Validation of $^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 PET Imaging Results with Histopathology from Salvage Surgery in Patients with Biochemical Recurrence of Prostate Cancer

Markus Kroenke,1,2, Lilit Schweiger,1,3, Thomas Horn,4, Bernhard Haller,5, Kristina Schwamborn,6, Alexander Wurzer,1,7, Tobias Maurer,8, Hans-Jürgen Wester,1, Matthias Eiber,1,3, and Isabel Rauscher,1,3

1Department of Nuclear Medicine, School of Medicine, Technical University of Munich, Munich, Germany; 2Department of Radiology and Nuclear Medicine, German Heart Center Munich, Technical University of Munich, Munich, Germany; 3Bavarian Cancer Research Center (BZKF), Munich, Germany; 4Department of Urology, School of Medicine, Technical University of Munich, Munich, Germany; 5Institute of Medical Informatics, Statistics and Epidemiology, School of Medicine, Technical University of Munich, Munich, Germany; 6Department of Pathology, School of Medicine, Technical University of Munich, Munich, Germany; 7Chair of Radiopharmacy, School of Medicine, Technical University of Munich, Munich, Germany; and 8Martini-Klinik and Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany

$^{18}$F-rhPSMA-7, and its single diastereoisomer form, $^{18}$F-rhPSMA-7.3, are prostate-specific membrane antigen (PSMA)-targeting radiopharmaceuticals. Here, we investigated their accuracy for the assessment of lymph node (LN) metastases validated by histopathology. Methods: Data from 58 patients with biochemical recurrence of prostate cancer after radical prostatectomy receiving salvage surgery after PET imaging with $^{18}$F-rhPSMA-7 or $^{18}$F-rhPSMA-7.3 were retrospectively reviewed. Two nuclear medicine physicians reviewed all PET scans and morphologic imaging in consensus. Readers were masked from the results of histopathology. PET and morphologic imaging were correlated with histopathology from resected LNs. Results: In 75 of 150 resected regions in 54 of 58 patients, tumor lesions were present in histopathology. The template-based specificity of PET ($^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 combined) and morphologic imaging was 93.3% and 100%, respectively. However, $^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 PET detected metastases in 61 of 75 histopathologically proven metastatic LN fields (81.3%) whereas morphologic imaging was positive in only 9 of 75 (12.0%). The positive predictive value was 92.4% for $^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 PET and 100% for morphologic imaging. $^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 PET performance was significantly superior to morphologic imaging (difference in the areas under the receiver-operating-characteristic curves, 0.222; 95% CI, 0.147–0.298; $P <$ 0.001). The mean size of PET-positive and histologically confirmed LN metastases was 6.3 ± 3.1 mm (range, 2–15 mm) compared with a mean size of 9.8 ± 2.5 mm (range, 7–15 mm) on morphologic imaging.

Key Words: $^{18}$F-rhPSMA-7; $^{18}$F-rhPSMA-7.3; prostate cancer; salvage surgery; biochemical recurrence; prostate-specific membrane antigen

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For correspondence or reprints, contact Isabel Rauscher (isabel.rauscher@tum.de).
*Contributed equally to this work.
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$^{18}$F-rhPSMA-7 is one such $^{18}$F-labeled PSMA-targeting ligand representing a class of radiohybrid PSMA (rhPSMA) ligands that can be labeled with $^{18}$F for imaging purposes but also with other radioactive isotopes such as $^{177}$Lu for endoradiotherapy (13). $^{18}$F-rhPSMA-7 is composed of 4 diastereoisomers ($^{18}$F-rhPSMA-7.1–7.4) (14). Of these, $^{18}$F-rhPSMA-7.3 was selected for clinical development on the basis of its superior characteristics in preclinical studies, including fast clearance from blood pool, liver, and kidneys as well as high tumor accumulation in LNCaP tumor-bearing mice (14). $^{18}$F-rhPSMA-7.3 is currently under investigation in 2 multicenter phase III trials for PET imaging (NCT04186845 and NCT04186819); it shows properties similar to those of the isomeric mixture $^{18}$F-rhPSMA-7, with both PSMA-ligands demonstrating high detection rates in patients with biochemical recurrence of PC (15,16).

However, to date, no histopathology-validated study on the use of $^{18}$F-rhPSMA-7.3 in patients with biochemical recurrence of PC has been published. Thus, the aim of this retrospective analysis was to assess the performance of $^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 PET
in patients with biochemical recurrence after radical prostatectomy undergoing subsequent salvage surgery for histopathologic comparison.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the institution’s database for all patients with biochemical recurrence of PC who underwent either $^{18}$F-rhPSMA-7 or $^{18}$F-rhPSMA-7.3 PET and subsequent salvage surgery between November 2017 and June 2020. Patients were excluded if they had not undergone radical prostatectomy as a primary treatment. In total, 58 patients were identified. The retrospective analysis was approved by the local ethics committee (permit 290/18S and 99/19). Administration of $^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 complied with the German Medicinal Products Act, AMG §13 2b, and the responsible regulatory body (government of Oberbayern).

$^{18}$F-rhPSMA Synthesis, Administration, and PET Imaging

$^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 were synthesized and used as previously reported (13,17,18). Twenty-three (40%) patients received $^{18}$F-rhPSMA-7, and 35 (60%) patients received the single-isomer $^{18}$F-rhPSMA-7.3. $^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 were administered (median activity, 320 MBq; range, 239–399 MBq) as an intravenous bolus a median of 72 min (range, 60–148 min) before scanning. In total, 49 patients underwent contrast-enhanced PET/CT (Biograph mCT Flow [Siemens Healthineers]; contrast agent: Imuran 300 [Bracco Imaging]), and 9 patients underwent PET/MRI (Biograph mMR; Siemens Healthineers). The multi-protocol PET/CT and PET/MRI examinations were conducted as previously reported (19,20). Furosemide (20 mg intravenously) was administered to all patients at the time of tracer application, and patients were asked to void urine before the scan.

All PET/CT scans were acquired in 3-dimensional mode with time of flight and in continuous table motion (flowMotion technology, Siemens (21)) with 1.1 mm/s, equal to 2 min per bed position. The PET/MRI scans were acquired in 3-dimensional mode and step-and-shoot with 4 min per bed position for PET/MRI. 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

All $^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 PET/CT and PET/MRI datasets were reviewed by 2 experienced board-certified nuclear medicine specialists in consensus. The readers were masked to the results of histopathology. First, the CT dataset of the PET/CT or the dedicated high-resolution axial T2-weighted turbo spin echo sequence of the pelvis up to the aortic bifurcation (slice thickness, 5 mm each) of the PET/MRI were analyzed. Second, after an interval of at least 4 wk, the corresponding $^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 PET scans were read by the same readers, with the morphologic imaging only being used for anatomic allocation. Findings were rated using a 5-point Likert scale as described previously (22): PET rating of 5 indicates a tumor manifestation (intense, focal uptake, uptake higher than in the liver); 4, probable tumor manifestation (uptake clearly higher than the background level in vessels but less than in the liver); 3, equivocal findings (faint uptake between muscle and vessels uptake); 2, probable benign findings (uptake equal to the adjacent muscle); 1, benign findings (no uptake). For both CT and MRI, the same Likert scale was applied with a rating of 5 indicating tumor manifestation (lymph node short-axis diameter > 10 mm); 4, probable tumor manifestation (short-axis diameter of 8–10 mm or a round configuration or a regional grouping); 3, equivocal findings (short-axis diameter of 8–10 mm, an oval configuration, and no regional grouping); 2, probable benign findings (short-axis diameter < 8 mm); and 1, benign findings (short-axis diameter < 5 mm). Finally, $S_{\text{UV, max}}$ and size (short-axis diameter) of the largest lymph node per template region rated with a score 4 or 5 were measured.

Surgery and Histopathology

The patients were selected for salvage surgery by an interdisciplinary tumor board based on clinical characteristics and the initial clinical reads of $^{18}$F-rhPSMA-7 or $^{18}$F-rhPSMA-7.3 PET. The salvage surgery was planned based on the information on PET and the surgical fields were limited to the pelvis including potential local recurrence. Depending on the location, adjacent lymph node template regions were resected as well. The lymph node template regions were separately collected. Uropathologists were masked to imaging results.

Statistical Analysis

The histopathologic results from resected lymph nodes were correlated with the results of morphologic imaging (MRI or CT) and $^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 PET in a patient- and template-based manner. Further, a separate template-based analysis of $^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 was performed. Results from the 5-point Likert scale were dichotomized to allow estimation of sensitivity, specificity, positive predictive value (PPV), and accuracy. For the statistical analysis, we decided that only scores indicating definitive or probable tumor manifestation on PET and morphologic imaging (scores ≥ 4) were counted as positive. This decision was based on a clinical consideration that invasive procedures (e.g., secondary lymphadenectomy and associated general anesthesia) with their potential risks are not justified if only equivocal findings (score 3) are present.

In 54 of 58 patients, pelvic tumor lesions were confirmed by histopathology. Overall, 150 template regions were resected, with 75 of these harboring tumor lesions (50%). Most ($n = 129$) were part of the typical pelvic lymph node template. Other resected regions were 9 retroperitoneal locations ($n = 6$ positive on histopathology) and 12 local regions due to suspicion of local recurrence ($n = 10$ positive on histopathology).

RESULTS

Patient Characteristics and Histopathologic Results

The data for 58 patients were reviewed. The patients were a median age of 68.5 y (age range, 51–85 y) and presented with a median prostate-specific antigen (PSA) level of 0.71 ng/mL (range, 0.16–8.39 ng/mL) before the PET scan. Detailed patient characteristics are presented in Table 1. Supplemental Tables 1 and 2 (supplementary materials are available at http://jnm.snmjournals.org) provide detailed per-patient information on patient characteristics, imaging methods, and results.

In 54 of 58 patients, pelvic tumor lesions were confirmed by histopathology. Overall, 150 template regions were resected, with 75 of these harboring tumor lesions (50%). Most ($n = 129$) were part of the typical pelvic lymph node template. Other resected regions were 9 retroperitoneal locations ($n = 6$ positive on histopathology) and 12 local regions due to suspicion of local recurrence ($n = 10$ positive on histopathology).

Imaging Results

The template-based areas under the ROC curves for $^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 were 0.891 (95% CI, 0.838–0.944) and for morphologic imaging 0.669 (95% CI, 0.595–0.742, Fig. 1). $^{18}$F-rhPSMA-7 and $^{18}$F-rhPSMA-7.3 PET performed significantly better than morphologic imaging for the detection of lymph node metastases.
The mean SUV\textsubscript{max} of histologically confirmed pelvic lymph node metastases rated as suspicious on PET was 16.7 ± 24.7 (range, 0–167). The corresponding SUV\textsubscript{max} for morphologic imaging was 0.16–6.6 (median, 1.0).

**TABLE 1**

Patient Characteristics \((n = 58)\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data (%)</th>
</tr>
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<tbody>
<tr>
<td>Age (y)</td>
<td>68.5</td>
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<td>Median</td>
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<tr>
<td>Range</td>
<td>51–85</td>
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<tr>
<td>iPSA (ng/mL)*</td>
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<td>Range</td>
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<tr>
<td>ISUP grade ((n))</td>
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</tr>
<tr>
<td>1–2</td>
<td>17 (29)</td>
</tr>
<tr>
<td>3–4</td>
<td>27 (47)</td>
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<tr>
<td>5</td>
<td>10 (17)</td>
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<tr>
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<td>4 (6.9)</td>
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<tr>
<td>Pathologic T stage at primary RPE ((n))</td>
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<tr>
<td>pT3a</td>
<td>11 (19)</td>
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<tr>
<td>≥pT3b</td>
<td>18 (31)</td>
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<tr>
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<td>6 (10)</td>
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<tr>
<td>Pathologic N stage at primary RPE ((n))</td>
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<tr>
<td>pN0</td>
<td>39 (67)</td>
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<tr>
<td>pN1</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Missing</td>
<td>9 (16)</td>
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<tr>
<td>Time between primary surgery and PET (mo)</td>
<td>48</td>
</tr>
<tr>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1–278</td>
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<tr>
<td>Prescan PSA (ng/mL)†</td>
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<tr>
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<tr>
<td>Range</td>
<td>0.16–8.39</td>
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<tr>
<td>Time between PET and salvage surgery (d)</td>
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<td>Median</td>
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<tr>
<td>Range</td>
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</tr>
<tr>
<td>Lymph node regions removed at salvage LAE</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>150</td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
</tr>
<tr>
<td>Range</td>
<td>1–9</td>
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<tr>
<td>Lymph node regions with metastases at salvage LAE</td>
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<tr>
<td>Median</td>
<td>1</td>
</tr>
<tr>
<td>Range</td>
<td>0–4</td>
</tr>
</tbody>
</table>

*Not available in 12 cases.
†Not available in 1 case.

**FIGURE 1.** Template-based ROC curves for combined data of 18\textsuperscript{F}-rhPSMA-7 and 18\textsuperscript{F}-rhPSMA-7.3 PET (black line) and morphologic imaging (CT/MRI) (dotted line) for assessment of lymph node metastases in all 150 lymph node regions. AUC = area under the curve.
3.3–146.6). The corresponding mean lesion size of these PET-positive, histologically confirmed lymph nodes was 6.3 ± 3.1 mm (range, 2–15 mm). The mean size of histologically confirmed lymph nodes rated as suspicious on morphologic imaging was 10.6 ± 2.7 mm (range, 7–15 mm). The mean size of histologically confirmed lymph nodes not rated as suspicious on morphologic imaging was 5.3 ± 2.3 mm (range, 2–14 mm).

A representative example of a correctly classified lymph node metastases by PET/CT is shown in Figure 2.

**DISCUSSION**

The value of PSMA PET for imaging patients with recurrence of PC after primary treatment has been extensively reported (5,6,20, 27–29). Here, we reviewed real-world clinical data supporting the utility of the novel PSMA-targeting radiopharmaceuticals 18F-rhPSMA-7 and 18F-rhPSMA-7.3. To date, the efficacy of both 18F-rhPSMA-7 and 18F-rhPSMA-7.3 for imaging PC patients has been demonstrated by several retrospective studies (15,16,30), including their high accuracy for lymph node staging in patients with primary PC (22,31). The presented data demonstrate a high specificity and PPV of 18F-rhPSMA-7 and 18F-rhPSMA-7.3 PET for lymph node metastases in patients with recurrent PC after radical prostatectomy validated by histopathology. On a template-based analysis, 18F-rhPSMA-7.3 offers a higher accuracy and sensitivity than morphologic imaging.

These results are in line with a similar, histopathologically validated analysis using 68Ga-PSMA-11 that showed a sensitivity, specificity, and PPV of 77.9%, 97.3%, and 94.6%, respectively, compared with 81.3%, 93.3%, and 92.4% in our analysis, respectively (5). Further, the difference in the areas under the receiver-operating-characteristic curves for morphologic images was 0.139 with 68Ga-PSMA-11 compared with 0.222 with 18F-rhPSMA-7 and 18F-rhPSMA-7.3 in our analysis (5). Similar to 68Ga-PSMA-11 PET, our data show

![Figure 2](image-url)
that these novel tracers can detect small lymph node metastasis (a lesion size smaller than 10 mm) in the recurrent PC setting (5). Salvage lymph node surgery represents a therapeutic option for patients experiencing biochemical recurrence after radical prostatectomy, and previous 11C-choline PET–guided data suggest that up to 40% of patients may experience recurrence-free survival after PET-guided salvage lymph node dissection (32). More recently, Horn et al. showed that in a subgroup of patients with recurrent PC undergoing PSMA PET–guided salvage surgery, complete biochemical response was achieved in 66% of patients (2). Moreover, it is believed that PET-guided salvage lymph node dissection may prolong the time until initiation of hormonal treatment, which is associated with significant morbidity (33,34). For salvage surgery with potential complications, a high specificity and PPV are of utmost importance to avoid unnecessary interventions. Interestingly, the specificity of morphologic imaging on a template base was also excellent, which is most likely related to the strict criteria for the determination of metastases. However, as known from the literature, the sensitivity of morphologic imaging is rather low as it can detect only lymph node metastases with already enlarged (>10 mm) lesions.

The pure enantiomeric form of 18F-rhPSMA-7, 18F-rhPSMA-7.3, has been selected as the lead rhPSMA compound for clinical development on the basis of preclinical assessments showing favorable safety and kinetic profiles for diagnostic imaging of PC (14,18). Because of the limited numbers, no sound comparison of the diagnostic performance of 18F-rhPSMA-7 versus 18F-rhPSMA-7.3 is possible in the present study. However, we note similar PPVs for the 2 compounds, which is the only descriptive statistical value to be unaffected by the potential selection bias that results from the present study design. Another limitation of this retrospective analysis is its potential selection bias due to the selection of patients and the lymph node template regions to be removed on the basis of the clinical reads of the 18F-rhPSMA-7 and 18F-rhPSMA-7.3 PET scans. Possible imaging-negative nodes could have been missed, which would impact the sensitivity estimate. Therefore, PPV is the only descriptive statistical value independent of this bias. Of note, specificity on the patient-based analysis was only informed by 4 cases (Supplemental Table 3). For different reasons, it was not always feasible to perform surgery shortly after PET examination (median time between PET and surgery, 59 d; range, 19–117 d). Thus, in principle, it cannot be excluded that there was tumor progression or even new tumor lesions at the time of surgery. The data presented in the supplemental materials for separate analyses of 18F-rhPSMA-7 and 18F-rhPSMA-7.3 should be interpreted with caution given the limited number of patients in each group. Further prospective studies with 18F-rhPSMA-7 are warranted to confirm the diagnostic accuracy for lymph node staging and to avoid potential bias.

CONCLUSION

18F-rhPSMA-7 and 18F-rhPSMA-7.3 PET are superior to morphologic imaging for detecting pelvic lymph node metastases and helping guide salvage lymph node surgery. They offer a high PPV, comparable to that reported for 68Ga-PSMA-11, while yielding the benefits of a radiofluorinated tracer such as the potential for scale production and wide-range distribution.

DISCLOSURE

Hans-Jürgen Wester, Alexander Wurzer, and Matthias Eiber have a patent application for rhPSMA. Hans-Jürgen Wester and Matthias Eiber received funding from Blue Earth Diagnostics Ltd. (Oxford, U.K., Licensee for rhPSMA) as part of an academic collaboration. Matthias Eiber reports prior consulting activities for Blue Earth Diagnostics Ltd., Novartis, Telix, Progenics, Bayer, Point Biopharma, and Janssen. Hans-Jürgen Wester is founder, shareholder, and advisor board member of Scintomics GmbH (Fuerstenfeldbruck, Germany). Siemens Medical Solutions (Erlangen, Germany) supported the application of Biograph mCT flow as part of an academic collaboration. Tobias Maurer reports prior consulting activities for Blue Earth Diagnostics Ltd., Novartis, Telix, ROTOP Pharma, Advanced Accelerator Applications International S.A., GE/MoAb, and Astellas. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What is the value of the radiopharmaceuticals 18F-rhPSMA-7 and 18F-rhPSMA-7.3 for assessing the presence of lymph node metastases before potential salvage lymphadenectomy?

PERTINENT FINDINGS: This histopathologically validated, retrospective study shows that 18F-rhPSMA-7 and 18F-rhPSMA-7.3 are superior to morphologic imaging and comparable to 68Ga-PSMA-11 for N staging of biochemical recurrent prostate cancer.

IMPLICATIONS FOR PATIENT CARE: 18F-rhPSMA-7 and 18F-rhPSMA-7.3 can detect small soft-tissue metastases with a high, template-based specificity of 93%.

REFERENCES