Journal of Nuclear Medicine, published on July 24, 2018 as doi:10.2967/jnumed.118.212233

Detection efficacy of [^{18}F]PSMA-1007 PET/CT in 251 Patients with biochemical recurrence after radical prostatectomy

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Disclosure:
Patent application for PSMA-617 for KK and UH. Patent application for PSMA-1007 for UH, FLG, KK.

Research Support:
Matthias Eiber was supported by the SFB 824 (DFG Sonderforschungsbereich 824, Project B11) from the Deutsche Forschungsgemeinschaft, Bonn, Germany

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3401/5000 words (Abstract: 146/150 words)

Short running title: [^{18}F]PSMA-1007 PET/CT for restaging of PCa

Research Support:

Matthias Eiber was supported by the SFB 824 (DFG Sonderforschungsbereich 824, Project B11) from the Deutsche Forschungsgemeinschaft, Bonn, Germany.

Introduction:

Recently, prostate-specific membrane antigen (PSMA) targeted PET-imaging has emerged as new method of staging and restaging of prostate cancer. Most published studies have investigated the diagnostic potential of ^{68}Ga-labeled PSMA-agents which are excreted renally. [^{18}F]PSMA-1007 is a novel PSMA-ligand with excellent preclinical characteristics which is only minimally excreted by the urinary tract, a potential advantage for pelvic imaging. The aim of this study was to investigate the diagnostic efficacy of [^{18}F]PSMA-1007 in biochemical recurrence (BCR) after radical prostatectomy (RP).

Methods: 251 patients from three academic centers with BCR after radical prostatectomy were evaluated in a retrospective analysis. Patients who had received second line androgen deprivation therapy and/or chemotherapy were excluded, however prior first line ADT exposure was allowed. The median PSA-level was 1.2 ng/ml (range: 0.2-228 ng/mL). All patients underwent a PSMA-PET/CT after injection of 301±46 MBq [^{18}F]PSMA-1007 at 92±26 min post injection. The detection rate of presumed recurrence sites was correlated with PSA-level and original primary Gleason score. A comparison to a subset of patients treated previously with androgen deprivation therapy (ADT) was undertaken.

Results: 204 of 251 patients (81.3%) patients had evidence of recurrence on [^{18}F]PSMA-1007 PET/CT. The detection rates were 94.1% (79/84), 90.1% (50/55), 74.5% (35/47) and 61.5% (40/65) for PSA-levels of ≥2, 1-<2, 0.5-<1 and 0.2-<0.5ng/mL, respectively. [^{18}F]PSMA-1007 PET/CT revealed local recurrence in 43.7% (62) of patients. Lymph node metastases were present in the pelvis in 40.6% (102), in the retroperitoneum in 19.5% (49) and in supradiaphragmatic locations in 12.0% (30) of patients. Bone and visceral metastases were detected in 40.2% (101) and 3.6% (9) patients. In higher Gleason score tumors (≤7vs.≥8) detection efficacy trended higher (76.3% vs. 86.7%) but was not statistically significant (*p=0.32*). However,

detection efficacy was higher in patients who had previously been on ADT (91.7% vs. 78.0%) within 6 months prior to imaging (*p=0.0179*).

Conclusion: [^{18}F]PSMA-1007 PET/CT offers high detection rates in BCR after radical prostatectomy which is comparable to or better than that published for ^{68}Ga-labelled PSMA-ligands.

Key Words:

- [^{18}F]PSMA-1007
- PET/CT
- hybrid imaging
- prostate cancer
- biochemical recurrence

INTRODUCTION

Biochemical recurrence (BCR) represents a major concern for prostate cancer patients who have undergone primary prostatectomy. The ability to localize sites of recurrent prostate cancer is important, for directing salvage therapy with curative intent. Today, only conventional imaging such as whole-body bone scan and cross-sectional abdominopelvic contrast enhanced CT imaging or enhanced MRI is recommended to detect recurrence, however these modalities have very limited sensitivity for recurrent disease *(1)*. Recent introduction of [^{68}Ga]PSMA-11 improved prostate cancer detection in the BCR setting. More than 3,000 patients have been reported worldwide *(2-6)* using some form of the ^{68}Ga PSMA-ligand tracer. Results have surpassed that of ^{18}F-Choline-PET/CT, formerly considered the best available PET agent for prostate cancer *(7,8)*. Most impressive has been the ability of ^{68}Ga PSMA PET to detect recurrent disease in patients with very low (0.2-0.5 ng/mL) and low (>0.5-1.0 ng/mL) PSA-values. This enables tailored decision making regarding further treatment plans *(9)*.

However, there are several reasons to consider ^{18}F-labeled PSMA compounds for BCR. Because of its longer half-life (110min vs. 68min) radiofluorinated tracers are more practical for centralized production and distribution leading to cost savings. Furthermore, since ^{18}F is cyclotron-produced, larger quantities can be produced compared to ^{68}Ga which is generator-produced in a serial fashion. Another potential advantage of ^{18}F is the lower positron energy compared to ^{68}Ga which improves spatial resolution. Therefore, there has been interest in the development of ^{18}F- labeled PSMA compounds *(10, 11)*.

One new candidate is [^{18}F]PSMA-1007, which exhibits rapid blood clearance but only minimal amounts of activity are excreted via the urinary tract *(11)*. A high concentration of PET agents in the urinary bladder and ureter can interfere with the diagnosis recurrent disease around the bladder *(11, 12, 13).* This can particularly hamper the detection of local recurrence in the prostate bed and regional pelvic lymph nodes *(13, 14).*

Thus, the purpose of this analysis was to assess the performance characteristics of [^{18}F]PSMA-1007 PET/CT for the detection and localization of recurrent disease in a multi institutional cohort of patients after radical prostatectomy. Specifically, we aimed to establish the detection rates for recurrence as a function of the absolute PSA-level in BCR patients and compare this to historical data with [^{68}Ga]PSMA-11. Further, we compared the impact of Gleason score at diagnosis and androgen deprivation therapy (ADT) on the efficacy of [^{18}F]PSMA-1007 PET/CT to localize recurrent prostate cancer.

MATERIALS AND METHODS

Study design and patient population

A total of 251 patients, with a median age of 70 (range 48-86), were included in this retrospective multi-center study (n=139 from Technical University of Munich, Germany; n=70 from University of Heidelberg, Germany; n=42 from FALP, Santiago de Chile, Chile). Patient characteristics are summarized in ***Tab.1***. 60 (23.9%) patients received first-line ADT within the last six months prior to the examination. 110 (43.8%) of patients have already undergone salvage RTx prior to [^{18}F]PSMA 1007 PET/CT. Mean time between surgery and [^{18}F]PSMA 1007 PET/CT was significantly longer in patients without vs. with prior salvage RTx ($p<0.0001$, 93.4 vs. 57.3 months).

The study was approved by the Ethics Committee of the Technical University Munich, the University of Heidelberg, Germany (*S-321*) and the Regional Ethics Committee of the SSM Oriente, Santiago de Chile, Chile. All patients gave written informed consent for anonymized evaluation and publication of their data. All reported investigations were conducted in accordance with the Helsinki Declaration and with local regulations. The serum PSA level at the time of the PET/CT scan was available in all patients. PSA-kinetic data could not be reliably obtained in this cohort due to its retrospective nature.

We identified patients who underwent [^{18}F]PSMA1007 PET/CT imaging for recurrent PC from the databases at three institutions (date range: 02/2017 to 01/2018). Only patients who underwent primary RP with or without salvage radiation, who had PSA-levels $\geq$0.2ng/ml were selected. Patients with advanced castration resistant prostate cancer who underwent second line ADT, chemotherapy, radionuclide therapy (Radium-223-dichloride, PSMA-targeted radioligand therapy) were excluded from the analysis.

Radiosynthesis, Quality Control and Application of [^{18}F]PSMA1007

[^{18}F]PSMA-1007 was synthesized as described previously (*15*). Reagent kits, unprotected PSMA-1007 precursor and PSMA-1007 reference standard were obtained from ABX, Radeberg, Germany. The radiosynthesis was performed as a single-step radiofluorination either on a modified Nuclear Interface FDG synthesis module (GE TracerLab FX FN analog), an ORA Neptis plug synthesis module or an IBA Synthera+ synthesis module using 1.6 mg PSMA-1007 precursor in DMSO for 10 minutes at 80°C, subsequent purification on two stacked solid phase extraction cartridges (PS-H+, $C18_{ec}$, Macherey-Nagel) and final dilution with phosphate buffered saline to obtain [^{18}F]PSMA-1007 after sterile filtration as a solution ready for injection. HPLC and TLC was performed to test the radiochemical and chemical purity, residual solvents were tested using gas chromatography and content of tetrabutylammonium (TBA) was determined using a TLC spot test. Further quality control (radionuclidic purity, appearance, pH, endotoxins, sterility, filter integrity) was done in compliance with current pharmacopoeias. [^{18}F]PSMA-1007 was given to patients via an intravenous bolus (mean 301±46 MBq, range 154–453 MBq).

Imaging Protocol

Heidelberg University Hospital:

All patients (*n=70*) were imaged on a Biograph mCT Flow scanner (Siemens Medical Solutions, Erlangen, Germany). PET was acquired in 3-D mode (matrix 200×200) using FlowMotion (Siemens). The emission data were corrected for randoms, scatter and decay. Reconstruction was performed with an ordered subset expectation maximization (OSEM) algorithm with two iterations/21 subsets and Gauss-filtered to a transaxial resolution of 5 mm at full-width at half-maximum (FWHM); Attenuation correction was performed using the unenhanced low-dose CT data. The CT-scans were reconstructed to a slice thickness of 5-mm, increment of 3-4 mm, soft tissue reconstruction kernel (B30), using CareDose (Siemens).

Technical University Munich:

All patients (*n=139*) were examined on a Biograph mCT scanner (Siemens Medical Solutions, Erlangen, Germany). A diagnostic CT scan was initially performed in the portal venous phase 80 s after intravenous injection of an iodinated contrast agent (Imeron 300) followed by the PET scan. All patients received diluted oral contrast (300 mg Telebrix) and rectal filling with a negative contrast agent (100–150 mL). All PET scans were acquired in 3D-mode with an acquisition time of 3-4 min per bed position. Emission data were corrected for randoms, dead time, scatter, and attenuation and 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).

FALP, Santiago de Chile:

All imaging (*n=42*) was acquired on a Biograph mCT20 scanner (Siemens Medical Solutions, Erlangen, Germany). A diagnostic CT-scan was performed in the equilibrium phase 60-70 s after intravenous injection of iodinated contrast agent (Optiray 300, Mallinckrodt Pharmaceuticals) and all patients received water as oral contrast. Subsequent PET scans were acquired in 3D-mode with an acquisition time of 1,5 min per bed position. Emission data were corrected for scatter and attenuation and reconstructed iteratively by an ordered-subsets expectation maximization algorithm (two iterations, 21 subsets) followed by a postreconstruction smoothing Gaussian filter (4-mm full width at one-half maximum).

Image Analysis

All images were read by two double board certified (radiology, nuclear medicine; *FLG, ME*) physicians in consensus. Focal uptake of [^{18}F]PSMA1007 higher than the surrounding background and not associated with physiological uptake was considered suspicious for malignancy. Typical pitfalls in PSMA-ligand PET-imaging (e.g. celiac and other ganglia, fractures, degenerative changes) were taken into account *(16)*. All lesions suspicious for recurrent PC were noted and grouped into: (a) local recurrence, (b) lymph node metastases (stratified by location into pelvic, retroperitoneal and supradiaphragmatic locations), (c) bone metastases and (d) other metastases (e.g. lung, liver).

Statistical Analysis

The detection rate (number of patients with at least one positive finding) was plotted against the absolute PSA-value. Mann–Whitney U tests were used to evaluate differences between single groups (Gleason Score, ADT) and to evaluate differences concerning PSA values among groups with and without pathological uptake. Chi-Square test was used to compare proportions. All tests were performed two-sided and a level of significance of α=5% was used. Statistical analyses were conducted with the software MedCalc, version 17.8.6, 2017 (MedCalc, Ostend, Belgium).

RESULTS

Radiosynthesis and Quality Control

[^{18}F]PSMA-1007 was obtained in radiochemical yields of 50±10 % after a total synthesis time of 25-45 minutes. The radiochemical purity of [^{18}F]PSMA-1007 was ≥95% (HPLC/TLC) with free [^{18}F]fluoride being the major impurity. The content of PSMA-1007 was below 10 µg/mL for the final product solution. The radiopharmaceutical specification in accordance with current pharmacopoeias was met for all productions of the [^{18}F]PSMA-1007 final product solution. No radiolysis of [^{18}F]PSMA-1007 was observed up to 8 hours after end of synthesis. No adverse events were reported associated with the use of 18F-PSMA-1007.

Detection Efficacy

Of the 251 patients, 204 (81.3%) showed one or more localized areas suspicious for recurrent PC. The detection efficacy of [^{18}F]PSMA-1007 PET/CT was 94.1% (79/84; 95%CI: 0.75-1) for a PSA value ≥2 ng/mL, 90.1% (50/55; 95%CI: 0.67-1) for a PSA value 1-<2 ng/mL, 74.5% (35/47; 95%CI: 0.52-1) for a PSA value 0.5-<1 ng/mL and 61.5% (40/65; 95%CI: 0.44-0.86) for a PSA value 0.2-<0.5 ng/ml (***Fig.1A***). Mean PSA was significantly lower in patients with negative [^{18}F]PSMA-1007 PET/CT compared to positive patients (6.8±22.4 vs. 0.95±1.56 ng/ml; *p<0.0001*). There was a trend towards a higher detection rate (86.3 vs. 77.3%, p=0.07) in patients after prior salvage RTx vs. without prior salvage therapy. However, PSA-values were significantly higher in patients after vs. without prior salvage RTx (median 1.3 vs. 0.98 ng/ml).

Lesion location

The different regions involved by recurrent disease are listed in ***Tab. 2***. ***Fig. 1B*** presents the percentage of positive lesions for different regions stratified by PSA-value. The relative number of lesions indicating local recurrence increased slightly with increasing with PSA-value. The number increased by 20.0% (12/65), 21.3% (10/47), 23.6% (13/55) and 31.0% (26/84) at PSA-values of 0.2-<0.5, 0.5-<1, 1-<2 and ≥2 ng/ml, respectively. Loco-regional pelvic lymph node metastases were present in 26.2% (17/65), 34.0% (16/47), 47.2% (26/55) and 51.2% (43/84) at PSA-values of 0.2-<0.5, 0.5-<1, 1-<2 and ≥2 ng/ml, respectively.

Distant lymph node metastases were only present in 6.1% (4/56) of patients with very early biochemical recurrence (PSA 0.2-<0.5 ng/ml). Involvement of supradiaphragmatic nodes was rare in in very early and early biochemical recurrence (PSA 0.2-<0.5 and 0.5-<1 ng/ml) representing only 4.6% (3/65) and 4.3% (2/47) of cases, respectively. However, they became more common at higher PSA levels: 12.7% (7/55) for PSA 1-<2 and ≥2 ng/ml and 21.4% (18/84) for PSA > 2 ng/ml. Retroperitoneal lymph node metastases were present in more than 10% of cases with PSA-values equal to or higher than 0.5 ng/ml (12.8% [6/47), 10.9% [6/54] and 39.3% [33/84] for PSA-values of 0.5-<1, 1-<2 and ≥2 ng/ml, respectively).

Interestingly, findings indicating bone metastases were already present in a considerable number of patients at low PSA-values. Rates of bone metastases increased with increasing PSA-values: 24.6% (16/65), 34.0% (16/47), 52.7% (29/55) and 47.6% (40/84) at PSA-values of 0.2-<0.5, 0.5-<1, 1-<2 and ≥2 ng/ml, respectively. Visceral lesions were

uncommon in all patient groups with 1.5% (1/65), 2.1% (1/47), 7.3% (4/55) and 3.6% (3/84) at PSA-values of 0.2-<0.5, 0.5-<1, 1-<2 and ≥2 ng/ml, respectively.

Influence of Anti-Androgen Therapy and Primary Histological Differentiation

In our cohort PSMA PET efficacy was statistically higher in patients with prior ADT (*p=0.0179*). Lesions were detected in 91.7% (55/60) of patients with prior exposure to ADT but only 78.0% (149/191) of patients with no therapy. PSA-values trended higher in patients with prior ADT history (mean 8.0 ± 13.9 vs. 5.0 ± 22.0 ng/ml, median 2.3 vs. 1.0), but this was not statistically different (*p=0.32*). A similar trend (p=0.08) towards a higher detection in patients with vs. without ADT can be found if the analysis is restricted to patients with PSA < 2 ng/ml. The corresponding detection rates were 72.3% (102/141) vs. 88.5% (23/26) in patient with vs. without ADT, respectively.

With respect to positivity of the PSMA scan vs. original Gleason score of the primary tumor, [^{18}F]PSMA-1007 PET/CT was positive in 76.3% (106/139) of patients with a Gleason score ≤7 and in 86.7% (72/83) of patients with a Gleason score ≥8 (*p=0.06*). Interestingly, there was no difference in mean PSA-values between these two groups (PSA mean: 4.1 ± 14.8 vs. 8.1 ± 28.7 ng/ml, *p=0.17*).

DISCUSSION

PSA-relapse after radical prostatectomy is common and is denoted by biochemical failure defined as a rise in PSA-level of equal and greater than 0.2 ng/mL (*17*). Localizing the recurrence can impact treatment decisions as local recurrence can be treated with focal radiation whereas distant metastases require more systemic therapies. Conventional imaging modalities (traditional bone scan and CT or MRI and other forms of PET) are notoriously insensitive for early recurrent disease (*4, 6, 18*) and especially for detection of lymph node and distant metastases which yields the highest impact on patient management (19). Therefore, the goal of this study was to evaluate [^{18}F]PSMA-1007 PET/CT to identify sites of recurrence.

A number of other PET agents have been introduced for detecting sites of BCR. Detection rates vary widely; between 34% and 88% for [^{11}C]choline, 43% to 79% for [^{18}F]Fluoromethylcholine and 59% to 80% for [^{11}C]acetate (*7, 20-25*). With the introduction of ^{68}Ga-PSMA-ligand PET/CT much improved rates of detection, especially in patients with very low and low PSA, was observed. Recently, another ^{18}F-labelled PSMA radioligand, ^{18}F-DCFPyl was introduced and is undergoing prospective evaluation. All of these agents are primarily excreted via the urinary route (*26*).

We recently evaluated [^{18}F]PSMA-1007 in a small number of patients with BCR (*27*). It showed favorable detection rates in PSMA-positive prostate cancer patients but was only minimally excreted by the urinary tract. It is important to mention that [^{18}F]PSMA-1007 can be produced in high radiochemical yields of 50±10 % on a variety of automated radiosynthesizers by direct radiofluorination of the unprotected radiolabeling precursor and composition of the final injection solution without (semi)preparative radio-HPLC

separation by simple solid phase extraction (*15*). This simple radiosynthesis can be easily set up as GMP-compliant production and results in activity amounts per batch which not only fulfills on-site clinical needs, but also can sustainably be used for distributing [^{18}F]PSMA-1007 to satellite PET/CT centers.

The straight forward GMP-compliant radiosynthesis of [^{18}F]PSMA-1007 without HPLC separation (feasible on different automated radiosynthesizers) bodes well for economic production of the agent. Indeed, the ease with which it was synthesized contributed to the ability to select 251 patients with a highly selected indication from an even larger patient cohort relatively quickly at 3 institutions. While this study is retrospective in nature, it nevertheless provides a good basis for future prospective trials as it indicates equal to or better performance of [^{18}F]PSMA-1007 compared to other PSMA-PET agents. For instance, these results suggest that [^{18}F]PSMA-1007 PET/CT exhibits a higher detection rate in patients with very low PSA-levels of 0.2-0.5 ng/mL compared to literature reports for [^{68}Ga]Ga-PSMA-11 (62% vs 46-58%) (*2*, *3*) Figure-5. Of note, early treatment of these patients has been shown to have better outcomes (28, 29) and therefore, more sensitive detection is an advantage. At higher PSA levels detection rates for [^{18}F]PSMA-1007 and [^{68}Ga]PSMA-11 appear similar, for example PSA-levels of 0.5-1 ng/mL (74% for [^{18}F]PSMA-1007 PET/CT vs. 73% (*2*, *3*) for [^{68}Ga]Ga-PSMA-11). A bar graph comparing published detection rates for [^{68}Ga]Ga-PSMA-11 and [^{18}F]PSMA-1007 derived from this study is shown as figure 5.

The slightly improved detection rate of [^{18}F]PSMA-1007 at low PSA-levels might also be related to the different energy profiles of the positron emitters ^{18}F and ^{68}Ga; the theoretically achievable resolution of ^{18}F is higher than ^{68}Ga, particularly in human PET-systems (*25*). Therefore, it could be assumed that ^{18}F-labelled PSMA-ligands might improve the sensitivity for tumor detection of very small tumors. A more likely source of advantage for [^{18}F]PSMA-1007 is that it is cleared via the hepatobiliary excretion. This could be diagnostically advantageous in particular for detecting local recurrence and locoregional pelvic lymph node metastases (*30, 31, 32*) We do not believe strong conclusions should be drawn from the higher rate of detection in patients with prior ADT exposure. It is likely these patients had more advanced disease than untreated patients as they showed rising PSA despite ADT and possibly radiation therapy. In addition, the data presented indicated higher PSA-values in the group of patient with vs. without ADT within 6 months prior to imaging which could constitute a confounding factor. The role of ADT in PSMA PET ligand uptake is highly controversial. At the cellular level ADT initially increases PSMA expression. However, it is unclear what happens in patients on chronic treatment as this leads to a decrease in the number of the tumor cells and the relative magnitude of these individual effects likely varies according to whether the tumor is castrate sensitive or castrate resistant.

A limitation of this study and most studies PSMA-PET studies is the lack of histopathological confirmation of the detected lesions. Many of the recurrences and nodes detected are quite small and difficult to biopsy. However, if histopathology validation is available it shows a very high positive predictive value of PSMA-ligand PET agents.

Results from a recent [^{18}F]PSMA-1007 study that included histopathologic confirmation showed a high correlation between PSMA-positive lesions and PSMA-positive histopathological findings in primary tumors and loco-regional metastases (sensitivity 94.7%; *11*). Another limitation of this study is that it was retrospective in nature and thus missing some potentially interesting information about the effect of PSA kinetics and patient outcomes. To overcome these limitations, hopefully prospective studies will be performed in the near future. Notably, in our study a PSA equal and greater than 0.2 ng/ml was defined as indicative for BCR. This is the most accepted cutoff despite extensive discussions in literature (33).

CONCLUSION

[^{18}F]PSMA-1007 PET/CT demonstrates a high detection rate for patients with biochemical recurrence after radical prostatectomy. [^{18}F]PSMA-1007 PET/CT could improve patient management by correctly identifying sites of recurrence early in the course of the disease. [^{18}F]PSMA-1007, perhaps due to its alternate route of excretion, that bypasses the urinary tract, shows specific advantages for detecting local recurrence and loco-regional nodes which are generally more prevalent at very low PSA levels.

REFERENCES

1. Rouviere O, Vitry T, Lyonnet D. Imaging of prostate cancer local recurrences: why and how? Eur Radiol. 2010;20:1254-1266.
2. Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the ^{68}Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42:197-209.
3. Eiber M, Maurer T, Souvatzoglou M, Beer AJ, Ruffani A, Haller B. Evaluation of hybrid ^{68}Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med. 2015;56:668-674.
4. Maurer T, Gschwend JE, Rauscher I, et al. Diagnostic efficacy of ^{68}Gallium-PSMA positron emission tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. J Urol. 2016;195:1436-1443.
5. Perera M, Papa N, Christidis D, et al. Sensitivity, specificity, and predictors of positive 68Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol. 2016;70:926-937.
6. Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of ^{68}Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. Eur J Nucl Med Mol Imaging. 2017;44:1258-1268.
7. Morigi JJ, Stricker PD, van Leeuwen PJ, et al. Prospective comparison of ^{18}F-fluoromethylcholine versus ^{68}Ga-PSMA PET/CT in prostate cancer patients who have rising PSA after curative treatment and are being considered for targeted therapy. J Nucl Med. 2015;56:1185-1190.
8. Afshar-Oromieh A, Haberkorn U, Eder M, Eisenhut M, Zechmann CM. [^{68}Ga]Gallium-labelled PSMA ligand as superior PET tracer for the diagnosis of prostate cancer: comparison with ^{18}F-FECH. Eur J Nucl Med Mol Imaging. 2012;39:1085-1086.
9. Rauscher I, Düwel C, Haller B, Rischpler C, Heck MM, Gschwend JE, Schwaiger M, Maurer T, Eiber M. Efficacy, Predictive Factors, and Prediction Nomograms for 68Ga-labeled Prostate-specific Membrane Antigen-ligand Positron-emission Tomography/Computed Tomography in Early Biochemical Recurrent Prostate Cancer After Radical Prostatectomy. European Urology 2018
10. Cho SY, Gage KL, Mease RC, et al. Biodistribution, tumor detection, and radiation dosimetry of ^{18}F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer. J Nucl Med. 2012;53:1883-1891.
11. Giesel FL, Hadaschik B, Cardinale J, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. Eur J Nucl Med Mol Imaging. 2017;44:678-688.
12. Eiber M, Weirich G, Holzapfel K, et al. Simultaneous ^{68}Ga-PSMA HBED-CC PET/MRI improves the localization of primary prostate cancer. Eur Urol. 2016;70:829-836.
13. Afshar-Oromieh A, Haberkorn U, Schlemmer HP, et al. Comparison of PET/CT and PET/MRI hybrid systems using a ^{68}Ga-labelled PSMA ligand for the diagnosis of recurrent prostate cancer:
14. Freitag MT, Radtke JP, Afshar-Oromieh A, et al. Local recurrence of prostate cancer after radical prostatectomy is at risk to be missed in ^{68}Ga-PSMA-11-PET of PET/CT and PET/MRI: comparison with mpMRI integrated in simultaneous PET/MRI. Eur J Nucl Med Mol Imaging. 2017;44:776-787.

15. Cardinale J, Martin R, Remde Y, Schäfer M, Hienzsch A, Hübner S, Zerges AM, Marx H, Hesse R, Weber K, Smits R, Hoepping A, Müller M, Neels OC, Kopka K. Procedures for the GMP-Compliant Production and Quality Control of 18FPSMA-1007: A Next Generation Radiofluorinated Tracer for the Detection of Prostate Cancer. Pharmaceuticals (Basel) 2017 Sep 27;10(4). pii: E77.
16. Hofman MS, Hicks RJ, Maurer T, Eiber M.Prostate-specific Membrane Antigen PET: Clinical Utility in Prostate Cancer, Normal Patterns, Pearls, and Pitfalls. Radiographics. 2018 Jan-Feb;38(1):200-217.
17. Giesel FL, Fiedler H, Stefanova M, Sterzing F, Rius M, Kopka K, Moltz JH, Afshar-Oromieh A, Choyke PL, Haberkorn U, Kratochwil C.PSMA PET/CT with Glu-urea-Lys-(Ahx)-[^{68}Ga(HBED-CC)] versus 3D CT volumetric lymph node assessment in recurrent prostate cancer.Eur J Nucl Med Mol Imaging. 2015 Nov;42(12):1794-800.
18. Perera M, Papa N, Christidis D, et al. Sensitivity, specificity, and predictors of positive ^{68}Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol. 2016;70:926-937.
19. Vargas HA, Martin-malburet AG, Takeda T, et al. Localizing sites of disease in patients with rising serum prostate-specific antigen up to 1ng/ml following prostatectomy: How much information can conventional imaging provide?. Urol Oncol. 2016;34(11):482.e5-482.e10.
20. Schmid DT, John H, Zweifel R, et al. Fluorocholine PET/CT in patients with prostate cancer: initial experience. Radiology. 2005;235:623–628.
21. Pelosi E, Arena V, Skanjeti A, et al. Role of whole-body ^{18}F-choline PET/CT in disease detection in patients with biochemical relapse after radical treatment for prostate cancer. Radiol Med (Torino). 2008;113:895–904.
22. Detti B, Scoccianti S, Franceschini D, et al. Predictive factors of [^{18}F]-choline PET/CT in 170 patients with increasing PSA after primary radical treatment. J Cancer Res Clin Oncol. 2013;139:521–528.
23. Cimitan M, Bortolus R, Morassut S, et al. [^{18}F]fluorocholine PET/CT imaging for the detection of recurrent prostate cancer at PSA relapse: experience in 100 consecutive patients. Eur J Nucl Med Mol Imaging. 2006;33:1387–1398.
24. Oyama N, Miller TR, Dehdashti F, et al. ^{11}C-acetate PET imaging of prostate cancer: detection of recurrent disease at PSA relapse. J Nucl Med. 2003;44:549–555.
25. Sanchez-Crespo A. Comparison of Gallium-68 and Fluorine-18 imaging characteristics in positron emission tomography. Appl Radiat Isot. 2013 Jun;76:55-62.
26. Rowe SP, Gorin MA, Pomper MG. Imaging of Prostate-Specific Membrane Antigen Using [18F]DCFPyL. PET Clin. 2017 Jul;12(3):289-296. doi: 10.1016/j.cpet.2017.02.006. Epub 2017 Apr 1.
27. Giesel F, Will L, Kesch C, Freitag M, Kremer C, Merkle J, Neels O, Cardinale J, Hadaschik B, Hohenfellner M, Kopka K, Haberkorn U, Kratochwil C. Biochemical recurrence of prostate cancer: initial results with ^{18}F-PSMA-1007 PET/CT.J Nucl Med. 2018 Feb 1. pii: jnumed.117.196329.
28. Emmett L, Van leeuwen PJ, Nandurkar R, et al. Treatment Outcomes from Ga-PSMA PET/CT-Informed Salvage Radiation Treatment in Men with Rising PSA After Radical Prostatectomy: Prognostic Value of a Negative PSMA PET. J Nucl Med. 2017;58(12):1972-1976.
29. Sterzing F, Kratochwil C, Fiedler H, et al. (68)Ga-PSMA-11 PET/CT: a new technique with high potential for the radiotherapeutic management of prostate cancer patients. Eur J Nucl Med Mol Imaging. 2016;43(1):34-41.

30. Giesel F, Will L, Lawal I, Lengana T, Kratochwil C, Vorster M, Neels O, Reyneke F, Haberkon U, Kopka K, Sathekge M. Intra-individual comparison of ^{18}F-PSMA-1007 and ^{18}F-DCFPyL PET/CT in the prospective evaluation of patients with newly diagnosed prostate carcinoma: A pilot study. J Nucl Med. 2017 Dec 21. pii: jnumed.117.204669.
31. Rahbar K, Weckesser M, Ahmadzadehfar H, Schäfers M, Stegger L, Bögemann M. Advantage of ^{18}F-PSMA-1007 over ^{68}Ga-PSMA-11 PET imaging for differentiation of local recurrence vs. urinary tracer excretion. Eur J Nucl Med Mol Imaging. 2018 Feb 14. doi: 10.1007/s00259-018-3952-0.
32. Will L, Giesel FL, Freitag MT, Berger AK, Mier W, Kopka K, Koerber SA, Rathke H, Kremer C, Kratochwil C, Kauczor HU, Haberkorn U, Weber TF. Integration of CT urography improves diagnostic confidence of ^{68}Ga-PSMA-11 PET/CT in prostate cancer patients. Cancer Imaging. 2017 Dec 20;17(1):30. doi: 10.1186/s40644-017-0132-6.
33. Cookson, M.S., Aus, G., Burnett, A.L., et al: Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association prostate guidelines for localized prostate cancer update panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol, **177**: 540, 2007

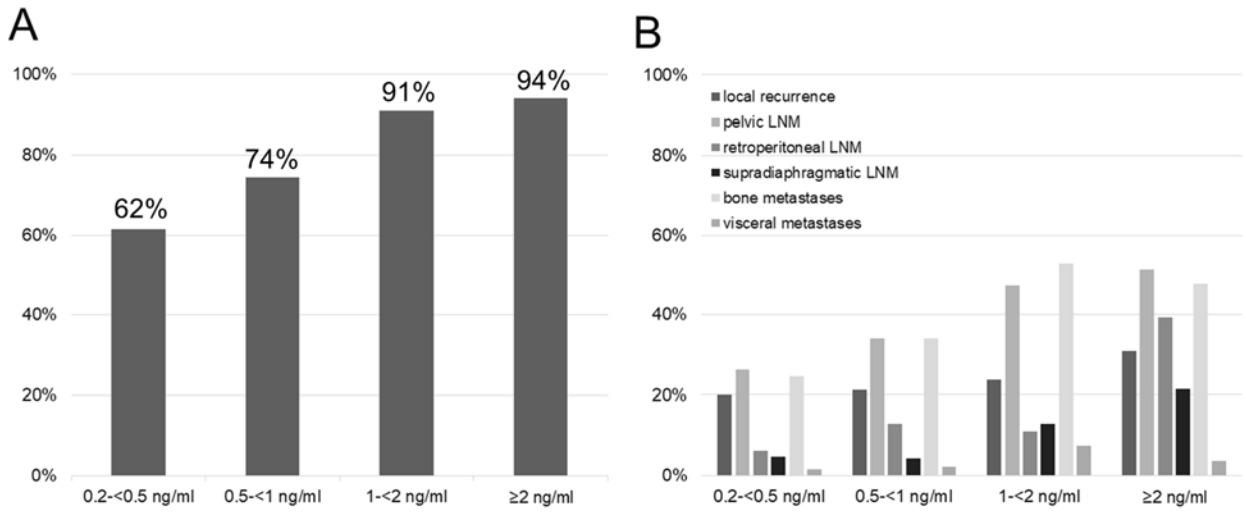

Figure 1. Overall detection rate of [^{18}F]PSMA-1007 PET/CT (A) and relative number of lesions grouped by different regions (B) in relation to PSA-level.

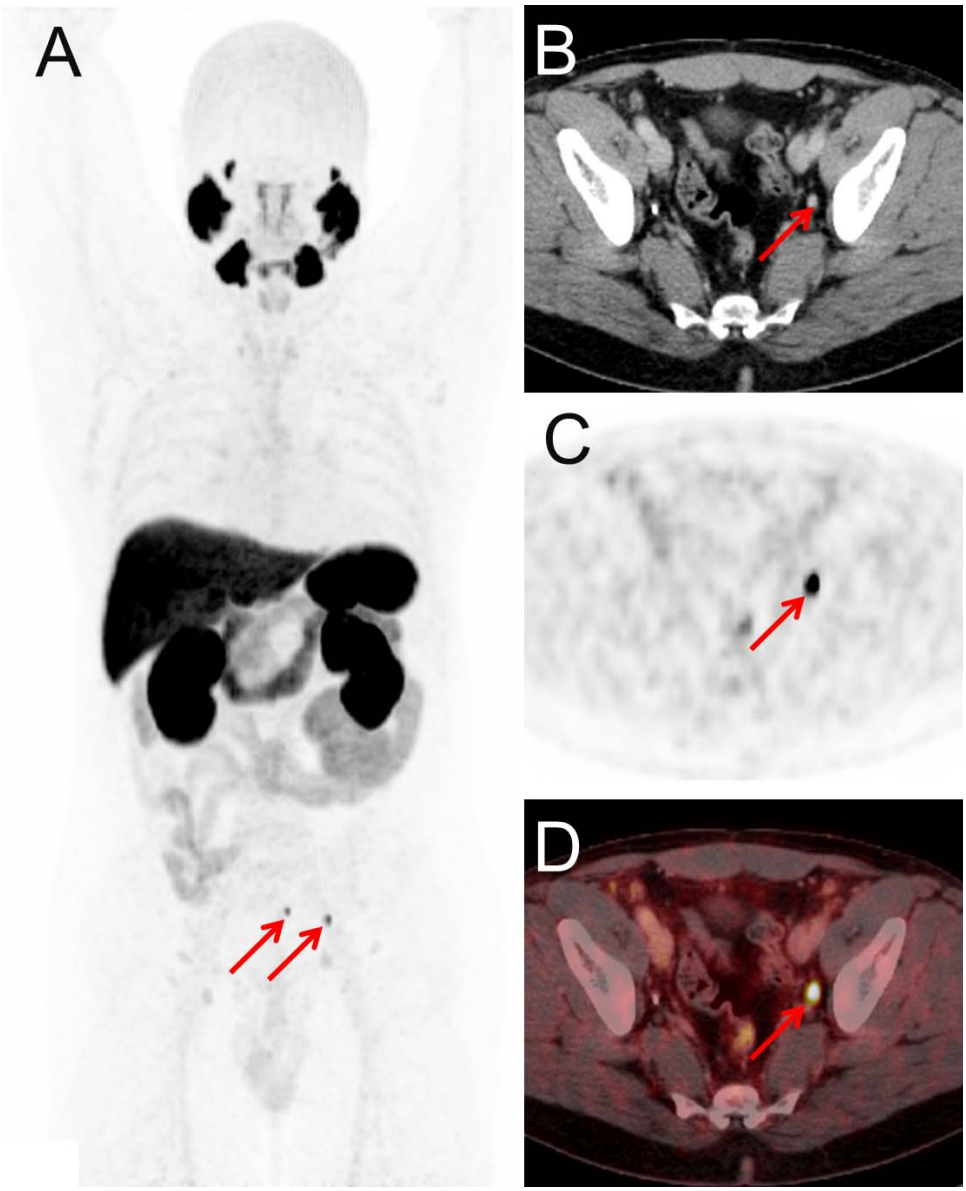

Figure 2. Set of images of a 57 year old patient with status post radical prostatectomy (2010, Gleason Score 8, pT3b, pN0), status post salvage radiation therapy to the prostate bed and rising PSA-value of 0.43 ng/mL (08/2017). Maximum-intensity projection of [^{18}F]PSMA1007 PET shows two intense tracer-associated lesions in the left pelvic region (A). Transaxial PET (C) and fused PET/CT images (D) show high [^{18}F]PSMA-1007 uptake in a subcentimeter (7 mm) lesions as determined by the corresponding CT (B). Subsequent radioguided salvage surgery proved the malignant nature of the lesions.

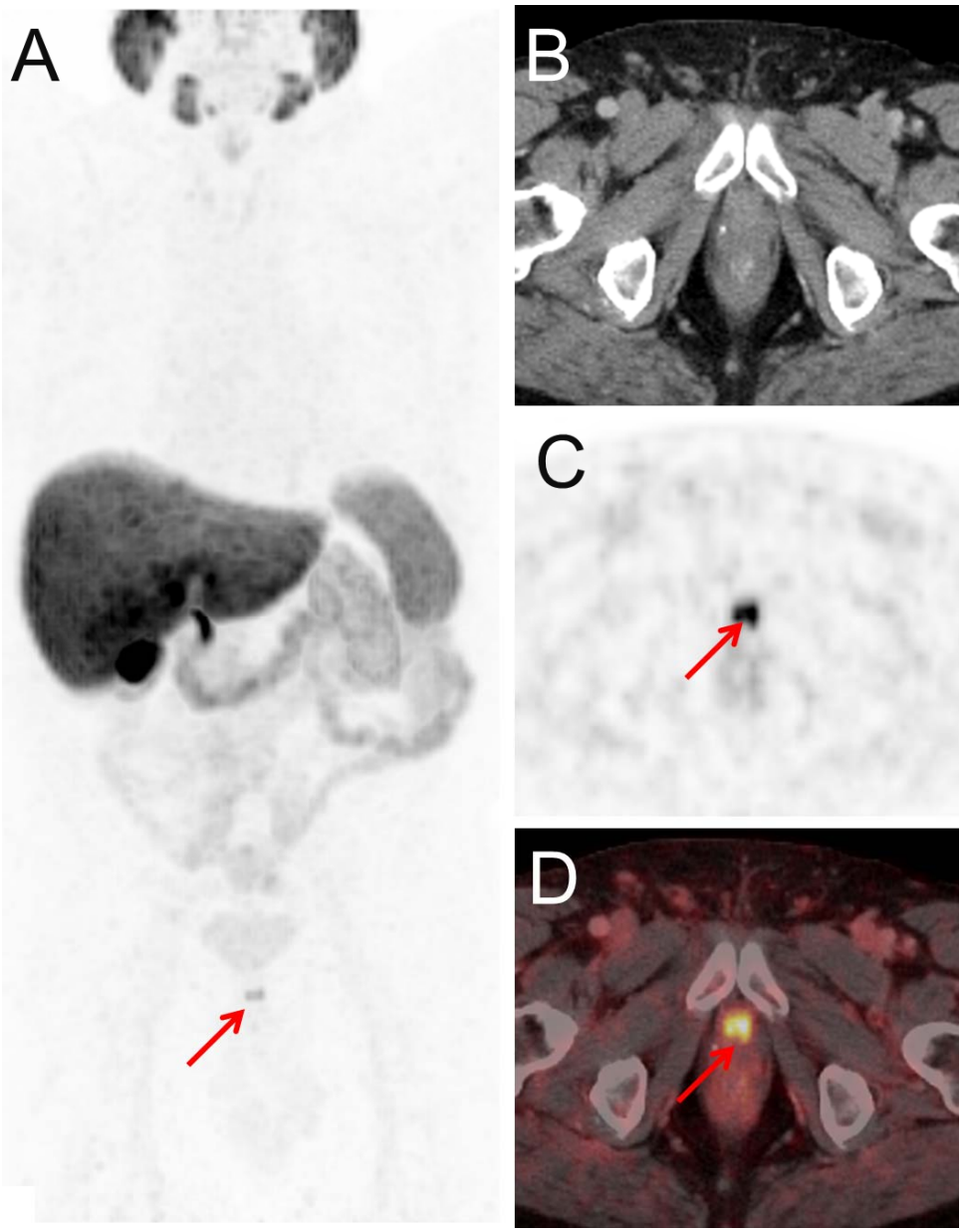

Figure 3. Set of images of a 64 year old patient with status post radical prostatectomy (08/2012, Gleason Score 9, pT3b, pN0) and rising PSA-value of 3.9 ng/mL (10/2017). Maximum-intensity projection of [^{18}F]PSMA-1007 PET shows an intense tracer-associated uptake in a lesion below the bladder (A). It can be localized in the region of the urethral anastomosis using transaxial PET (C) and fused PET/CT images (D). Post-imaging salvage radiation to the prostatic fossa was performed combined with a single injection of a GnRH-analog in 10/2017 resulting in a drop of PSA-value below detection threshold (<0.07 ng/ml, last measurement 02/2018).

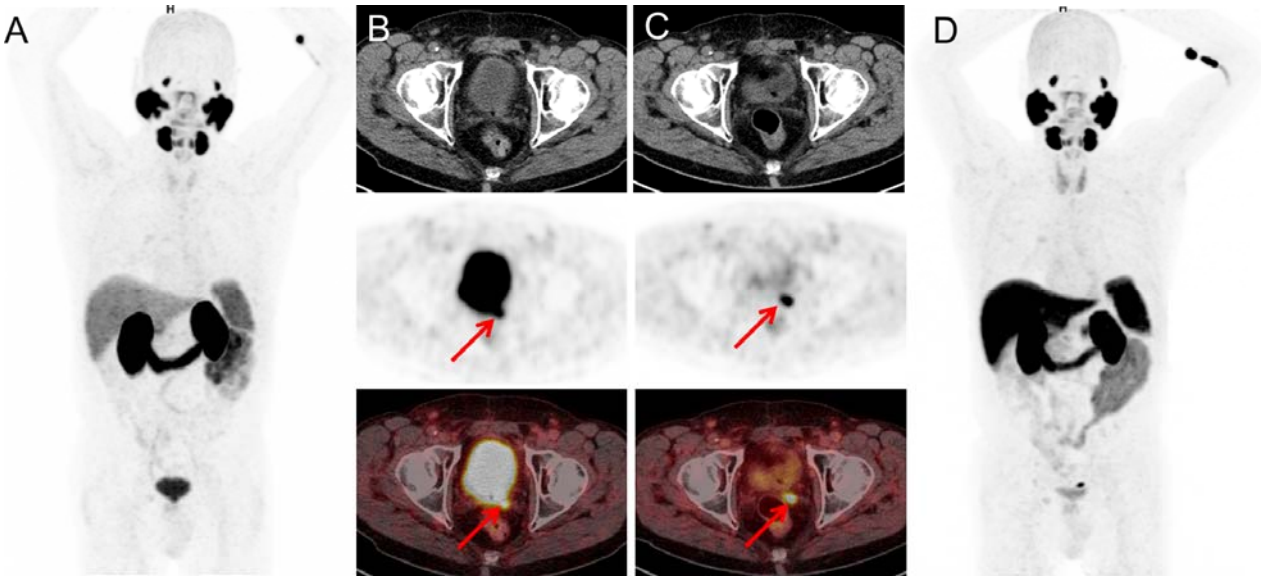

Figure 4. Set of images of a 76 year old patient with status post radical prostatectomy (2006, Gleason Score 7b, pT3a, pN0) and slowly rising PSA-value of 0.78 ng/mL (10/2017). The patient underwent primarily a [^{68}Ga]PSMA-11 PET/CT (A,B) resulting in the suspicion of local recurrence. No definite diagnosis could be made based on adjacent high activity retention in the urinary bladder. Subsequent [^{18}F]PSMA-1007 PET/CT (C, D) three month later clearly depicts PSMA-ligand uptake in the left seminal vesicle with high contrast and very low retention in the bladder.

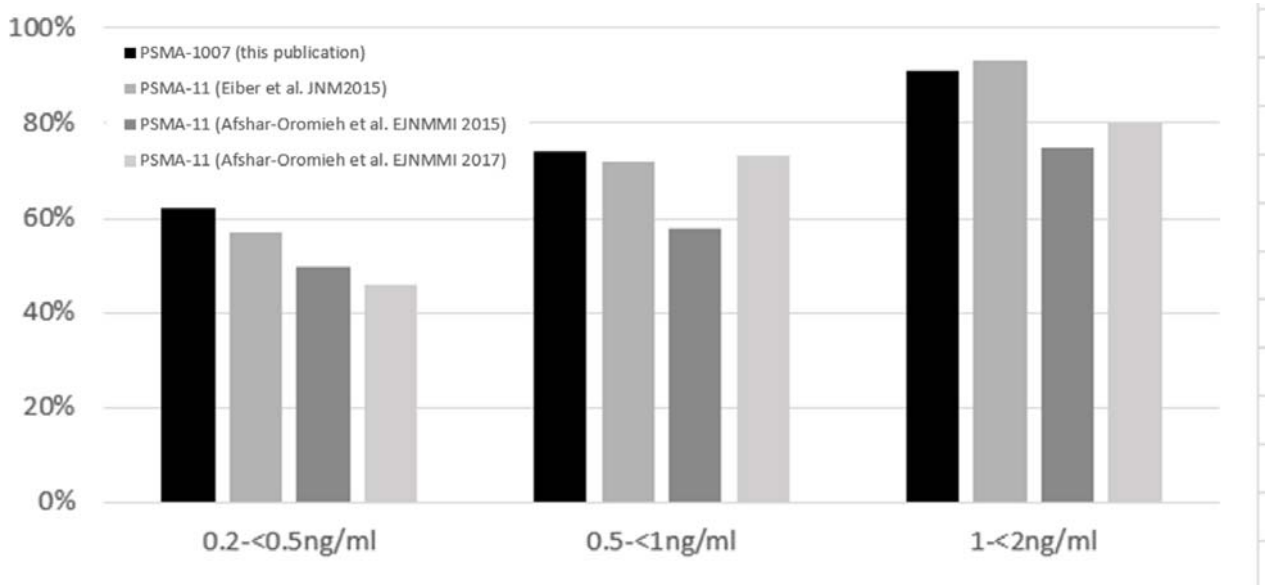

Figure 5. Comparison of detection rates between [^{18}F]PSMA-1007 and [6^{8}Ga]PSMA-11 derived from different studies.

TABLES

Table 1: Clinical and pathologic characteristics of the 251 patients

Characteristics		*n* = 251
Age at PET/CT, median (years)		70 (range 48-86)
Further treatment	External radiation after RP	110 (43.8%)
	Antihormonal treatment	74 (29.5%)
ADT within 6 months prior to imaging		60 (23.9%)
Gleason Score	≤ 6	13 (5.2%)
	7	125 (49.8%)
	≥ 8	85 (33.1%)
	Unknown	28 (11.2%)
Pathologic Primary Tumor Staging (pT)	pT2	74 (29.5%)
	pT3	92 (36.7%)
	pT4	7 (2.8%)
	Unknown	78 (31.1%)
Pathologic Regional LN Staging (pN)	pN0	123 (49.0%)
	pN1	41 (16.3%)
	pNx	87 (34.7%)
Positive Margin	R0	80 (31.8%)
	R1	53 (21.1%)
	Unknown	118 (47.0%)
Initial PSA-value, median (ng/ml)		10.9 (0.6-250)
Salvage radiation therapy prior to PET/CT		110 (43.8%)
Time between surgery and PET/CT, median (months)		57 (range 1-321)
Last PSA value prior to PET/CT, median (ng/ml)		1.2 (range 0.2-228)

Table 2. Different regions involved by recurrent PC in ^{18}F-PSMA1007-PET/CT. Please note that more than one region can be involved per patient.

Region	No. (percentage) of patients
Local recurrence	62 (24.7%)
Lymph node metastases	
- pelvic	102 (40.6%)
- retroperitoneal	49 (19.5%)
- supradiaphragmatic	30 (12.0%)
Bone metastases	101 (40.2%)
Other (lung, liver, …) metastases	9 (3.6%)