
¹⁸F-rhPSMA-7 PET for the Detection of Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy

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¹⁸F-labeled prostate-specific membrane antigen (PSMA) PET tracers are increasingly used in preference to ⁶⁸Ga-PSMA-11 for restaging biochemical recurrence (BCR) of prostate cancer. They are associated with longer half-lives, larger-scale production, and lower positron range than their ⁶⁸Ga-labeled counterparts. Here, we describe the efficacy of an ¹⁸F-labeled radiohybrid PSMA, rhPSMA-7, a novel theranostic PSMA-targeting agent for imaging BCR of prostate cancer. **Methods:** Datasets from 261 consecutive patients with noncastrate BCR after radical prostatectomy who underwent ¹⁸F-rhPSMA-7 PET/CT at our institution between June 2017 and March 2018 were reviewed retrospectively. All lesions suspected of being recurrent prostate cancer were recorded. The detection rate for sites of presumed recurrence was correlated with patients' prostate-specific antigen (PSA) level, primary Gleason score, and prior therapy (androgen deprivation therapy and external-beam radiation therapy). **Results:** The 261 patients had a median PSA level of 0.96 ng/mL (range, 0.01–400 ng/mL). The median injected activity of ¹⁸F-rhPSMA-7 was 336 MBq, with a median uptake time of 76 min. In total, 211 patients (81%) showed pathologic findings on ¹⁸F-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% patients (7/22) with a PSA of less than 0.2 ng/mL, suggestive lesions were present. ¹⁸F-rhPSMA-7 PET/CT revealed local recurrence in 43% of patients (113). Lymph node metastases were present in the pelvis in 42% of patients (110), in the retroperitoneum in 17% (45), and in a supradiaphragmatic location in 8.0% (21). Bone and visceral metastases were detected in 21% (54) and 3.8% (10), respectively. Detection efficacy was not influenced by prior external-beam radiation therapy (79.1% vs. 82.1%, *P* = 0.55), androgen deprivation therapy within the 6 mo preceding imaging (80.6% vs. 80.9%, *P* = 0.54), or primary Gleason score (77.9% for ≤7 vs. 82.6% for ≥8, *P* = 0.38). **Conclusion:** ¹⁸F-rhPSMA-7 PET/CT offers high detection rates in early BCR after radical prostatectomy, especially among patients with low PSA values.

Key Words: biochemical recurrence; hybrid imaging; PET; prostate cancer; prostate-specific membrane antigen

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Prostate cancer relapse after 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 y after 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 higher in prostate cancer cells than 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 ⁶⁸Ga-PSMA-11 compares favorably with an existing agent, choline, in terms of image contrast and detection rate (6). A recent large, retrospective study revealed ⁶⁸Ga-PSMA-11 to detect recurrent prostate cancer with high specificity, and a metaanalysis of data from over 1,300 patients reported a pooled, subject-level ⁶⁸Ga-PSMA detection rate of 76% for BCR of prostate cancer (7,8). Most recently, a prospective bicentric study confirmed the high sensitivity of ⁶⁸Ga-PSMA-11 in patients with low PSA values and reported a high positive predictive value for ⁶⁸Ga-PSMA-11-positive lesions (9). ¹⁸F-labeled PSMA radiotracers are also under clinical evaluation and offer several potential advantages such as a longer half-life, larger-batch production, and lower positron range than their ⁶⁸Ga-labeled counterparts. ¹⁸F-DCFPyL is a second-generation small-molecule PSMA inhibitor that is currently under investigation in a phase III study (NCT03739684), and a further example, ¹⁸F-PSMA-1007, shows a favorable profile, with low bladder excretion (10).

Radiohybrid PSMA (rhPSMA) ligands are a new class of theranostic PSMA-targeting PET agents with several favorable features, including a fast process for radiolabeling with ¹⁸F and radiometals (11). The lead compound in this class, ¹⁸F-rhPSMA-7, has shown promising initial data for the detection and localization of recurrent prostate

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cancer, as well as rapid blood clearance (11). 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 (12–14), ¹⁸F-rhPSMA-7 has notably low bladder retention when imaging 1 h after injection (11).

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

MATERIALS AND METHODS

Patients

Data from patients with BCR of prostate cancer who underwent clinically indicated ¹⁸F-rhPSMA-7 PET/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 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). Administration of ¹⁸F-rhPSMA-7 complied with the German Medicinal Products Act, AMG §13 2b, and the responsible regulatory body (government of Oberbayern).

Synthesis and Administration of ¹⁸F-rhPSMA-7

¹⁸F-rhPSMA-7 was synthesized as described previously (11). A median activity of 336 MBq of ¹⁸F-rhPSMA-7 (mean, 333 ± 44 MBq; range, 191–417 MBq) was administered by intravenous bolus at a median of 76 min (mean, 82 ± 22 min; range, 50–220 min) before scanning. An uptake time of around 1 h (50–70 min) is recommended for future use, on the basis of an additional investigation of biodistribution at different time points (11).

Imaging Protocol

All patients underwent ¹⁸F-rhPSMA-7 PET/CT on a Biograph mCT flow scanner (Siemens Medical Solutions). A diagnostic CT scan was performed in the portal venous phase 80 s after intravenous injection of contrast agent (Iomeron 300), followed by the PET scan. All patients received diluted oral contrast medium (300 mg of ioxitalamate [Telebrix; Guerbet]). All PET scans were acquired in 3-dimensional mode with an acquisition time of 1.1 mm/s. Emission data were corrected for randoms, dead time, scatter, and attenuation and were reconstructed iteratively by an ordered-subsets expectation maximization algorithm (4 iterations, 8 subsets) followed by a postreconstruction smoothing gaussian filter (5 mm in full width at half maximum).

Image Analysis

Images were reviewed by an experienced, board-certified nuclear medicine physician and a board-certified radiologist. All lesions suspected of being recurrent prostate cancer were noted. Any focal tracer uptake higher than the surrounding background and not associated with physiologic uptake was considered suggestive of malignancy. Typical pitfalls in PSMA-ligand PET imaging were considered, 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 (15). All lesions suggestive of recurrent prostate cancer were noted and categorized as local recurrence (prostate bed), lymph node metastases (stratified further by location as pelvic, retroperitoneal, or supradiaphragmatic), bone metastases, or other metastases (e.g., lung or liver).

Statistical Analysis

The detection rate for sites of presumed recurrence was plotted against the baseline PSA value for both patient-level recurrence (number of patients with at least 1 positive finding) and regional level (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 external-beam radiation therapy).

Two-sample *t* tests were used to evaluate differences between single groups (Gleason score, ADT), and Mann–Whitney *U* tests were used to evaluate differences in PSA values between groups with and without pathologic uptake. All tests were 2-sided and used a significance level of $\alpha = 5\%$. Statistical analyses were conducted with MedCalc software (version 13.2.0).

TABLE 1
Patient Characteristics (*n* = 261)

Characteristic	Data
Age at time of scan (y)	72 (49–88)
Further treatment	
External radiation after RP	105 (40)
Antihormonal treatment	97 (3)
ADT in 6 mo preceding scan	67 (26)
Gleason score	
≤6	12 (4.6)
7	110 (42)
≥8	87 (33)
Unknown	52 (20)
Pathologic primary tumor staging at RP	
pT2	76 (29)
pT3	138 (53)
pT4	6 (2.3)
Unknown	41 (15)
Pathologic regional lymph node staging at RP	
pN0	146 (56)
pN1	66 (25)
pNx	49 (19)
Positive margin at RP	
R0	94 (36)
R1	73 (28)
Unknown	94 (36)
Initial PSA value (ng/mL)	10.5 (0.09–290)
Time between surgery and PET (mo)	56 (0–336)
Last PSA value before PET (ng/mL)*	0.961 (0.01–400.0)
Injected activity (MBq)	336 (191–417)
Uptake time (min)	76 (50–220)

*PSA value obtained within 4 wk before ¹⁸F-rhPSMA-7 PET examination.

RP = radical prostatectomy.

Qualitative data are expressed as numbers followed by percentages in parentheses; continuous data are expressed as median followed by range in parentheses.

RESULTS

In total, 261 patients were included in this study. They had a median age of 72 y and a median prescan PSA level of 0.961 ng/mL; 67 (26%) had received ADT within the 6 mo preceding the scan (Table 1).

¹⁸F-rhPSMA-7 Detection Efficacy

Detection Rate. Of the 261 patients, 211 (81%) showed one or more localized areas suggestive of recurrent prostate cancer. The detection efficacy of ¹⁸F-rhPSMA-7 PET/CT correlated positively with PSA level and was 95% (76/80; 95% confidence interval [CI], 0.88–0.99) for a PSA value of ≥ 2 ng/mL, 86% (42/49; 95% CI, 0.73–0.95) for a PSA value of 1 to <2 ng/mL, 86% (44/51; 95% CI, 0.74–0.94) for a PSA value of 0.5 to <1 ng/mL, 71% (42/59; 95% CI, 0.58–0.82) for a PSA value of 0.2 to <0.5 ng/mL, and 32% (7/22; 95% CI, 13.7–54.9) for a PSA value of <0.2 ng/mL (Fig. 1). The mean PSA level was significantly lower among patients with negative results on ¹⁸F-rhPSMA-7 PET/CT than among those with positive results ($P = 0.004$; Table 2).

Lesion Location. ¹⁸F-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 level (Fig. 2). Local recurrence in the prostate bed ranged from 18% at PSA < 0.2 ng/mL to 49% at PSA ≥ 2 ng/mL, whereas pelvic lymph node metastases were present in 14% at PSA < 0.2 ng/mL to 64% at PSA ≥ 2 ng/mL. Although retroperitoneal lymph node metastases were rare at lower PSA levels, 36% of patients with PSA ≥ 2 ng/mL had positive retroperitoneal lymph nodes. Distant lymph node metastases were rare in very early BCR, with no supradiaphragmatic lymph node metastases observed at PSA < 0.5 ng/mL. However, 20% of patients with PSA ≥ 2 ng/mL were found to have positive supradiaphragmatic lymph nodes. Bone metastases were visible early in the recurrence timeline. ¹⁸F-rhPSMA-7-avid bone lesions were present in 9% of patients with PSA < 0.2 ng/mL and 33% of patients with PSA ≥ 2 ng/mL. Visceral metastases were absent or low across all PSA levels. Only 7.5% of patients with PSA ≥ 2 ng/mL were found to have visceral metastases. Figure 3 and Supplemental Figures 1 and 2 present example images from the study (supplemental materials are available at <http://jnm.snmjournals.org>).

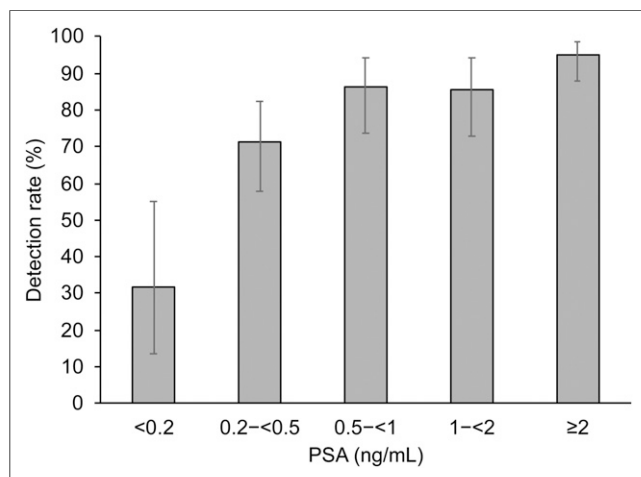


FIGURE 1. Overall detection rate of ¹⁸F-rhPSMA-7 PET stratified by PSA value.

TABLE 2
PSA Level in Patients with Positive Vs. Negative ¹⁸F-rhPSMA-7 PET/CT Results

P	PSA, mean \pm SD (ng/mL)	
	Positive results	Negative results
0.004	8.18 \pm 39.12 (n = 211)	0.91223 \pm 2.06 (n = 50)

Influence of Prior Therapy and Primary Histologic Differentiation

We observed no significant difference between the detection rate among patients who had previously received external-beam radiation therapy (79% [83/105]) and those who had not (82% [128/156], $P = 0.55$). Receiving ADT in the 6 mo preceding the scan also did not appear to affect the results (81% [54/67] for prior ADT compared with 81% [157/194] for no prior ADT, $P = 0.54$). When considering the histologic differentiation at the primary diagnosis, ¹⁸F-rhPSMA-7 PET/CT was positive in 78% (95/122) of patients with a Gleason score of 7 or less and in 83% (72/87) of patients with a Gleason score of at least 8 ($P = 0.38$).

DISCUSSION

A PSA level of greater than 0.2 ng/mL is the current definition of BCR of prostate cancer after radical prostatectomy (16–18). A rising PSA level after radical prostatectomy usually precedes a clinically detectable recurrence by years (19). However, as it cannot differentiate between local, regional, or systemic disease, precise imaging techniques are required to identify areas of involvement to facilitate the delivery of optimized therapy.

The performance of conventional imaging techniques, such as ¹¹C-choline PET, is limited at low PSA values, and its use is not recommended for patients with a PSA level of below 1 ng/mL (3,20,21). PSMA-targeting tracers, particularly ⁶⁸Ga-PSMA-11, have been shown to more effectively determine the site of disease and, as a result, have had a major impact on patient management (7,22). Although not currently approved by the European Medicines Agency or the U.S. Food and Drug Administration, ⁶⁸Ga-PSMA-11 PET is in increasing use in research studies, where it has shown encouraging results.

In the present retrospective analysis investigating a large, homologous cohort of patients with BCR after prostatectomy, the novel PSMA-targeting radiotracer ¹⁸F-rhPSMA-7 was shown to be highly effective for prostate cancer restaging, with the site of disease recurrence being located in 81% of all patients and in 95% of those with a PSA level of 2 ng/mL or greater. Common with other PET tracers, the detection rate for ¹⁸F-rhPSMA-7 increases with increasing PSA level (23–25).

Previous data suggest that ¹⁸F-labeled PSMA tracers can achieve higher detection rates than reported for ⁶⁸Ga-labeled PSMA, especially at low PSA values, and the present data corroborate this, notably for PSA levels of less than 0.5 ng/mL (26). The different energy profiles of ¹⁸F and ⁶⁸Ga may play a role in the enhanced detection of ¹⁸F-labeled PSMA tracers; theoretically, the achievable resolution of ¹⁸F is higher than that of ⁶⁸Ga (26,27). Our data indicate that, in general, ¹⁸F-rhPSMA-7 detects suspected BCR at a rate equivalent to that reported for ⁶⁸Ga-PSMA-11, but in patients with very low PSA values (especially below 0.5 ng/mL) higher rates have been observed than reported for ⁶⁸Ga-PSMA-11 (8,23). However, only limited conclusions can be drawn from comparisons with the literature. Patient cohorts can vary substantially between

TABLE 3
Distribution of ¹⁸F-rhPSMA-7–Avid Lesions Stratified by PSA Value

PSA value (ng/mL)	Local recurrence	Metastatic site				
		Pelvic lymph nodes	Retroperitoneal lymph nodes	Supradiaphragmatic lymph nodes	Bone	Viscera
<0.2	4/22 (18%)	3/22 (13.6%)	0/22 (0%)	0/22 (0%)	2/22 (9.1%)	0/22 (0%)
0.2–<0.5	27/59 (46%)	13/59 (22.0%)	4/59 (6.8%)	0/59 (0%)	7/59 (12%)	0/59 (0%)
0.5–<1	21/51 (41%)	19/51 (37.3)	4/51 (7.8%)	1/51 (2.0%)	11/51 (22%)	3/51 (5.9%)
1–<2	22/49 (45%)	24/49 (49.0%)	8/49 (16%)	4/49 (8.2%)	8/49 (16%)	1/49 (2.0%)
≥2	39/80 (49%)	51/80 (63.8%)	29/80 (36%)	16/80 (20.0%)	26/80 (33%)	6/80 (7.5%)
All patients	113/261 (43%)	110/261 (42%)	45/261 (17%)	21/261 (8%)	54/261 (21%)	10/261 (4%)

different reports, and sophisticated protocols (e.g., forced diuresis or additional delayed imaging) might further influence the performance of ⁶⁸Ga-PSMA-11 by allowing for better assessment of local disease (28). The ¹⁸F-rhPSMA-7 detection rate in our retrospective analysis is similar to that recently published for ¹⁸F-PSMA-1007 (26).

The previously described low urinary retention of ¹⁸F-rhPSMA-7 at 1 h after injection might have an ancillary effect on the enhanced detection efficacy (11). High accumulation of ⁶⁸Ga-PSMA-11 in the bladder during imaging is known to impair detection of small local recurrences, especially if near the bladder (14). In a recent study of a large cohort undergoing ⁶⁸Ga-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 (29), compared with 46% and 41%, respectively, in the present study (Table 3). Differences in the patient cohorts may also have influenced results, and on the basis of different protocols, ⁶⁸Ga-PSMA-11 retention in the bladder can be reduced (28).

Improved detection during very early recurrence is of great clinical importance to tailoring the salvage therapy approach. Salvage radiotherapy for patients with increasing PSA after

prostatectomy provides the best chance for cure when delivered early (3,30,31). 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 5 y (32–36). Because of 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 (24,37,38). It was further shown that detection of lymph nodes and distant metastases has the highest impact on patient management (22).

Despite a largely homologous cohort, we evaluated the impact of primary histologic classification and prior treatment on the detection rate for ¹⁸F-rhPSMA-7. In our patient cohort, the detection rate for ¹⁸F-rhPSMA-7 was broadly consistent across a range

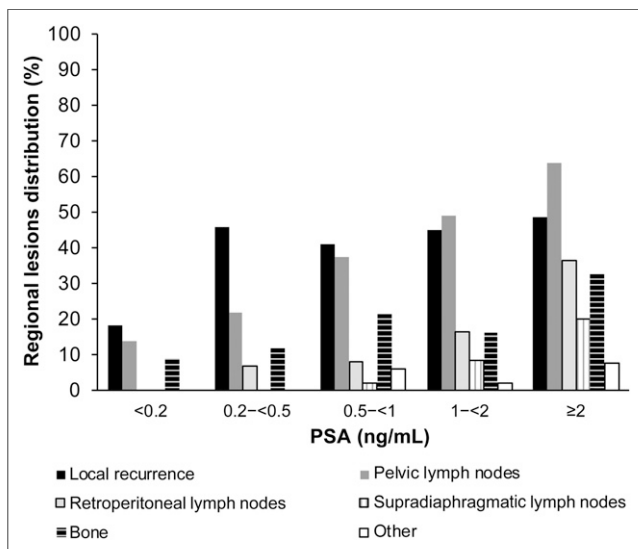


FIGURE 2. Presence of ¹⁸F-rhPSMA-7–avid lesions stratified by PSA value.

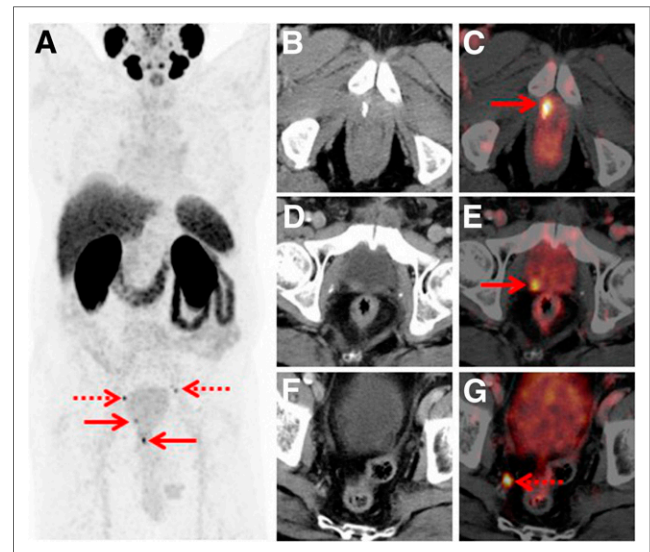


FIGURE 3. Set of images from 77-y-old patient who underwent radical prostatectomy in 2015 (Gleason score of 9, pT3b, pN1) and was experiencing rising PSA (0.15 ng/mL). (A) Whole-body maximum-intensity projection shows 4 sites with focal PSMA-ligand uptake in pelvis (arrows). (B–G) Axial fused PET/CT and CT images demonstrate local recurrence at anastomosis (B and C, arrow), additional local recurrence at dorsal bladder wall (D and E, arrow), and tiny lymph node metastasis in right pelvis (F and G, arrow). Targeted external-beam radiation treatment lead to subsequent PSA drop.

of Gleason scores. Despite data indicating that PSMA overexpression increases with Gleason score (39), these reports focus mainly on the Gleason score of the primary tumor. In fact, a patient cohort presenting with BCR might already imply selection of more aggressive phenotypes of prostate cancer; the initial primary Gleason score might therefore be less relevant.

Some preliminary studies also suggest that the use of ADT may evoke overexpression of PSMA (40), but this may be a temporal relationship that requires further study. The use of ADT at the time of scanning has been shown to be associated with positive ^{68}Ga -PSMA-11 PET results more frequently than does scanning of those not receiving ADT (8), and a recent case study demonstrated an increased number of lesions after 4 wk of treatment with ADT despite a lower PSA level (40). However, similar to our previous study with ^{68}Ga -PSMA-11, we showed here that the use of ADT within the 6 mo preceding the scan did not significantly influence the detection rate with ^{18}F -rhPSMA-7 (23). In addition, 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 the 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 tumor cells, constituting an effect in the opposite direction (40).

Similarly to recently published data for ^{18}F -PSMA1007 (41), we observed PSMA-ligand uptake in the bones, which could partly be attributed to uptake not specific to prostate cancer. PSMA-ligand uptake in healing bone fractures, degenerative changes, or fibrocartilage lesions has been described previously (15,42,43). In this scenario, CT plays an important role, and its respective findings are essential for a correct differential diagnosis. The assessment of uptake not related to prostate cancer, using ^{18}F -rhPSMA-7, is currently under investigation by our group.

Finally, we must emphasize that ^{18}F -rhPSMA-7 yields a substantial logistical advantage over ^{68}Ga -labeled counterparts, as the former can be produced with high yield (50%–70%) using automated radiosynthesizers within a short time frame (<1,000 s) at room temperature (11). The simple radiosynthesis is easily conducted in a manner compliant with good manufacturing practices, 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 labeling, is potentially beneficial for applications outside early BCR. In the field of prostate cancer, a highly prevalent disease, pretherapeutic 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 lacked histopathologic confirmation of the detected lesions. As known from other investigations, many recurrent lesions in prostate cancer are small and difficult to biopsy. However, when histopathologic validation has been used, results confirmed the high positive predictive value of PSMA-based PET agents (44). Second, we acknowledge that our study was retrospective, with the associated inherent limitations. Nevertheless, it provided substantial evidence for designing future prospective trials.

CONCLUSION

In this large population of patients with recurrent prostate cancer after radical prostatectomy, a novel PSMA-based PET

tracer, ^{18}F -rhPSMA-7, offered high detection rates that were 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.

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 and Wolfgang Weber are consultants for Blue Earth Diagnostics. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What is the detection efficacy of ^{18}F -rhPSMA7 PET/CT in noncastrate patients with biochemically recurrent prostate cancer?

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

IMPLICATIONS FOR PATIENT CARE: If approved in the future, ^{18}F -rhPSMA7 will allow patients easier and wider access to PSMA-ligand PET imaging.

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