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Matched-pair comparison of ^{68}Ga-PSMA-11 and ^{18}F-rhPSMA-7 PET/CT in patients with primary and biochemical recurrence of prostate cancer: frequency of non-tumor related uptake and tumor positivity

Original Research

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ABSTRACT

Purpose: Radiohybrid prostate-specific membrane antigen (rhPSMA) ligands are a new class of prostate cancer theranostic agents. ^{18}F-rhPSMA-7, offers the advantages of ^{18}F-labelling and low urinary excretion compared with ^{68}Ga-PSMA-11. Here, we compare frequency of non-tumor related uptake and tumor positivity with ^{68}Ga-PSMA-11 and ^{18}F-rhPSMA-7 in patients with primary or recurrent prostate cancer.

Methods: This retrospective matched-pair comparison matched 160 ^{18}F-rhPSMA-7 with 160 ^{68}Ga-PSMA-11 PET/CT studies for primary staging (n=33) and biochemical recurrence (n=127) according to clinical characteristics. Two nuclear medicine physicians reviewed all scans, first, identifying all PET-positive lesions, then differentiating lesions suspicious for prostate cancer from those that were benign, based on known pitfalls and ancillary information from CT. For each region, SUVmax of the lesion with the highest PSMA-ligand uptake was noted. Tumor positivity rates were determined and SUVmax were compared separately for each tracer.

Results: ^{18}F-rhPSMA-7 and ^{68}Ga-PSMA-11 PET revealed 566 and 289 PSMA-ligand positive lesions, respectively. Of these, 379 and 100 lesions, equaling 67.0 % and 34.6 % of all PSMA-positive lesions were considered benign, respectively. The distribution of their etiology was similar (42%, 24%, 25% in ^{18}F-rhPSMA-7 vs. 32%, 24%, 38% in ^{68}Ga-PSMA-11 for ganglia, bone and unspecific lymph nodes, respectively). All primary tumors were positive with both agents (n=33 each) while slightly more metastatic lesions were observed with ^{68}Ga-PSMA-11 in both disease stages (113 for ^{18}F-rhPSMA-7 and 124 for ^{68}Ga-PSMA-11). SUVmax of ^{18}F-rhPSMA-7 and ^{68}Ga-PSMA-11 did not differ ($P>0.05$) in local recurrence or primary prostate cancer, however, the tumor-to-bladder ratio was significantly higher with ^{18}F-rhPSMA-7 (4.9±5.3

vs 2.2±3.7, p=0.02 for local recurrence and 9.8±9.7 vs 2.3±2.6, p<0.001 for primary prostate cancer).

Conclusion: The tumor positivity rate was consistently high for ^{68}Ga-PSMA-11 and ^{18}F-rhPSMA-7. Both tracers revealed a considerable number of areas of uptake that were reliably identified as benign by trained physicians making use of corresponding morphological imaging and known PSMA pitfalls. These were more frequent with ^{18}F-rhPSMA-7. However, the matched-pair comparison could have introduced a source of bias. Adequate reader training can allow physicians to differentiate benign uptake from disease and be able to benefit from the logistical and clinical advantages of ^{18}F-rhPSMA-7.

Keywords

Positron emission tomography (PET); prostate cancer; prostate specific membrane antigen (PSMA); radiohybrid PSMA (rhPSMA); ^{18}F-rhPSMA-7; ^{68}Ga-PSMA-11

INTRODUCTION

Prostate specific membrane antigen (PSMA)-ligand positron emission tomography (PET) is already recommended in various guidelines as the preferred imaging tool to localize disease in biochemical recurrence of prostate cancer (*1,2*). In the primary setting, a recently published prospective multicenter study in high-risk prostate cancer patients has confirmed the ability of ^{68}Ga-PSMA-11 PET/CT to accurately assess site and extent of disease providing superior accuracy in comparison to conventional imaging (*3*).

However, PSMA-ligand PET may not be as specific for prostate cancer as initially thought, underlined by an increasing number of published case series describing increased PSMA-ligand uptake in lesions attributed to benign origin such as ganglia, healing bone fracture, fibrous dysplasia, liver hemangioma, or non-prostate cancer malignancies (*4,5*).

Nowadays, ^{68}Ga-labelled PSMA-ligands are increasingly replaced by ^{18}F-labeled compounds offering various advantages including (A) lower positron energy of ^{18}F potentially improving spatial resolution and reducing blurring effects, (B) longer half-life of ^{18}F, and (C) high yield production in cyclotrons, the latter two result in large batch production suitable for long-distance distribution and potential cost savings. So far, various ^{18}F–labeled PSMA-ligands (e.g. ^{18}F-PSMA-1007, ^{18}F-DCFPyL, ^{18}F-rhPSMA-7) have been developed showing similar detection rates in both primary staging and restaging compared to ^{68}Ga-PSMA-11 PET (*6-9*). However, a recent matched-pair comparison in patients with recurrent prostate cancer described an approximately 5 times higher number of PSMA-positive lesions attributed to benign origin (e.g. unspecific lymph nodes or ganglia) with ^{18}F-PSMA-1007 in comparison with ^{68}Ga-PSMA-

11, while similar cancer detection rates were observed (*10*). This raises questions about the frequency of non-prostate cancer related PSMA-positive lesions in other ^{18}F–labeled PSMA ligands. Radiohybrid PSMA (rhPSMA) ligands are a new class of PSMA-targeting agents allowing fast and efficient ^{18}F-labeling as well as the use of radiometals such as ^{68}Ga or ^{177}Lu (*11*). Due to rapid blood clearance, but only minimal urinary excretion, potential advantages for local tumor assessment exist, as high tracer retention in the urinary tract and bladder is known to impair image interpretation.

Thus, the aim of this retrospective, matched-pair analysis was to compare differences in non-tumor related PSMA-ligand uptake and cancer detection efficacy of ^{18}F-rhPSMA-7 and ^{68}Ga-PSMA-11 PET/CT in patients with primary prostate cancer, and those with biochemical recurrence.

MATERIAL AND METHODS

Patient Population

Data from 127 patients (median age 72±7 years; range 52–84 years) with biochemical recurrence of prostate cancer after radical prostatectomy (median PSA value 0.70 ng/mL; range 0.15–64.00 ng/mL) and 33 patients (median age 71±8 years; range 52–83 years) with primary prostate cancer who underwent ^{18}F-rhPSMA-7 PET/CT at our institution between July 2017 and June 2018 were retrospectively included. Data from 127 corresponding patients (median age 69±8 years; range 47–83 years) with biochemical recurrence of prostate cancer after radical prostatectomy (median PSA value: 0.65 ng/mL; range 0.20–30.00 ng/mL) and 33 patients

(median age 69±6 years; range 56–75 years) with primary prostate cancer who had undergone ^{68}Ga-PSMA-11 PET/CT were identified in our institution´s database, matched on the basis of various clinical parameters.

For the restaging cohort, the following clinical parameters were used: Gleason score (6–7 vs. 8–10), PSA values at time of PET (0.2–0.5 ng/mL, >0.5–1.0 ng/mL, >1.0-2.0 ng/mL vs. >2 ng/mL), primary T-stage (≤2 vs. ≥3), primary N-stage (0 vs. 1) and use of androgen deprivation therapy within the 6 months preceding examination (yes vs. no). Patients receiving (salvage) radiation therapy in regard of prostate cancer were excluded. The following criteria were used for the primary staging cohort: biopsy Gleason score (6–7 vs. 8–10), PSA values at time of PET (<10 ng/mL, >10–20 ng/mL, >20–30 ng/mL vs. >30 ng/mL). None of them has received androgen deprivation therapy before. The patient characteristics of the matched-pair cohorts are summarized in Supplemental Table 1 (restaging cohort) and Supplemental Table 2 (primary staging cohort).

All patients signed a written informed consent form for the purpose of anonymized evaluation and publication of their data. All reported investigations were conducted in accordance with the Helsinki Declaration and with national regulations. The retrospective analysis was approved by the Ethics Committee of the Technical University Munich (permit 290/18S and 5665/13). The administration of ^{18}F-rhPSMA-7 and ^{68}Ga-PSMA-11 complied with The German Medicinal Products Act, AMG §13 2b, and the responsible regulatory body (Government of Oberbayern).

^{18}F-rhPSMA-7 and ^{68}Ga-PSMA-11 PET/CT

^{18}F-rhPSMA-7 was synthesized as recently reported by Wurzer et al. (*11*). ^{18}F-rhPSMA-7 (mean±SD: 329±48 MBq, range 191–436 MBq) was administered as an intravenous bolus a mean±SD of 80±20 min (range, 50–198 min) prior to the PET scan. ^{68}Ga-PSMA-11 was synthesized as reported by Eder et al. (*12*). ^{68}Ga-PSMA-11 was administered as an intravenous bolus (mean±SD: 143±31 MBq; range 51–248 MBq) and PET acquisition was started at a mean±SD time of 55±9 min (range 42–116 min) after tracer injection. All patients received 40 mg furosemide and diluted oral contrast (Mannitol 25ml/l). Contrast-enhanced PET/CT (Biograph mCT flow, Siemens Medical Solutions, Erlangen, Germany) was conducted as described previously (*13,14*). All PET scans were acquired in 3D mode with an acquisition time of 3–4 min per bed position or 1.1–1.5 mm/sec using flow technique. 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), time of flight information and resolution recovery (TrueX). Matrix and image size were 200 x 200.

Image Analysis

All ^{68}Ga-PSMA-11 and ^{18}F-rhPSMA-7 PET/CT images (total n=320) were reviewed by two board-certified nuclear medicine physicians in consensus (MK and IR). First, all PSMA-positive lesions were noted and grouped into a) local, b) pelvic, c) abdomino- and supradiaphragmatic, d) bone and e) others (e.g. lung, liver). In a second step, lesions suspicious for prostate cancer were differentiated from most probably benign lesions (e.g. ganglia, unspecific lymph nodes, fractures, degenerative changes) taking into consideration the known

pitfalls of PSMA PET imaging and information from contrast-enhanced CT. For each anatomical region, SUVmax of the lesion with the highest PSMA-ligand uptake was noted for both lesions suspicious for malignancy and lesions attributed to benign origin. To estimate the influence of high activity retention in the bladder, the SUVmax of the urinary bladder was measured and the tumor-to-bladder ratio (TBR) for local tumors calculated. In addition, the shortest distance between local recurrence and bladder wall was measured in millimeter (mm).

Statistical Analysis

Statistical analyses were performed using MedCalc software (version 13.2.0, 2014; MedCalc, Ostend, Belgium). All quantitative data are expressed as mean values ± standard deviations. P values <0.05 were considered significant. Positivity rates for both primary and recurrent prostate cancer were determined and SUVmax of most probably benign and suspicious lesions were compared separately for ^{68}Ga-PSMA-11 and ^{18}F-rhPSMA-7 PET/CT using two-sided t-test.

RESULTS

Distribution and Localization of PSMA-ligand Positive Lesions Attributed to Benign Origin

In total, ^{18}F-rhPSMA-7 and ^{68}Ga-PSMA-11 PET/CT revealed 566 and 289 lesions with focal PSMA-ligand uptake, respectively. Across both patient cohorts, ^{18}F-rhPSMA-7 PET revealed 379 lesions attributed to benign origin equaling 67.0% of all lesions, compared with 100 lesions equaling 34.6% for ^{68}Ga-PSMA-11 PET. In terms of absolute numbers, the amount of lesions attributed to benign origin was 3.8 higher for ^{18}F-rhPSMA-7 PET compared with ^{68}Ga-

PSMA-11 PET (4.8, 3.9 and 2.5 times more benign lesions in ganglia, bone and unspecific lymph nodes, respectively), see also Table 1, Figure 1 and Supplemental Figure 1.

The main site of PSMA-ligand positive lesions attributed to benign origin were ganglia, bone lesions and unspecific lymph nodes with 32%, 24%, 38%, respectively, of the positive non-prostate cancer findings in ^{68}Ga-PSMA-11 and 42%, 24%, 25% in ^{18}F-rhPSMA-7 PET, respectively. Most unspecific bone uptake was found in the ribs and in the spine, details on the exact distribution is presented in Supplemental Table 3. Uptake in soft tissue lesions attributed to benign origin was seen rarely in both ^{68}Ga-PSMA-11 and ^{18}F-rhPSMA-7 PET (6% and 8%, respectively). Details on absolute numbers and percentage of lesions rated as benign can be found in Table 1.

SUVmax of lesions attributed to benign origin was significantly higher ($p<0.05$) in ^{18}F-rhPSMA-7 PET compared with ^{68}Ga-PSMA-11 PET in ganglia (SUVmax of 5.2±1.2, range 3.0–10.1 vs. 4.5±1.0, range 3.2–7.0, respectively) and bone (SUVmax of 6.4 ±3.5, range 3.2–24.2 vs. 5.0±2.4, range 2.4–12.4, respectively), but not in unspecific lymph nodes (SUVmax of 4.9±1.9, range 3.0–16.8 vs. 4.8±1.2, range 3.5–9.6). Examples of both ^{68}Ga-PSMA-11- and ^{18}F-rhPSMA-7-ligand uptake in benign lesions such as ganglia or axillary lymph nodes are presented in Figure 2 and 3. Supp. Figure 2 demonstrates a histopathologically negative ^{18}F-rhPSMA-7-positive lesion in the ischiac bone and Supp. Figure 3 visualizes three different ^{18}F-rhPSMA-7-positive bone lesions in the ribs: one singular rib metastasis, one fibro-osseous lesion and one most probably benign unspecific uptake.

Lesion Detection and Localization Attributed to Recurrent Prostate Cancer

In total, 187 ^{18}F-rhPSMA-7 positive lesions attributed to prostate cancer were found in 123 of the 160 patients and 189 ^{68}Ga-PSMA-11 positive lesions in 124 of 160 patients. The overall detection efficacy in patients with biochemical recurrence after radical prostatectomy as function of the PSA value was identically for both ^{18}F-rhPSMA-7 and ^{68}Ga-PSMA-11: It was 56%, 77%, 64% and 95% for PSA levels <0.5 ng/mL, 0.5–<1 ng/mL, 1-<2 ng/mL and >2 ng/mL, respectively. In this matched-pair approach, a higher number of local recurrences were found with ^{18}F-rhPSMA-7 compared with ^{68}Ga-PSMA-11 (n=42 vs. n=32) and a lower number of lymph node metastases (n=61 vs. n=80, respectively; Figure 1C). A summary of lesions rated as malignant in patients with primary and biochemical recurrence of prostate cancer according to their origin is presented in Table 2.

Uptake and TBR of Local Recurrence and Primary Disease

All primary tumors were positive in ^{18}F-rhPSMA-7 and ^{68}Ga-PSMA-11 (n=33 each) while a slightly higher number of metastatic lesions was observed with ^{68}Ga-PSMA-11 (113 for ^{18}F-rhPSMA-7 and 124 for ^{68}Ga-PSMA-11). SUVmax of ^{18}F-rhPSMA-7 in all local recurrences and primary tumors showed a trend to higher absolute values compared with ^{68}Ga-PSMA-11, however the difference was not significant (19.3±23.8 vs. 11.6±10, p=0.06 and 28.3±22.6 vs. 18.9±20.9, p=0.08, respectively). TBR was significantly higher with ^{18}F-rhPSMA-7 compared with ^{68}Ga-PSMA-11 in both local recurrence and primary tumor (4.9±5.3 vs. 2.2±3.7, p=0.02 and 9.8 ±9.7 vs. 2.3 ±2.6, p<0.001, respectively). In ^{18}F-rhPSMA-7 and ^{68}Ga-PSMA-11 PET, local recurrence was located directly adjacent to the urinary bladder in 19/42 patients (45.2%) and 19/32 (59.4%) respectively. In addition, local recurrent lesions identified by PSMA-ligand imaging but not directly adjacent to the urinary bladder presented with a similar distance to the

bladder wall in ^{18}F-rhPSMA-7 PET and ^{68}Ga-PSMA-11 PET (mean 8±3mm (range 3–12mm) and 8±5mm (range 4–18mm), respectively). A summary of lesions rated as malignant in patients with primary and biochemical recurrence of prostate cancer according to their origin is presented in Table 2.

DISCUSSION

Since the introduction of ^{68}Ga-PSMA-11 PET in 2011, there have been increasing reports of ^{68}Ga-PSMA-11 uptake in benign lesions such as ganglia and fractures (*15-18*). We conducted a matched-pair analysis in patients with primary and recurrent prostate cancer to explore uptake in benign lesions by ^{18}F-rhPSMA-7 compared with ^{68}Ga-PSMA-11 PET. Further, we evaluated the tumor positivity rates for ^{18}F-rhPSMA-7 and ^{68}Ga-PSMA-11 which were found to be similar, with the two tracers identifying sites of disease in a comparable way with the limitation of a matched-pair approach being a potential source of bias. Taking into consideration the known pitfalls of PSMA imaging, along with the information from the corresponding contrast-enhanced (CE)CT scans, our experienced readers were able to disregard 'hot spots' likely to be benign uptake. Such benign areas of uptake occurred more frequently with ^{18}F-rhPSMA-7 (66.8% of all ^{18}F-rhPSMA-7-positive lesions) than with ^{68}Ga-PSMA-11 (34.6% of all ^{68}Ga-PSMA-11-positive lesions), Our previous work including only patients with biochemical recurrence after radical prostatectomy shows that ^{18}F-PSMA-1007 also identified more benign lesions than ^{68}Ga-PSMA-11 PET when reported as a proportion of the total number of lesions identified by each tracer, respectively (66.4% vs. 29.2%) (*10*). As demonstrated by both of these studies, areas of benign uptake are common with both ^{18}F- and ^{68}Ga-based PSMA ligands, although more frequent with

^{18}F-rhPSMA-7, and readers must be diligent in ruling these out as potential areas of malignancy, making use of resources such as corresponding CT scans.

In our analysis, the detection rate for recurrent prostate cancer was identical for both ^{68}Ga-PSMA-11 and ^{18}F-rhPSMA-7 ligands (both approximately 70%) and is within the range of several other studies (*6,8,19*). Further, detection rates increased with PSA level in patients presenting with recurrent disease from 56% at a PSA level <0.5ng/mL up to 95% at PSA >2ng/mL. The comparable low detection rate (64%) in patients presenting with a PSA level 1–<2 ng/mL might be related to the low patient number in this subgroup. A higher number of local recurrence was observed in ^{18}F-rhPSMA-7 PET compared with ^{68}Ga-PSMA-11 (42 vs. 32 lesions; Figure 1 C) in our study, potentially due to the lower excretion via the urinary tract in ^{18}F-rhPSMA-7 PET leading to improved detection rates in regions directly adjacent to the urinary bladder as also described for ^{18}F-PSMA-1007 (*20,21*). Further, the tumor-to-background ratio was significantly higher in local recurrences in ^{18}F-rhPSMA-7 PET. ^{68}Ga-PSMA-11 identified a greater number of pelvic lymph node metastases than ^{18}F-rhPSMA-7 (95 vs. 76 in both cohorts, respectively; Table 2). However, all results should be interpreted with caution, given the nature of this matched-pair comparison, as despite matching based on clinical similarities, the different patient populations could have introduced a source of bias as well as the different scanning routines can have an effect, especially on the SUV.

It is possible that the nature of the ^{18}F isotope contributes to the increased proportion of PSMA-positive benign lesions with ^{18}F-PSMA-7 PET compared with ^{68}Ga-PSMA-11. This might be related its lower positron energy compared with ^{68}Ga, which improves spatial resolution and also a higher signal from ^{18}F-PSMA-7 because of its longer half-life and higher injected

activities compared with ^{68}Ga-PSMA-11. Preclinical characteristics indicate a higher affinity and internalization rate of both ^{18}F-rhPMSA-7 and ^{18}F-PSMA-1007 in PSMA expressing cells/tumors in comparison with ^{68}Ga-PSMA-11 which could contribute to a higher signal from PSMA-expressing tissue (*11,18*). These results are in line with a recently published small histology-controlled dual PET/CT study in patients with intermediate- or high-risk prostate cancer (n=16) of Kuten et al. Here, both ^{68}Ga-PSMA-11 and PSMA-1007 PET ligands found all "dominant lesions" within the prostate while ^{18}F-PSMA-1007 PET revealed additional low grade lesions, which often show lower PSMA expression (*22*).

The most common pitfalls in our study included ganglia (either cervical, coeliac or sacral), bone lesions and unspecific lymph nodes (e.g. inguinal, axillary or mediastinal) and bone lesions with 42%, 24%, 25% in ^{18}F-rhPSMA-7 and 32%, 24%, 38% in ^{68}Ga-PSMA-11, respectively. This is similar to the distribution in previously published ^{18}F-PSMA-1007 PET patients matched to ^{68}Ga-PSMA-11 PET patients (43%, 24%, 31% in ^{18}F-PSMA-1007 PET and 29%, 27%, 42% in ^{68}Ga-PSMA-11) (*10*). Concordant with our results, Krohn et al. showed PSMA-ligand uptake in coeliac ganglia in 41% of patients (*23*). Along with the typical localization and shape of cervical, coeliac, and sacral ganglia on CT images differentiation from lymph node metastases should be easily possible to the well-trained reader. Two ongoing multicenter trials (NCT04186845 and NCT04186819) with ^{18}F-rhPSMA-7, will provide standardized reader training on such recognizable pitfalls and will test the performance of ^{18}F-rhPSMA-7 against a truth standard.

The reason for uptake of the PSMA ligands in histologically normal lymph nodes is not fully understood yet, although immunohistochemistry studies show that PSMA is not only

expressed in cancerous tissues, but also in intranodal vascular endothelia of lymph nodes (*24*). The differentiation between unspecific and metastatic PSMA-ligand uptake in lymph nodes for either tracer can be overcome with adequate training, and corresponding morphological imaging can provide key information to delineate benign from malignant uptake (oval vs. round configuration, contrast enhancement, presence/ absence of fat hilum sign) as can reading within the clinical context (e.g. pattern and extent of metastatic spread, PSA-level).

Benign PSMA-ligand positive bone findings have been described before and accounted for 24% of all PSMA-positive lesions attributed to benign origin in our study (*4,15,25*). Fracture lines, osteophytes or fibro-osseous lesions can be easily resolved with side-by-side evaluation of PET and CT images, however, there is a comparably high number of PSMA-ligand uptake in the bone (mainly ribs and spine) without clear correlate on CT images which remain a diagnostic challenge. On the basis of low to intermediate PSMA-ligand uptake and considering the patient history many of those were classified as “unspecific”.

There are several limitations to our study. First, this is a retrospective matched-pair comparison. Therefore, the comparison of detection rates is inherently of lower validity then a dual imaging protocol using both tracers. While we aimed for similar clinical characteristics in the two cohorts, the different patient populations are a source of potential bias. However, at least, the cohorts should be sufficient to compare benign/ unspecific tracer uptake. Second, a rigorous validation of PSMA-ligand positive lesions by (immuno-) histopathology was not performed. However, the very high positive predictive value for PSMA-ligand PET considering known limitations/pitfalls has been shown in several studies (*26*). As lesions attributed to benign origin such as ganglia or unspecific lymph nodes are usually not validated histopathologically,

corresponding CECT images served as reference. However, a lot of institutions only perform low-dose CT in combination with the PET scan what might influence the specificity of the scans, even more with ^{18}F-rhPSMA-7 given the higher number of non-tumor related PSMA-ligand uptake. Therefore, we recommend, especially before starting local therapies the use of PSMA-ligand PET with CECT to avoid e.g. follow-up imaging and biopsies in order to clarify unclear findings leading to increasing costs for the public health system.

Third, patients receiving ^{18}F-rhPSMA-7 were scanned later in comparison to ^{68}Ga-PSMA-11 (80 min vs. 55 min p.i., respectively). Thus, direct comparison of SUVmax values in our study have to be handled with caution as several studies suggest that in later imaging time points, the majority of lesions present with higher SUV (*27,28*). Further, mean injected activity of ^{18}F-rhPSMA-7 was higher than with ^{68}Ga-PSMA-11 (mean 329 MBq vs. 143 MBq, respectively) but is within the range of activities used in different prospective studies (e.g. CONDOR, OSPREY, LIGHTHOUSE, SPOTLINE). However, a precise comparison of both tracers would need same acquisition times and same amount of activities injected. A further limitation of this work is the use of point spread function recovery algorithm, which may exacerbate the benign uptake of the ^{18}F isotope. Further prospective studies are necessary and warranted to overcome these limitations.

CONCLUSION

The tumor positivity rate was consistently high for each tracer. Both ^{68}Ga-PSMA-11 and ^{18}F-rhPSMA-7 revealed a considerable number of areas of uptake that were reliably identified as benign by trained physicians making use of corresponding CECT imaging and known PSMA pitfalls. Notwithstanding the potential biases introduced by the case matching methodology and

different scanning routines, the frequency of these findings was clearly higher with ^{18}F-rhPSMA-7, in keeping with prior work on ^{18}F-PSMA-1007. Adequate reader training can allow physicians to differentiate benign uptake from disease and be able to benefit from the logistical advantages of ^{18}F-rhPSMA-7.

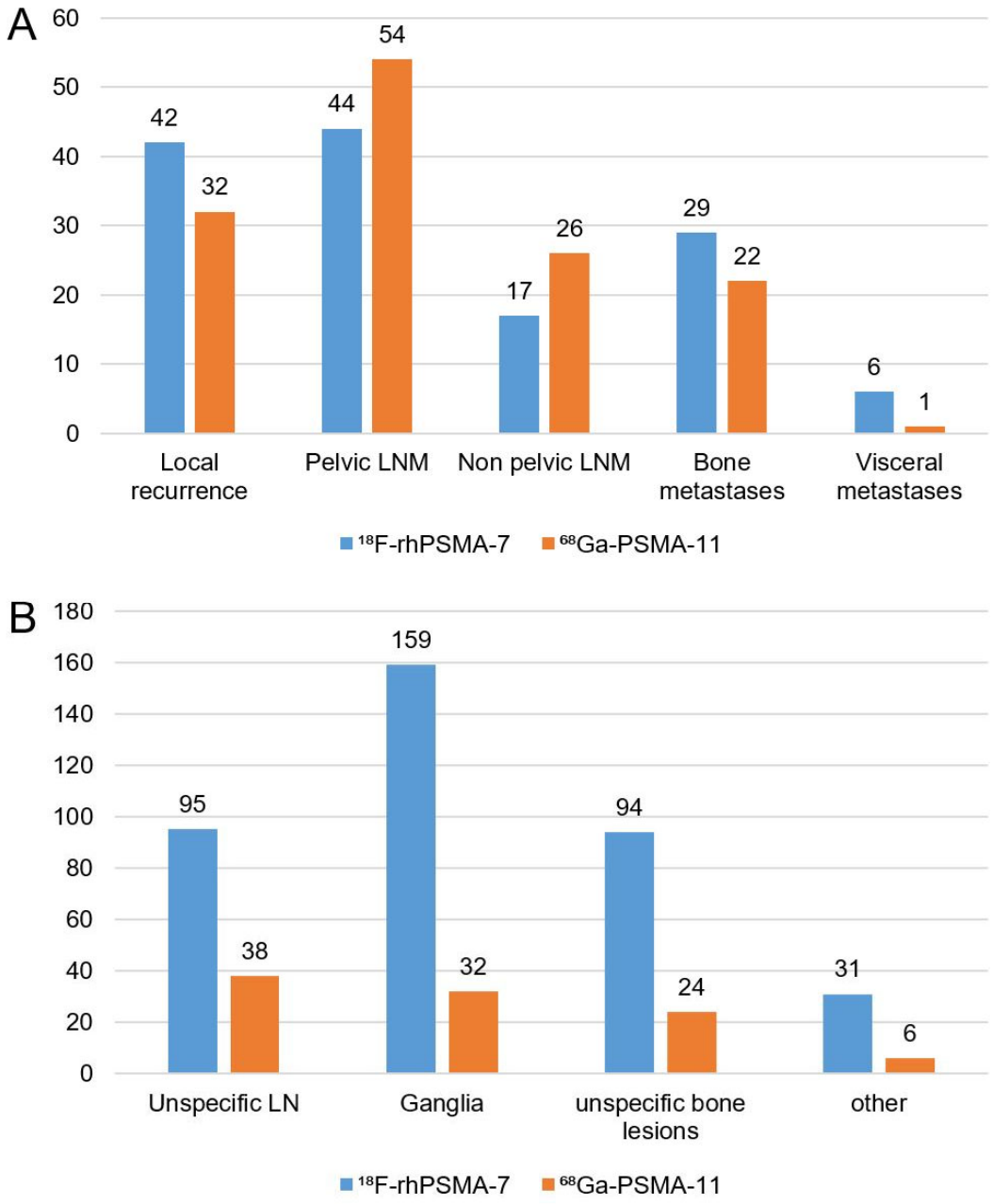
KEY POINTS

Question: Is the frequency of non-tumor related PSMA-ligand uptake and detection efficacy in matched-pair cohorts of ^{68}Ga-PSMA-11 and ^{18}F-rhPSMA-7 PET/CT patients with both primary and recurrent prostate cancer comparable?

Pertinent Findings: Both ^{68}Ga-PSMA-11 and ^{18}F-rhPSMA-7 revealed areas of benign uptake. The proportion was clearly greater with ^{18}F-rhPSMA-7 but can be overcome with adequate reader training. The tumor positivity rates were similar for both radiopharmaceuticals.

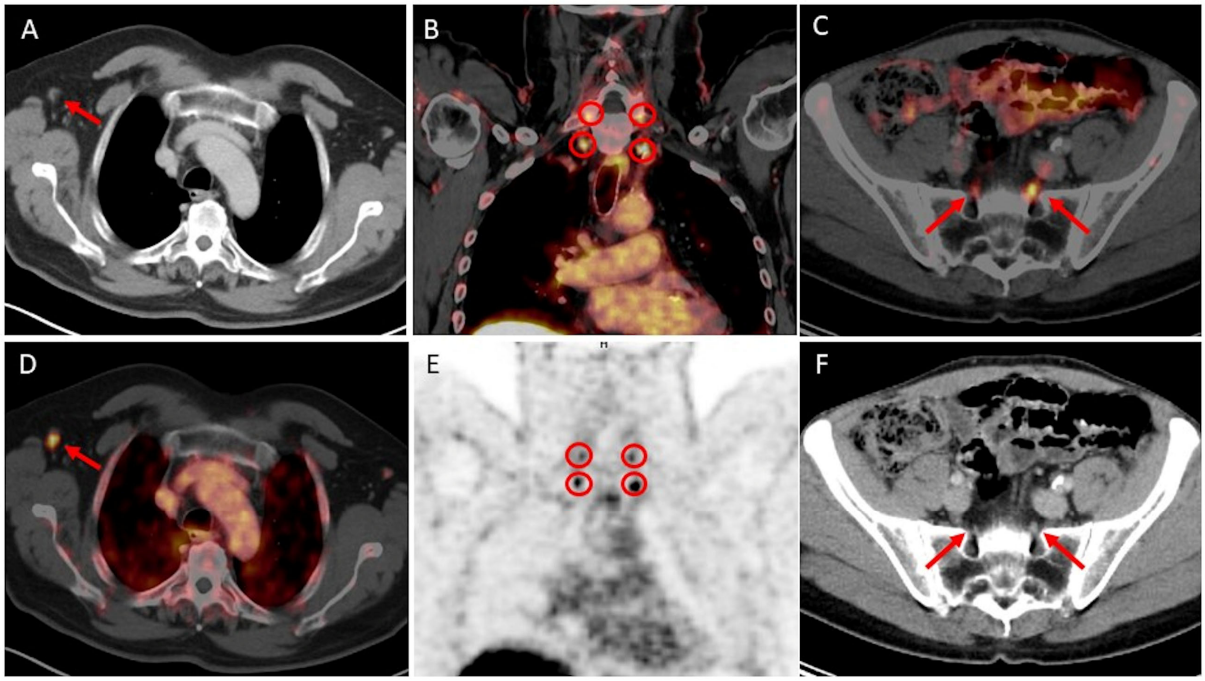
Implications for Patient Care: After adequate reader training physicians should reliably identify pitfalls fully exploiting the logistical advantages of ^{18}F-rhPSMA-7 and its low urinary excretion.

Figure 1: Localization of benign lesions in both patient cohorts (A) and localization of tumor lesions in patients with biochemical recurrence of prostate cancer after radical prostatectomy (B) in both ^{18}F-rhPSMA-7- and ^{68}Ga-PSMA-11 PET



LNM lymph node metastases; LN lymph nodes

Figure 2:



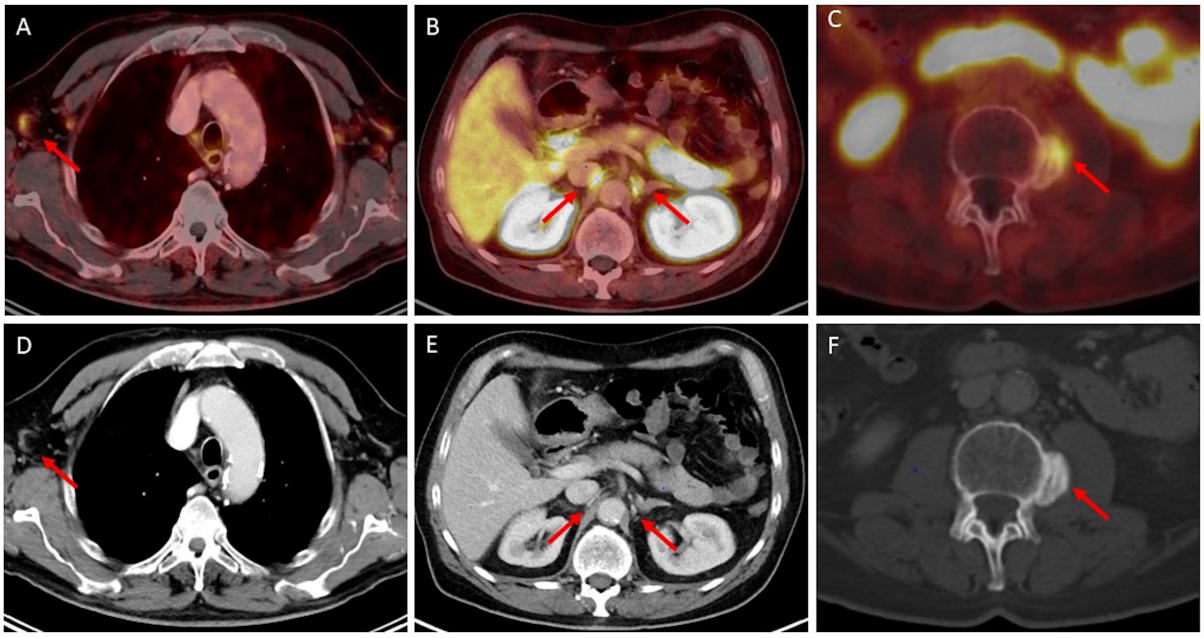
Examples of benign PSMA-ligand uptake in ^{18}F-rhPSMA-7 PET/CT:

A, D: unspecific ^{18}F-rhPSMA-7-ligand uptake in a right axillary lymph node with corresponding CT showing symmetric, non-enlarged lymph nodes with fat hilum sign

B, E: Four ^{18}F-rhPSMA-7-ligand positive cervical ganglia loco-typico

C, F: Two ^{18}F-rhPSMA-7-ligand positive sacral ganglia

Figure 3:



Examples of benign PSMA-ligand uptake in ^{68}Ga-PSMA-11 PET/CT:

A, D: unspecific ^{68}Ga-PSMA-11-ligand uptake in a right axillary lymph node with corresponding CT showing an oval, non-enlarged lymph nodes with fat hilum sign

B, E: Two ^{68}Ga-PSMA-11-ligand positive coeliac ganglia loco-typico

C, F: ^{68}Ga-PSMA-11-ligand positive osteophyt in the lumbar spine

Table 1: No. and percentage of **regions** attributed to benign origin from all PSMA-positive **regions** with ^{18}F-rhPSMA-7 and ^{68}Ga-PSMA-11 PET according to their origin

	^{68}Ga-PSMA-11 PET		**^{18}F-rhPSMA-7 PET**	
	No. of benign regions (%)	**No. of benign regions of all regions (%)**	**Absolute No. of benign regions (%)**	**No. of benign regions of all regions (%)**
Total No. of lesions attributed to benign origin	100	100/289 (34.6%)	379	379/566 (67.0%)
Unspecific LN total	38/100 (38.0%)	38/132 (28.8%)	95/379 (24.8%)	95/171 (55.6%)
- pelvic		8/72		26/81
- abdomen + supradiaphragmatic		30/60		69/90
Ganglia total	32/100 (32.0%)	32	159/379 (42.0%)	159
- cervical		13		62
- coeliac		17		84
- sacral		2		13
Bone total	24/100 (24.0%)	24/52 (46.2%)	94/379 (24.1%)	94/124 (75.8%)
- fracture		2		7
- degeneration		5		46
- unclear		3		5
- unspecific bone uptake		14		36
Others total	6/100 (6.0%)	6/8 (87.5%)	31/379 (8.2%)	31/37 (83.7%)
- unspecific soft tissue uptake		6		29
- unclear uptake°		-		2

* unspecific uptake e.g. thyroid, cutaneous, an adenoma of the adrenal gland, atelectasis with known PSMA-ligand uptake according to literature

° unclear uptake likely not tumor related

Table 2: No. and percentage of **involved regions** rated as malignant in ^{18}F-rhPSMA-7 and ^{68}Ga-PSMA-11 PET according to their location in both the staging and restaging cohort

	^{68}Ga-PSMA-11 PET		**^{18}F-rhPSMA-7 PET**	
	No. of patients	**No. of involved regions**	**No. of patients**	**No. of involved regions**
No. of patients with suspicious lesions	124/160 (77.5%)	189	123/160 (76.9%)	187
Local	65/160 (40.6%)	65/189 (34.4%)	75/160 (46.9%)	75/187 (40.1%)
LNM	78/160 (48.8%)	95/189 (50.3%)	61/160 (38.1%)	76/187 (41.1%)
- pelvic		65		55
- extrapelvic		30		21
Bone metastases	28/160 (17.5%)	28/189 (14.8%)	30/160 (18.8%)	30/187 (16.0%)
Other metastases	1/160 (0.6%)	1/189 (0.6%)	6/160 (3.8%)	6/187 (3.2%)

LNM lymph node metastases

SUPPLEMENTALS

Supp. Table 1: Patient characteristics restaging cohort

Characteristics		**^{68}Ga-PSMA-11**	**^{18}F-rhPSMA-7**
No. of Patients		127	127
Age at PET/CT, median± SD (range) in years		68±8 (47-83)	70±7 (52-84)
Biopsy Gleason Score	6-7	79	80
	8-10	48	47
Initial pathologic primary tumor stage (pT)	≤pT2	50	50
	≥pT3	77	77
Initial pathologic regional lymph node stage (pN)	pN0	95	95
	pN1	32	32
Additional ADT after radical prostatectomy		22	22
PSA-value (ng/ml) prior to PET/CT	Median (range)	2.05 (0.20-30.00)	0.87 (0.20-13.59)
	<0.5	48	48
	>0.5-1.0	40	40
	>1.0-2.0	17	17
	>2.0	22	22

ADT androgen deprivation therapy, STD standard deviation

Supp. Table 2: Patient characteristics primary staging cohort

Characteristics		**^{68}Ga-PSMA-11**	**^{18}F-rhPSMA-7**
No. of Patients		33	33
Age at PET/CT, median± SD (range) in years		67±6 (56-75)	70±8 (52-83)
Biopsy Gleason Score	6-7	10	10
	8-10	23	23
PSA-value (ng/ml) prior to PET/CT	Median (range)	10.35 (3.80-81.56)	14 (1,37-81.00)
	<10	14	14
	>10-20	9	9
	>20-30	4	4
	>30	6	6

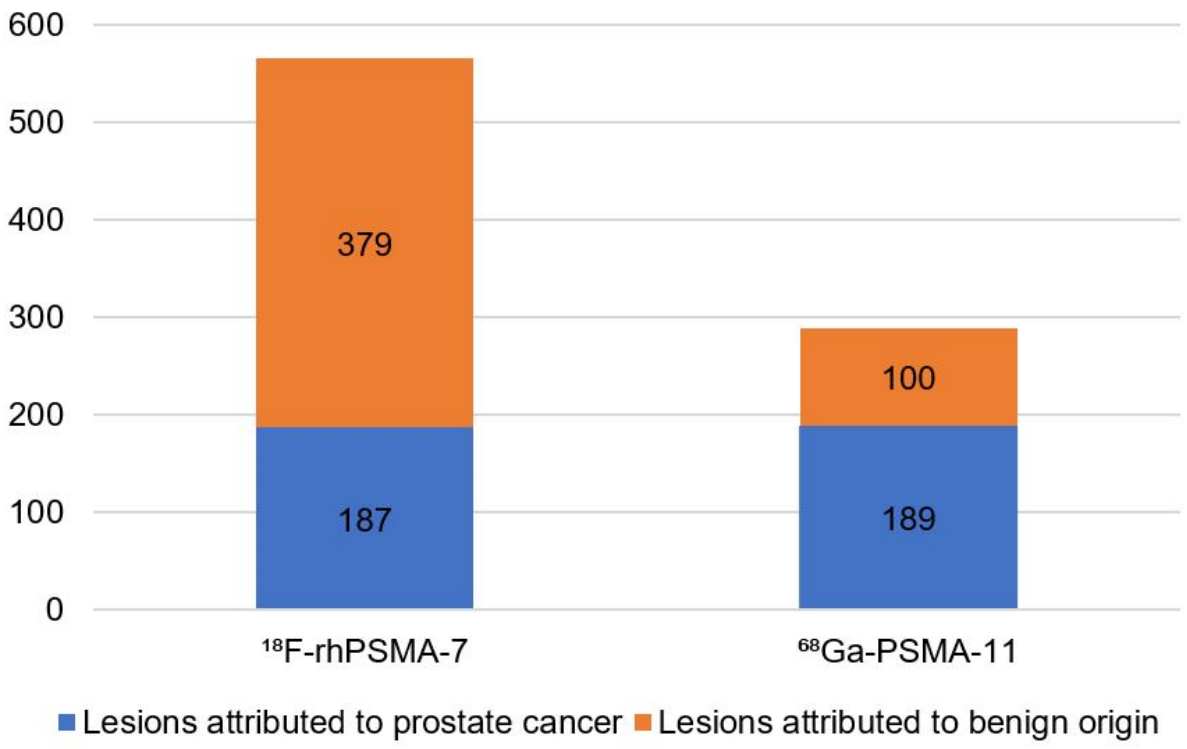
SD standard deviation

Supp. Table 3: Localization of unspecific uptake in bone lesions in ^{18}F-rhPSMA-7 PET and ^{68}Ga-PSMA-11 PET in both primary and recurrent disease

Localization	**^{18}F-rhPSMA-7 PET/CT**	**^{68}Ga-PSMA-11 PET**
Total no.	120	56
SUVmax (p=0.02)	6.1±2.9 (range 3.4-20.8*)	5.0±2.4 (range 2.4-12.4)
ribs	45	17
spine	43	20
pelvis	24	12
scapula	4	3
sternum	3	2
extremities	1	2

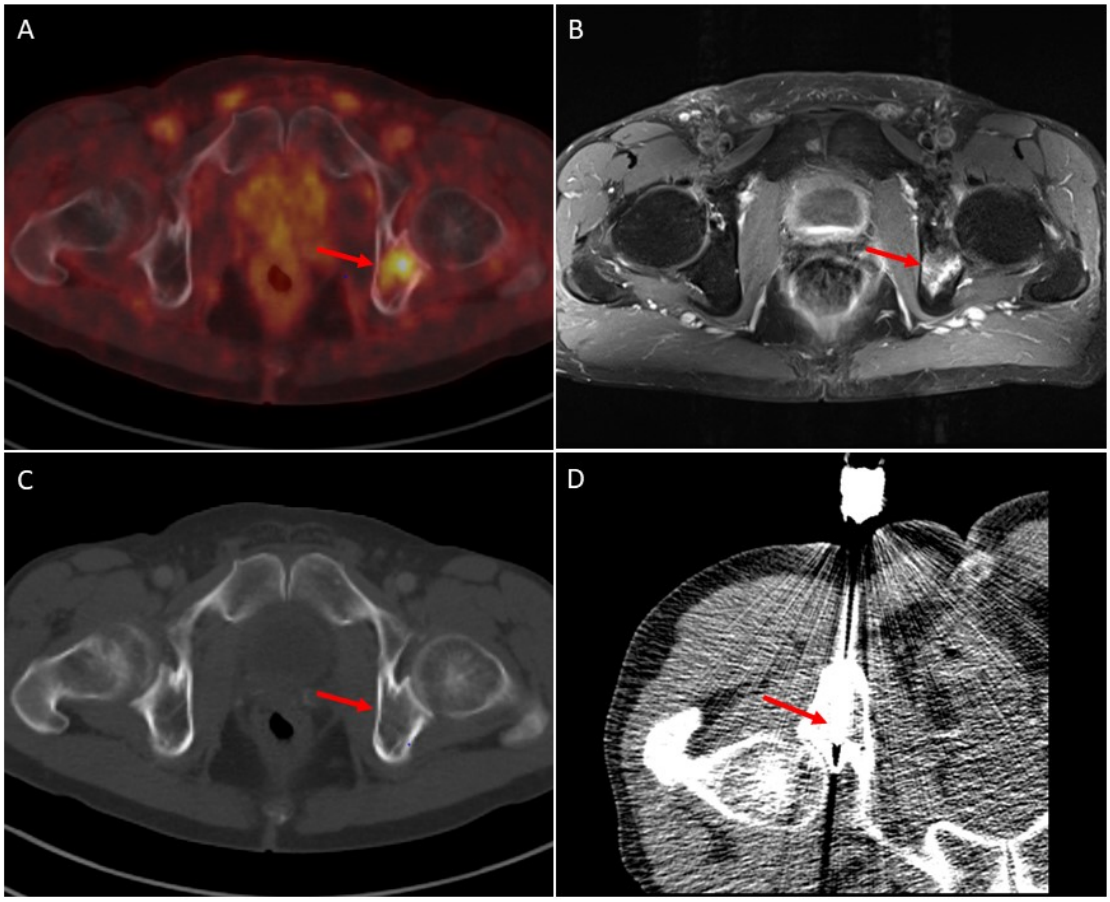
* patient presenting with partly focal, partly diffuse PSMA-ligand uptake in the left pelvis (SUVmax 20.8) due to M. Paget with typical findings on CT images including osteolysis, trabecular coarsening, cortical thickening, and osseous expansion

Supp. Figure 1



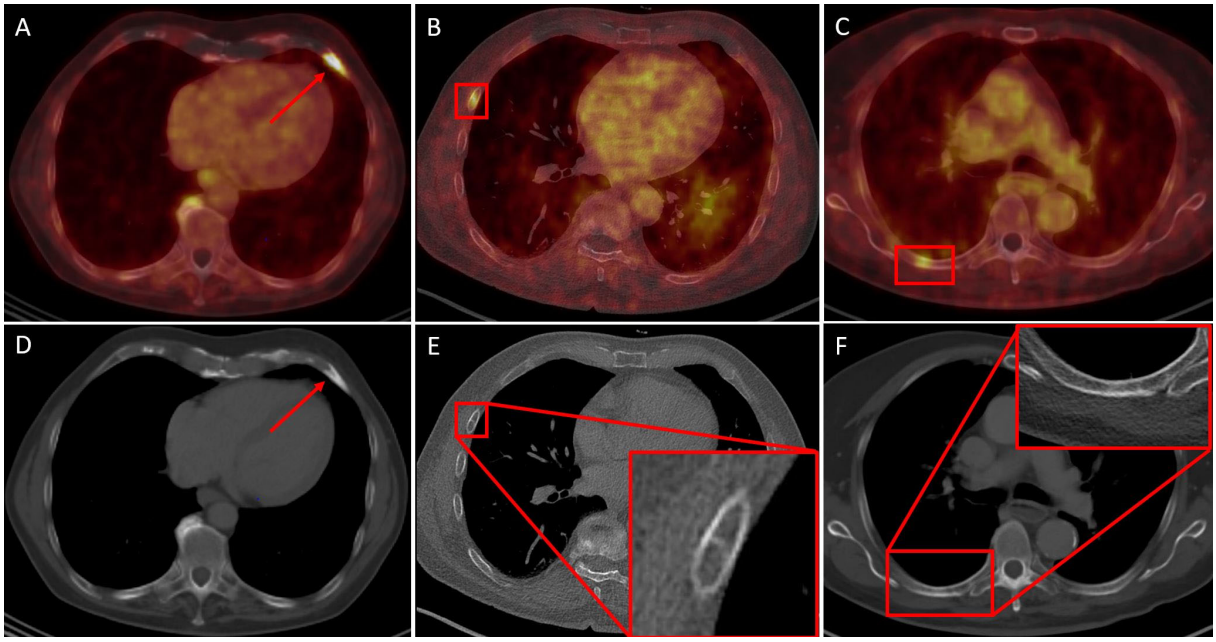
Total number of lesions with PSMA-ligand uptake attributed to prostate cancer and attributed to benign origin in both patient cohorts

Supp. Figure 2:



75-year-old patient (pT3a, pN0, GS 8, iPSA 58 ng/mL) with biochemical recurrence of prostate cancer (PSA level, 0.3 ng/mL) after radical prostatectomy presenting with a 18F-rhPSMA-7-positive suspicious bone lesion in the left ischiac bone in fused 18F-rhPSMA-7 PET/CT (A). Corresponding T1 fat saturated MRI after gadolinium (B) shows a contrast-enhanced lesion and the corresponding CT present without any suspicous findings (C). Histopathologic evaluation after CT-guided biopsy of the left ischiac bone (D) indicated bone tissue with vital spongy trabeculae, lipomatous bone marrow with only focal medullary fibrosis and discrete bone growing- and remodeling processes with no sign of malignancy.

Supp. Figure 3:



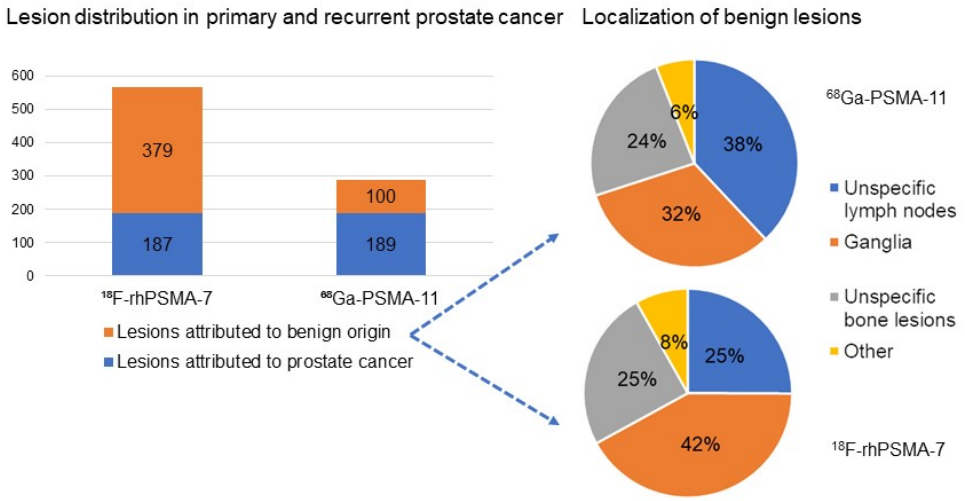
Three different patients with biochemical recurrence of prostate cancer after radical prostatectomy who underwent ^{18}F-rhPSMA-7 PET/CT:

A, D: ^{18}F-rhPSMA-7-ligand positive sclerotic bone metastasis in the left 5th rib (arrow) and a ^{18}F-rhPSMA-7-positive spondylophyt of the 10th thoracic vertebrae (dotted arrow).

B, E: ^{18}F-rhPSMA-7-positive fibro-osseous lesion with marginal sclerosis in the right 6th rib.

C, F: unspecific ^{18}F-rhPSMA-7 uptake in the right 6th rib with slight inhomogeneous bone structure, morphologically unchanged compared to CT images 2 years ago.

Graphical Abstract



REFERENCES

1. 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.

2. Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. *Eur Urol.* 2017;71;630-642.

3. Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet.* 2020;395;1208-1216.

4. 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;38;200-217.

5. Sheikhbahaei S, Werner RA, Solnes LB, et al. Prostate-Specific Membrane Antigen (PSMA)-Targeted PET Imaging of Prostate Cancer: An Update on Important Pitfalls. *Semin Nucl Med.* 2019;49;255-270.

6. Giesel FL, Knorr K, Spohn F, et al. Detection Efficacy of (18)F-PSMA-1007 PET/CT in 251 Patients with Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy. *J Nucl Med.* 2019;60;362-368.

7. Mena E, Lindenberg ML, Turkbey IB, et al. (18)F-DCFPyL PET/CT Imaging in Patients with Biochemically Recurrent Prostate Cancer After Primary Local Therapy. *J Nucl Med.* 2020;61;881-889.

8. Eiber M, Kroenke M, Wurzer A, et al. (18)F-rhPSMA-7 PET for the Detection of Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy. *J Nucl Med.* 2020;61;696-701.

9. Kroenke M, Wurzer A, Schwamborn K, et al. Histologically Confirmed Diagnostic Efficacy of (18)F-rhPSMA-7 PET for N-Staging of Patients with Primary High-Risk Prostate Cancer. *J Nucl Med.* 2020;61;710-715.

10. Rauscher I, Kronke M, Konig M, et al. Matched-Pair Comparison of (68)Ga-PSMA-11 PET/CT and (18)F-PSMA-1007 PET/CT: Frequency of Pitfalls and Detection Efficacy in Biochemical Recurrence After Radical Prostatectomy. *J Nucl Med.* 2020;61;51-57.

11. Wurzer A, Di Carlo D, Schmidt A, et al. Radiohybrid Ligands: A Novel Tracer Concept Exemplified by (18)F- or (68)Ga-Labeled rhPSMA Inhibitors. *J Nucl Med.* 2020;61;735-742.

12. Eder M, Neels O, Muller M, et al. Novel Preclinical and Radiopharmaceutical Aspects of [68Ga]Ga-PSMA-HBED-CC: A New PET Tracer for Imaging of Prostate Cancer. *Pharmaceuticals (Basel).* 2014;7;779-796.

13. Souvatzoglou M, Eiber M, Martinez-Moeller A, et al. PET/MR in prostate cancer: technical aspects and potential diagnostic value. *Eur J Nucl Med Mol Imaging.* 2013;40 Suppl 1;S79-88.

14. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of Hybrid ^{68}Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. *J Nuc Med.* 2015;56;668-674.

15. Sheikhbahaei S, Afshar-Oromieh A, Eiber M, et al. Pearls and pitfalls in clinical interpretation of prostate-specific membrane antigen (PSMA)-targeted PET imaging. *Eur J Nucl Med Mol Imaging.* 2017;44;2117-2136.

16. Keidar Z, Gill R, Goshen E, et al. 68Ga-PSMA PET/CT in prostate cancer patients - patterns of disease, benign findings and pitfalls. *Cancer Imaging.* 2018;18;39.

17. Shetty D, Patel D, Le K, Bui C, Mansberg R. Pitfalls in Gallium-68 PSMA PET/CT Interpretation-A Pictorial Review. *Tomography.* 2018;4;182-193.

18. Eder M, Schafer M, Bauder-Wust U, et al. 68Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. *Bioconjug Chem.* 2012;23;688-697.

19. Perera M, Papa N, Roberts M, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. *Eur Urol.* 2020;77;403-417.

20. Rahbar K, Weckesser M, Ahmadzadehfar H, et al. 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;45;1076-1077.

21. Rahbar K, Afshar-Oromieh A, Seifert R, et al. Diagnostic performance of (18)F-PSMA-1007 PET/CT in patients with biochemical recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* 2018;45;2055-2061.

22. Kuten J, Fahoum I, Savin Z, et al. Head-to-Head Comparison of (68)Ga-PSMA-11 with (18)F-PSMA-1007 PET/CT in Staging Prostate Cancer Using Histopathology and Immunohistochemical Analysis as a Reference Standard. *J Nucl Med.* 2020;61;527-532.

23. Krohn T, Verburg FA, Pufe T, et al. [(68)Ga]PSMA-HBED uptake mimicking lymph node metastasis in coeliac ganglia: an important pitfall in clinical practice. *Eur J Nucl Med Mol Imaging.* 2015;42;210-214.

24. Afshar-Oromieh A, Sattler LP, Steiger K, et al. Tracer uptake in mediastinal and paraaortal thoracic lymph nodes as a potential pitfall in image interpretation of PSMA ligand PET/CT. *Eur J Nucl Med Mol Imaging.* 2018;45;1179-1187.

25. Jochumsen MR, Dias AH, Bouchelouche K. Benign Traumatic Rib Fracture: A Potential Pitfall on 68Ga-Prostate-Specific Membrane Antigen PET/CT for Prostate Cancer. *Clin Nucl Med.* 2018;43;38-40.

26. Rauscher I, Maurer T, Beer AJ, et al. Value of 68Ga-PSMA HBED-CC PET for the Assessment of Lymph Node Metastases in Prostate Cancer Patients with Biochemical Recurrence: Comparison with Histopathology After Salvage Lymphadenectomy. *J Nucl Med.* 2016;57;1713-1719.

27. Afshar-Oromieh A, Sattler LP, Mier W, et al. The Clinical Impact of Additional Late PET/CT Imaging with (68)Ga-PSMA-11 (HBED-CC) in the Diagnosis of Prostate Cancer. *J Nucl Med.* 2017;58;750-755.

28. Afshar-Oromieh A, Hetzheim H, Kubler W, et al. Radiation dosimetry of (68)Ga-PSMA-11 (HBED-CC) and preliminary evaluation of optimal imaging timing. *Eur J Nucl Med Mol Imaging.* 2016;43;1611-1620.