Raveenthiran et al. (*24*)	2019	^{68}Ga-PSMA-11	276	75.3%	90.6%
Meredith et al. (*23*)	2016	^{68}Ga-PSMA-11	107	80%	100%

n.r. = not reported

FIGURES

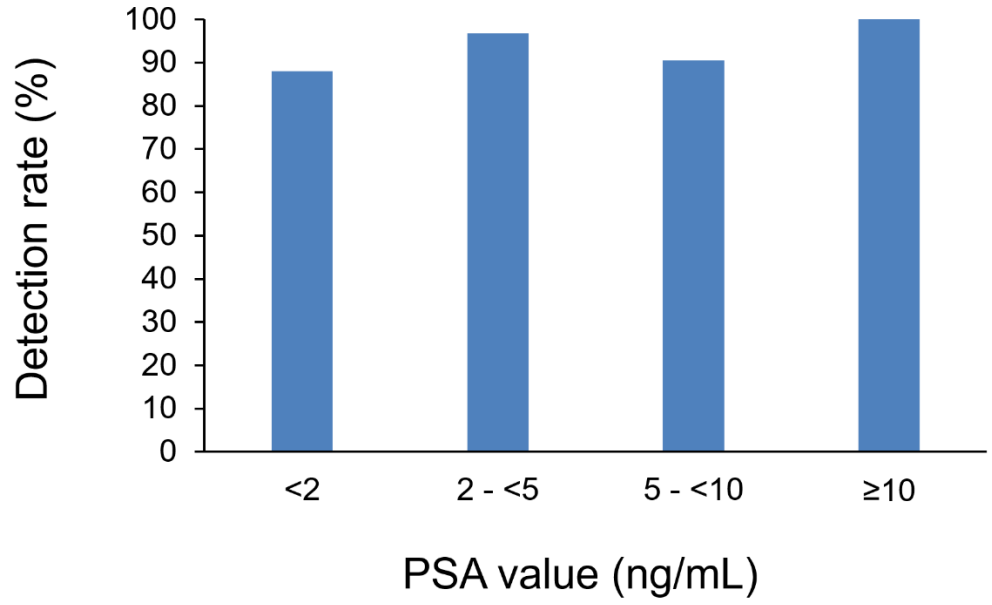


Figure 1. Overall detection rate for all patients (n=97) stratified by PSA value.

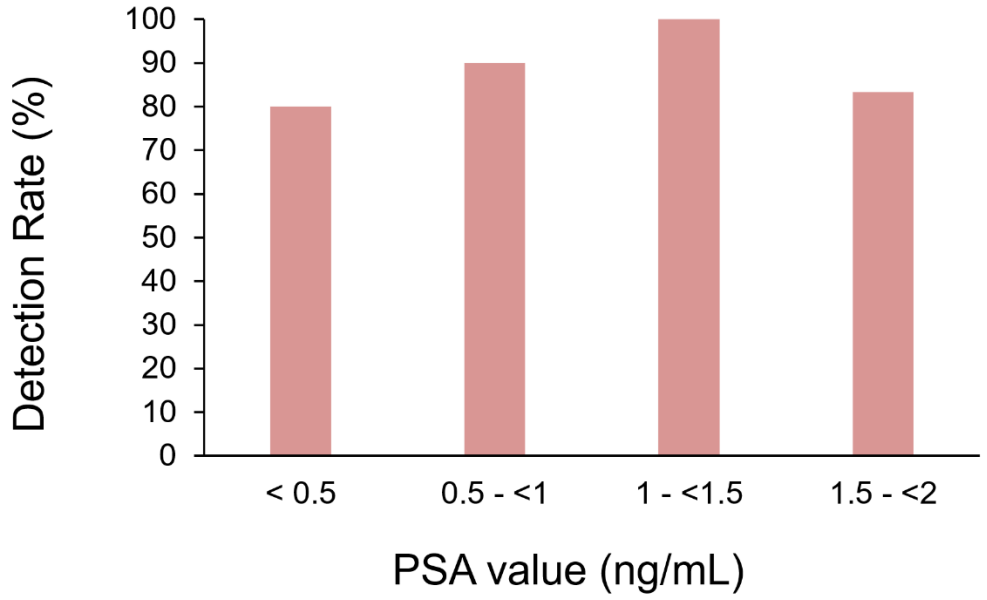


Figure 2. Detection rate stratified by PSA value in patients with PSA <2 ng/mL not meeting Phoenix criteria for BCR after radiotherapy (n=25).

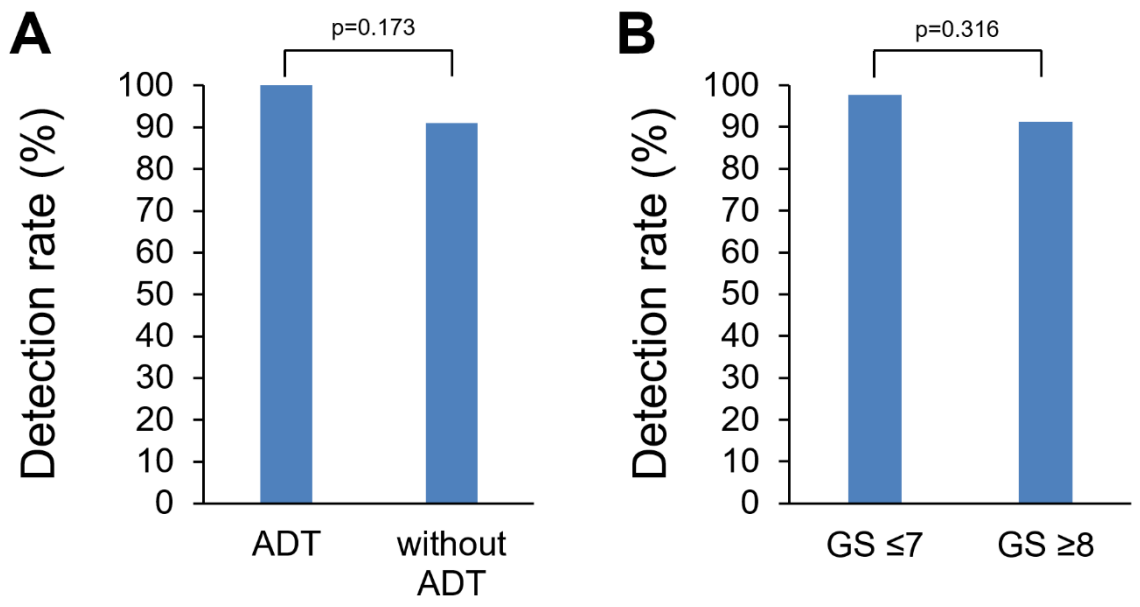


Figure 3. Detection rates stratified by prior ADT use within 6 months preceding ^{18}F-rhPSMA-7 PET/CT (A) and primary Gleason Score (B).

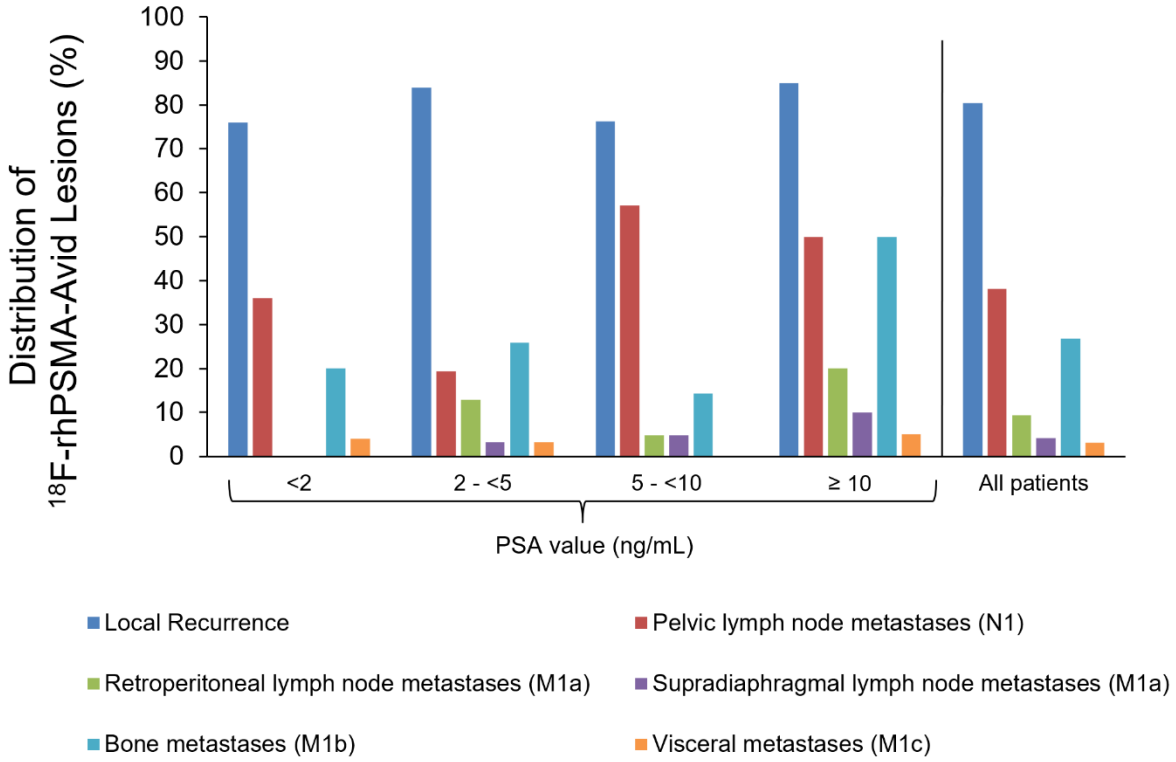
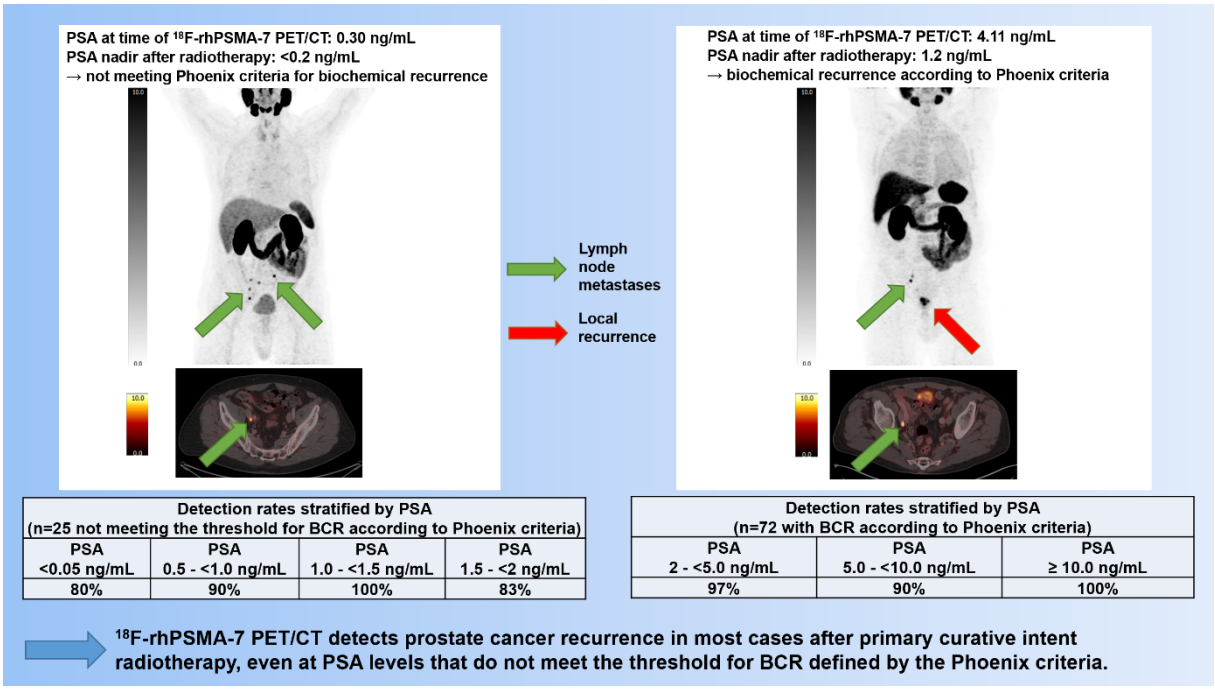


Figure 4. Localization of ^{18}F-rhPSMA-7 positive tumor lesions for all patients and stratified by PSA value.

Graphical Abstract



Detection rates stratified by PSA (n=25 not meeting the threshold for BCR according to Phoenix criteria)			
PSA <0.05 ng/mL	PSA 0.5 - <1.0 ng/mL	PSA 1.0 - <1.5 ng/mL	PSA 1.5 - <2 ng/mL
80%	90%	100%	83%

Detection rates stratified by PSA (n=72 with BCR according to Phoenix criteria)		
PSA 2 - <5.0 ng/mL	PSA 5.0 - <10.0 ng/mL	PSA ≥ 10.0 ng/mL
97%	90%	100%

^{18}F-rhPSMA-7 PET/CT detects prostate cancer recurrence in most cases after primary curative intent radiotherapy, even at PSA levels that do not meet the threshold for BCR defined by the Phoenix criteria.