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Matched-pair comparison of ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET/CT: frequency of pitfalls and detection efficacy in biochemical recurrence after radical prostatectomy

Original Research

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ABSTRACT

Purpose: ^{18}F-labeled prostate-specific membrane antigen (PSMA)-ligand positron emission tomography (PET) has several principal advantages compared to ^{68}Ga-PSMA-11. The purpose of this retrospective study was to evaluate the frequency of non-tumor related uptake and the detection efficacy comparing ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET/computed tomography (CT) in recurrent prostate cancer (PC) patients.

Methods and Materials: 102 patients with biochemical recurrent PC after radical prostatectomy undergoing ^{18}F-PSMA-1007 PET/CT imaging were included. On the basis of various clinical variables patients with corresponding ^{68}Ga-PSMA-11 PET/CT scans were matched. All PET/CTs (total n=204) were reviewed by one nuclear medicine physician. First, all PET positive lesions were noted. Then, lesions suspicious for recurrent PC were differentiated from lesions attributed to benign origin based on known pitfalls and information from CT. For each region, SUVmax of the lesion with the highest PSMA-ligand uptake was noted. Detection rates were determined and SUVmax were compared separately for ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007.

Results: In total, ^{18}F-PSMA-1007 PET and ^{68}Ga-PSMA-11 revealed 369 and 178 PSMA-ligand positive lesions, respectively. ^{18}F-PSMA-1007 PET revealed approximately 5 times more lesions attributed to benign origin compared to ^{68}Ga-PSMA-11 PET (245 vs. 52 lesions, respectively). The most frequent benign lesions observed were ganglia, unspecific LN and bone lesions with 43%, 31%, 24% in ^{18}F-PSMA-1007 and 29%, 42%, 27% in ^{68}Ga-PSMA-11 PET, respectively. SUVmax of lesions attributed to benign origin was significantly higher ($p<0.0001$) in ^{18}F-PSMA-

1007 PET. Further, a similar number of lesions was attributed to recurrent PC (124/369 for ^{18}F-PSMA-1007 PET and 126/178 for ^{68}Ga-PSMA-11 PET).

Conclusion: In ^{18}F-PSMA-1007 PET, a considerably higher number of lesions with increased PSMA-ligand uptake attributed to benign lesions is present compared to ^{68}Ga-PSMA-11 PET. This necessitates sophisticated reader training emphasizing known pitfalls and reporting within the clinical context.

INTRODUCTION

Biochemical recurrence (BCR) represents a major concern for patients with prostate cancer (PC) who have undergone primary radical prostatectomy (RPE) (*1*). The ability to localize site and extent of recurrent PC is of utmost importance for directing salvage therapy. However, conventional imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) have very limited sensitivity for detecting recurrent disease (*2*). The introduction of ^{68}Ga-prostate-specific membrane antigen (PSMA)-11 positron emission tomography (PET) in 2012 has led to significantly improved detection rates in the BCR setting. Various mainly retrospective studies indicate superior detection efficacy compared to conventional imaging and choline-based PET, especially at low prostate-specific antigen (PSA)-levels (*3*). Along with the rapid adoption of PSMA-ligand PET worldwide there is an exponentially increasing number of published case series and reports describing increased PET-signal in ganglia or other benign lesions (e.g. Paget´s disease, thyroid adenoma) suggesting that PSMA-ligand PET is not as specific as initially thought (*4*).

Recently, ^{68}Ga-labelled PSMA-ligands have increasingly been replaced by ^{18}F-labelled counterparts. There are some major principle advantages of radiofluorinated tracers compared to ^{68}Ga-labelled PSMA-ligands such as (A) longer half-life (110min vs. 68min), (B) centralized production and distribution leading to cost savings, (C) possibility of large batch production (cyclotron-produced ^{18}F vs. generator-produced ^{68}Ga) and (D) lower positron energy of ^{18}F compared to ^{68}Ga potentially improving spatial resolution and reducing blurring effects. So far, published experience with ^{18}F–labeled PSMA-ligands is limited and include only small patient numbers. In a head-to-head comparison of 14 patients with recurrent PC ^{18}F-DCFPyL PET/CT

performed equally well compared to ^{68}Ga-PSMA-11 PET/CT (*5*). A follow-up study from Dietlein et al. using PSA-adjusted BCR cohorts indicated that ^{18}F-DCFPyL was non-inferior to ^{68}Ga-PSMA-11 and suggested an improved sensitivity of ^{18}F-DCFPyL in the PSA range of 0.5–3.5 ng/ml (*6*). Most recently, ^{18}F-PSMA-1007 PET has been introduced in PC imaging. It exhibits rapid blood clearance but only minimal urinary excretion yielding potential advantages for local tumor assessment as high tracer retention in the bladder and ureters is known to impair image interpretation (*7-11*).

Thus, the purpose of this retrospective analysis was (A) to assess potential differences in the frequency of non-tumor related PSMA-ligand uptake and (B) to compare detection efficacy using matched-pair cohorts of ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET/CT in BCR after RPE.

MATERIAL AND METHODS

Patient Population

102 patients (median age 71±8; range 51-84 years) with BCR after RPE (median PSA-value 0.87 ng/ml; range 0.20-13.59 ng/ml) imaged at our institution between 08/2017 and 02/2018 using ^{18}F-PSMA-1007 PET/CT were retrospectively included. 102 corresponding patients (median age 70±7; range 50-82 years) with BCR after RPE (median PSA-value: 0.91 ng/ml; range 0.18-30.00) ng/ml who have undergone ^{68}Ga-PSMA-11 PET/CT were identified in the institution´s database on the basis of the following clinical parameters: 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 androgen deprivation therapy within the last 6 months prior examination (yes vs. no). Characteristics of the matched-pair cohorts are summarized in Table 1.

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 analyses were approved by the Ethics Committee of the Technical University Munich (permit 257/18 S and 5665/13).

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

^{18}F-PSMA-1007 was synthesized as described previously (*9,12*). Reagent kits, unprotected PSMA-1007 precursor and PSMA-1007 reference standard were obtained from ABX, Radeberg, Germany. ^{18}F-PSMA-1007 was given to patients via an intravenous bolus (mean 325±40 MBq; range 248–453 MBq) with PET acquisition starting at a mean time of 94±22 min (range 45-163 min) after tracer injection. ^{68}Ga-PSMA-11 was synthesized as described previously by Eder et al. *(13)*. ^{68}Ga-PSMA-11 was applied to patients via an intravenous bolus (mean 147±27 MBq; range 94–232 MBq) and PET acquisition was started at a mean time of 54±7 min (range 41-85 min) after tracer injection. All patients 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). 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).

Image Analysis

Both ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET/CTs (total n=204) were reviewed by one nuclear medicine physician. First, all PSMA-ligand PET positive lesions were noted and grouped into a) local recurrence, b) abdomino-pelvic lymph nodes (LN), c) supradiaphragmatic LN, d) bone and e) others (e.g. lung, liver). In a second step, lesions suspicious for recurrent PC were differentiated from probably benign lesions (e.g. ganglia, unspecific lymph nodes, degenerative changes) based on known pitfalls and information from CT. For each anatomical region, SUVmax of the lesion with the highest PSMA-ligand uptake was noted for both lesions suspicious for recurrent PC 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-background ratio (TBR) for local recurrent lesions was calculated. In addition, the shortest distance between local recurrence and bladder wall was measured in millimeter (mm).

Statistical Analysis

Statistical analyses were performed with software (MedCalc, 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. Detection rates were determined and SUVmax of most probably benign and suspicious lesions were compared separately for ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET/CT using Mann-Whitney U test.

RESULTS

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

In total, ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET/CT revealed 178 and 369 lesions with focal PSMA-ligand uptake, respectively. ^{18}F-PSMA-1007 PET revealed 245 lesions attributed to benign origin compared to 52 lesions in ^{68}Ga-PSMA-11 PET (Figure 1 A). SUVmax of lesions attributed to benign origin was significantly higher ($p<0.0001$) in ^{18}F-PSMA-1007 PET than in ^{68}Ga-PSMA-11 PET (median SUVmax of 5.3 (range 3.0-42.7) vs. 4.4 (range 2.8-7.5), respectively, Table 1S). The main site of PSMA-ligand positive lesions attributed to benign origin were ganglia, unspecific LN and bone lesions with 43%, 31%, 24% in ^{18}F-PSMA-1007 and 29%, 42%, 27% in ^{68}Ga-PSMA-11 PET, respectively. Uptake in soft tissue lesions attributed to benign origin was seen rarely in both ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET (2% each). For details see Fig. 1B and Table 3. Representative examples of ^{18}F-PSMA-1007 positive lesions attributed to benign origin are shown in Fig. 2. Please note that a substantially higher number of most probably unspecific PSMA-ligand uptake in the bone was observed in ^{18}F-PSMA-1007 PET compared to ^{68}Ga-PSMA-11 PET (36 compared to 6 lesions, respectively). Table 4 describes in more detail the localization of unspecific uptake in bone lesions being predominantly in the ribs. A representative example of a patient with an unspecific bone lesion can be seen in Figure 3.

Lesion Detection and Localization Attributed to Recurrent PC

A similar number of PSMA-ligand positive lesions was attributed to recurrent PC (126 and 124 suspicious lesions in ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET, respectively). This resulted in a higher percentage of lesions attributed to recurrent PC in ^{68}Ga-PSMA-11 (70.8%, 126/178) vs.

^{18}F-PSMA-1007 PET (33.6%, 124/369, Figure 1 A). On patient base, lesions suspicious for recurrent PC were detected in 82 patients both in ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET/CT resulting in an identical detection rate of 80.4%. SUVs of suspicious lesions were similar (p=0.816) for ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET (median SUVmax 9.9 (range 3.3-112.5) and 9.4 (range 2.7-234.4) for ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET, respectively, Supplemental Table 1).

Main sites for lesions attributed to recurrent PC were abdomino-pelvic lymph nodes in 34% vs. 29%, local recurrence in 26% vs. 22%, supradiaphragmatic lymph nodes in 17% vs. 27%, bone metastases in 21% vs. 18% and other soft tissue metastases in 2% vs. 4% in ^{68}Ga-PSMA-11 PET vs. ^{18}F-PSMA-1007 PET, respectively (Table 2). TBR was significantly higher ($p< 0.0001$) in patients with ^{18}F-PSMA-1007 PET (median TBR 2.50; range 0.77-19.70) compared to patients with ^{68}Ga-PSMA-11 PET (median TBR 0.99; range 0.11-10.39). Notably, local recurrence detected in ^{18}F-PSMA-1007 PET was more often directly adjacent to the urinary bladder (59.3%, 16/27 cases) compared to ^{68}Ga-PSMA-11 PET (48.5%, 16/33 cases). In addition, local recurrent lesions identified by PSMA-ligand imaging but not directly adjacent to the urinary bladder were closer to the bladder wall in ^{18}F-PSMA-1007 PET compared to ^{68}Ga-PSMA-11 PET (mean 2±3mm (range 2-10mm) vs. 4±5mm (range 3-20mm), respectively). Two representative examples of local recurrence in ^{18}F-PSMA-1007 PET/CT and ^{68}Ga-PSMA-11 PET/CT are presented in Supplemental Fig. 1.

Lesion Validation

Validation of malignant PSMA-ligand positive findings was available in 59/102 (57.8 %) and 31/102 (30.4%) patients undergoing ^{68}Ga-PSMA-11-PET and ^{18}F-PSMA-1007 PET/CT with at

least one of the following procedures: (a) targeted radiation therapy with consecutive PSA decline ≤0.2 ng/ml (n=20 for ^{68}Ga-PSMA-11-PET and n=10 for ^{18}F-PSMA-1007 PET) (b) positive histopathology after salvage lymph node dissection (n=5 for ^{68}Ga-PSMA-11-PET and n=2 for ^{18}F-PSMA-1007 PET) and (c) follow-up ^{68}Ga-PSMA-11-ligand PET/CT confirming the initial suspicious lesion(s) or disappearance of suspected metastatic sites after local/systemic treatment and corresponding PSA decline (n=34 for ^{68}Ga-PSMA-11-PET and n=19 for ^{18}F-PSMA-1007 PET).

DISCUSSION

This exploratory matched-pair study mainly focuses on pitfalls and different interpretation in ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET/CT imaging. In our study, ^{18}F-PSMA-1007 PET revealed almost 5-times as many PSMA-ligand positive findings attributed to benign origin (mostly ganglia, unspecific lymph nodes and bone lesions) compared to ^{68}Ga-PSMA-11 PET. Further, detection rate for recurrent PC in ^{18}F-PSMA-1007 PET was comparable to ^{68}Ga-PSMA-11 PET in patients after RPE (80.4% for both ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET/CT, respectively. However, it has to be noted, that despite the matched-pair approach with similar clinical characteristics two different patient populations were compared leading to a potential bias.

The presence of PSMA-ligand positive benign lesions (e.g. in ganglia or healing rib fractures) is known since the introduction of ^{68}Ga-PSMA-11 PET, but has increasingly been documented in case reports/series and review articles in the last years (*14-16*). To the best of our knowledge, our study is the first documenting the presence of a substantial higher number of PSMA-ligand positive benign lesions in ^{18}F-PSMA-1007 PET (66.4% vs. 29.2% of all PSMA-positive lesions

in ^{18}F-PSMA-1007 vs. ^{68}Ga-PSMA-11, respectively). The presence of significantly more PSMA-ligand positive benign lesions in ^{18}F-PSMA-1007 PET might be related to the lower positron energy of ^{18}F compared to ^{68}Ga improving spatial resolution in ^{18}F-PSMA-1007 PET and higher signal in ^{18}F-PSMA-1007 PET due to longer half-life and higher injected activities. Finally, preclinical characteristics indicate a higher affinity and internalization rate of ^{18}F-PSMA-100 compared to ^{68}Ga-PSMA-11 which could contribute to higher signal from PSMA-expressing tissue (*17,18*).

In ^{18}F-PSMA-1007 PET, the most prevalent pitfall lesion in our study was non-specific physiological radiotracer uptake in cervical, coeliac, or sacral ganglia (67% vs. 12% prevalence in ^{18}F-PSMA-1007 and ^{68}Ga-PSMA PET, respectively). The initial report on PSMA-ligand uptake in coeliac ganglia by Krohn et al. describes visually detectable uptake in 41% patients (*19*). Another recent publication demonstrates any visually detectable uptake in nearly all of the patient in any of coeliac, cervical and sacral ganglia. In addition, the authors demonstrate that ^{68}Ga-PSMA-11 uptake is higher in coeliac ganglia compared to the cervical and sacral ganglia (*20*). As these quantitative data are in line with our findings (table 1S), the number of positive patients seem to be different. However, it has to be considered that in both aforementioned studies any uptake in ganglia was investigated. In our analysis, we focused only on clearly positive cases which could potentially lead to false findings.

The second most common pitfall lesion observed in our study was unspecific uptake in LN (e.g. inguinal, axillary or mediastinal). The reason for PSMA-ligand uptake in histopathologically normal LN is not understood yet. However, immunohistochemistry studies show that PSMA is not only present in tumor-associated tissues, but also in inflammatory-associated neovasculature.

The differentiation between suspicious and unspecific PSMA-ligand uptake in LN is challenging. However, can often be resolved when looking at the shape and configuration of PSMA-positive lymph nodes on CT images (e.g. oval vs. round configuration, presence of fat hilum) and when reading within the clinical context (e.g. pattern of metastasis in PC, PSA-level, extent of disease). CT also plays an important role in the evaluation of benign PSMA-ligand positive bone lesions. PSMA-ligand uptake in healing bone fracture, degenerative changes or fibrocartilage lesions has been described before. These were also observed in our study and can be easily resolved recognizing the respective findings in CT (e.g. fracture line, osteophytes) (*4,14,21*). However, especially in ^{18}F-PSMA-1007 PET, a high number of PSMA-ligand uptake in the bone (mainly ribs) was observed showing no clear correlate on CT images. Based on low to intermediate (not high) uptake and considering the patient history many of those were designated as "unspecific uptake" with PSMA-ligand PET/CT follow-up being available only in a limited number of patients. Notable, free ^{18}F cannot be regarded as a substantial issue for the unspecific PSMA-ligand uptake in the bones as mean free ^{18}F in all patients was only 1.8 ± 1.0%, (range 0-3.6%).

The detection rate observed in our study is in line with a recent study of Giesel et al. in 251 patients with BCR after RPE undergoing ^{18}F-PSMA-1007 PET/CT (*9*). A recently published study of Rahbar et al. on ^{18}F-PSMA-1007 PET/CT in 100 patients with BCR PC observed a substantially higher detection rate of 95% (*11*). However, it has to be noted that median PSA level in this study was considerably higher than in our study (median PSA-level of 0.87 (range 0.20-13.59) in comparison to 1.34 ng/ml (range 0.04–41.3 ng/ml)).

In general, recent studies suggest a higher detection rate of ^{18}F-PSMA-1007 PET compared to ^{68}Ga-PSMA-11 PET due to the higher spatial resolution of ^{18}F and the superior differentiation of

ureter/ bladder activity from local recurrence/ locoregional LN metastases with ^{18}F-PSMA-1007. The agent is only minimally excreted via the urinary tract posing a potential advantage (*22*). Interestingly, the results of our matched-pair study did not show a clear difference in diagnostic efficacy of ^{18}F-PSMA-1007 vs. ^{68}Ga-PSMA-11. Moreover, the number of local recurrent lesions was even higher in ^{68}Ga-PSMA-11 PET than in ^{18}F-PSMA-1007 PET. This might potentially be explained by the matched-pair approach (no double examination within one patient) and the limited number of patients studied. As we matched for clinical parameters (e.g. Gleason Score, primary T-and N stage) the locoregional distribution of tumor lesions might not be fully matched. However, it has to be emphasized that the TBR was significantly higher in ^{18}F-PSMA-1007 PET and a considerably higher number of local recurrences directly adjacent to the urinary bladder was observed in ^{18}F-PSMA-1007 PET supporting the benefit of low background activity in the bladder for lesion detection.

The lack of histopathology represents one major limitation of the present study – similar to most investigations analyzing the performance of imaging in recurrent PC. However, for PSMA-ligand PET several studies have already proven a very high positive predictive value when known limitations and pitfalls are considered (*23*). However, lesion validation of malignant PSMA-ligand positive findings was available in 58 and 30% in patients undergoing ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET/CT which is in the range of other studies (*24,25*). As lesions attributed to benign origin (e.g. ganglia, unspecific lymph nodes) are usually not validated histopathologically corresponding CT images served as validation in approximately 80% of the benign lesions. Unfortunately, validation of unspecific PSMA-ligand uptake was only available is a minority of patients. A detailed comparison of ^{68}Ga-PSMA-11 PET and ^{18}F-PSMA-1007 PET would necessitate a head-to-head study within the same patients. Due to ethical reasons this needs to be

performed with a prospective study and is beyond the scope of a retrospective analysis. Nevertheless, we believe that a matched-pair comparison using a variety of clinical parameters such as PSA, Gleason score, T-and N-stage is a reasonable approach. However, further prospective studies are necessary and warranted to overcome these limitations.

CONCLUSION

A considerably higher number of visually detectable findings with increased PSMA-ligand uptake attributed to benign origin is present in ^{18}F-PSMA-1007 PET compared to ^{68}Ga-PSMA-11 PET. Therefore, especially for ^{18}F-PSMA-1007, side-by-side evaluation of PET and CT images as well as sophisticated reader training emphasizing known pitfalls and reporting within the clinical context is obligatory for correct and reliable PSMA-ligand PET/CT interpretation. Detection efficacy of lesions attributed to recurrent PC was comparable in our matched-pair analysis in patients with BCR after RPE.

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-PSMA-1007 PET/CT patients with BCR after RPE comparable?

Pertinent Findings: The results of our retrospective matched-pair study indicate that, despite similar detection rates, ^{18}F-PSMA-1007 PET revealed almost 5-times as many PSMA-ligand positive findings attributed to benign origin compared to ^{68}Ga-PSMA-11 PET.

Implications for Patient Care: Sophisticated reader training emphasizing known pitfalls, reporting within the clinical context and side-by-side evaluation of PET and CT images is obligatory for adequate PSMA-ligand PET/CT interpretation, especially for ^{18}F-PSMA-1007.

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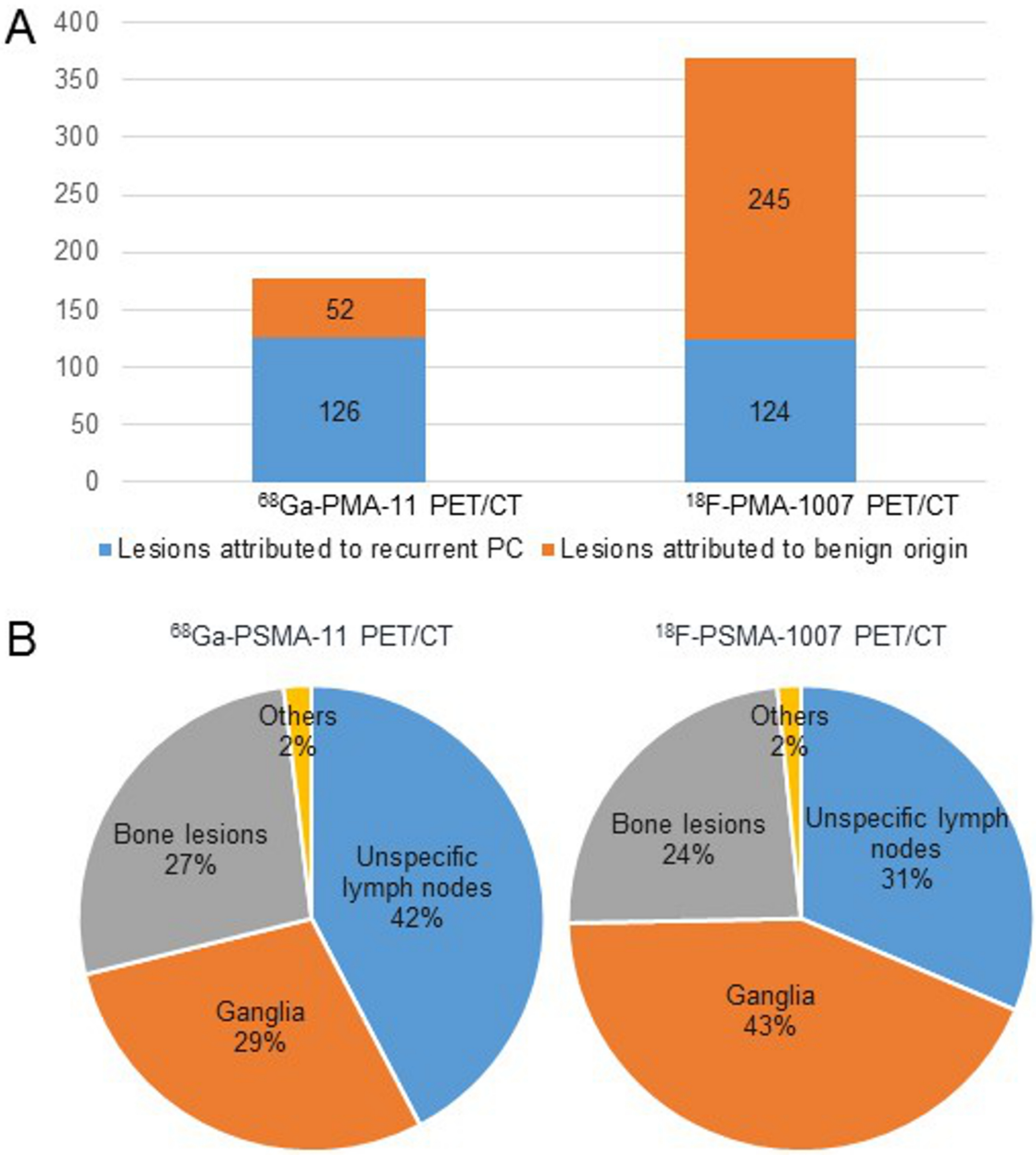


FIGURE 1:

A: Distribution of suspicious and benign lesions on all PSMA-ligand positive lesions in ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET/CT

B: Origin of lesions attributed to benign origin in ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 PET/CT

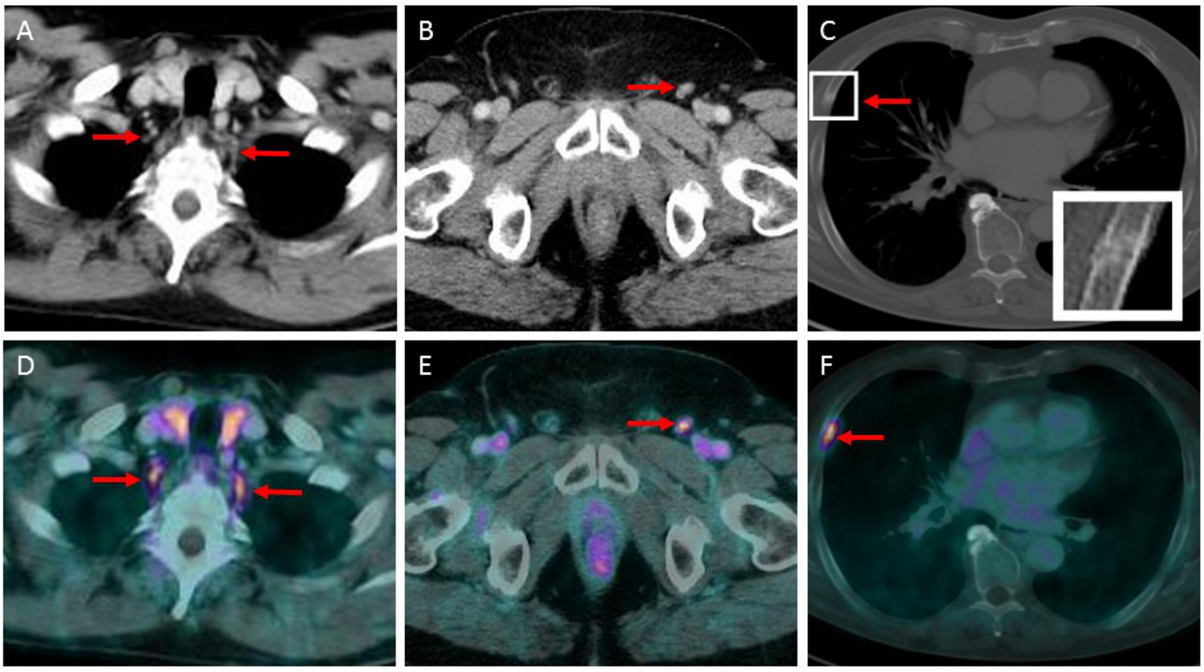


FIGURE 2:

Computed tomography images (top row) and fused ^{18}F-PSMA-1007 PET/CT examinations (bottom row) of a patient presenting with PSMA-ligand positive, typically tear-drop shaped cervical ganglia on both sides prevertebral (A, D), unspecific PSMA-ligand uptake in a non-enlarged left inguinal lymph node (B, E) and focal PSMA-ligand uptake in a non-displaced fracture of the rib with a corresponding fracture line and callus formation on CT images (C, F).

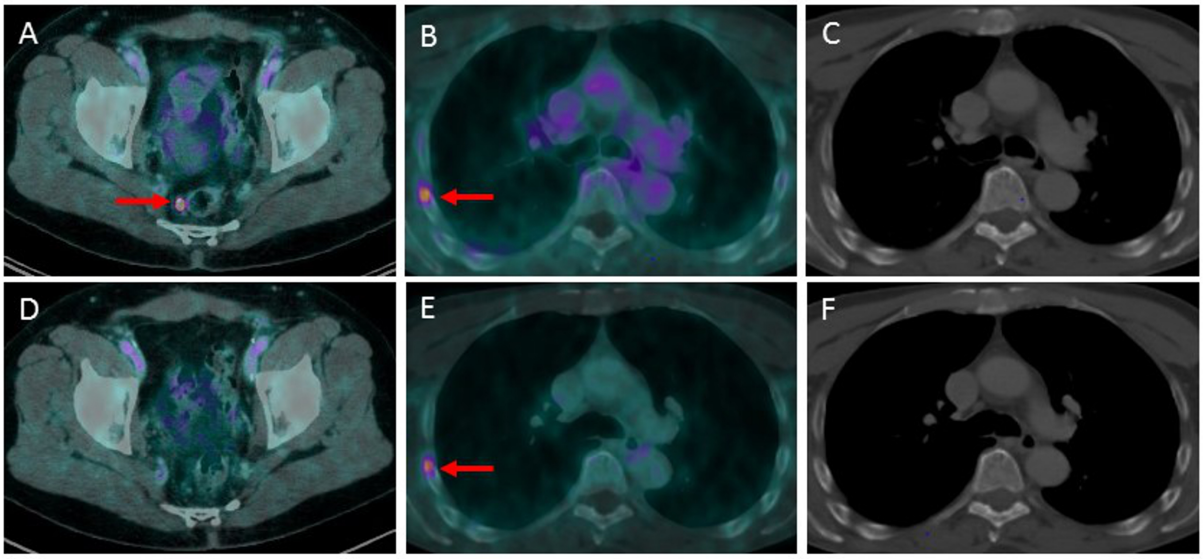


FIGURE 3:

Baseline ^{18}F-PSMA-1007 PET/CT (A-C) of a 65-year old patient with biochemical recurrent prostate cancer after radical prostatectomy presenting with a PSA-value of 1.4 ng/ml showing a singule PSMA-positive lymph node metastasis pararectal (A, red arrow). This lymph node was removed during PSMA-Radioguided Surgery with subsequent PSA-decline <0.2 ng/ml and follow-up ^{18}F-PSMA-1007 PET/CT showing no PSMA-ligand uptake anymore (D). Please note that in this patient an unspecific focal PSMA-ligand uptake in the right 4th rib was observed (B, red arrow; SUVmax 4.4) which was still present on follow-up PET/CT (E, SUV max 4.6) and with no morphological correlate on corresponding CT images (C and F).

Table 1: Patient Characteristics

Characteristics		**^{68}Ga-PSMA-11 PET**	**^{18}F-PSMA-1007 PET**
No. Patient		102	102
Age at PET/CT, median± STD (range) in years		69±7 (50-82)	70±8 (51-84)
Initial Gleason Score	6-7	63	63
	8-10	39	39
Initial pathologic primary tumor stage (pT)	≤pT2	46	46
	≥pT3	56	56
Initial pathologic regional lymph node stage (pN)	pN0	76	76
	pN1	26	26
Additional ADT after RPE		24	24
PSA-value (ng/ml) prior to PET/CT	Median (range)	0.91 (0.18-30.00)	0.87 (0.20-13.59)
	0.2-0.5	35	35
	>0.5-1.0	20	20
	>1.0-2.0	21	21
	>2.0	26	26

ADT androgen deprivation therapy, RPE radical prostatectomy, STD standard deviation

Table 2: No. and percentage of lesions rated as malignant in ^{18}F-PSMA-1007 PET and ^{68}Ga-PSMA-11 PET according to their origin

	^{68}Ga-PSMA-11 PET		**^{18}F-PSMA-1007 PET**	
	No. of patients	**No. of lesions**	**No. of patients**	**No. of lesions**
No. of patients with suspicious lesions	82/102 (80.4%)	126	82/102 (80.4%)	124
Local recurrence	33/102 (32.4%)	33/126 (26.2%)	27/102 (26.5%)	27/124 (21.8%)
LNM	51/102 (50.0%)	64/126 (50.8%)	55/102 (53.9%)	70/124 (56.5%)
- abdomino-pelvic		43		36
- supradiaphragmatic		21		34
Bone metastases	26/102 (25.5%)	26/126 (20.6%)	22/102 (21.6%)	22/124 (17.7%)
Other metastases	3/102 (2.9%)	3/126 (2.3%)	5/102 (4.9%)	5/124 (4.0%)

Table 3: No. and percentage of lesions attributed to benign origin (pitfall lesions) in ^{18}F-PSMA-1007 PET and ^{68}Ga-PSMA-11 PET according to their origin

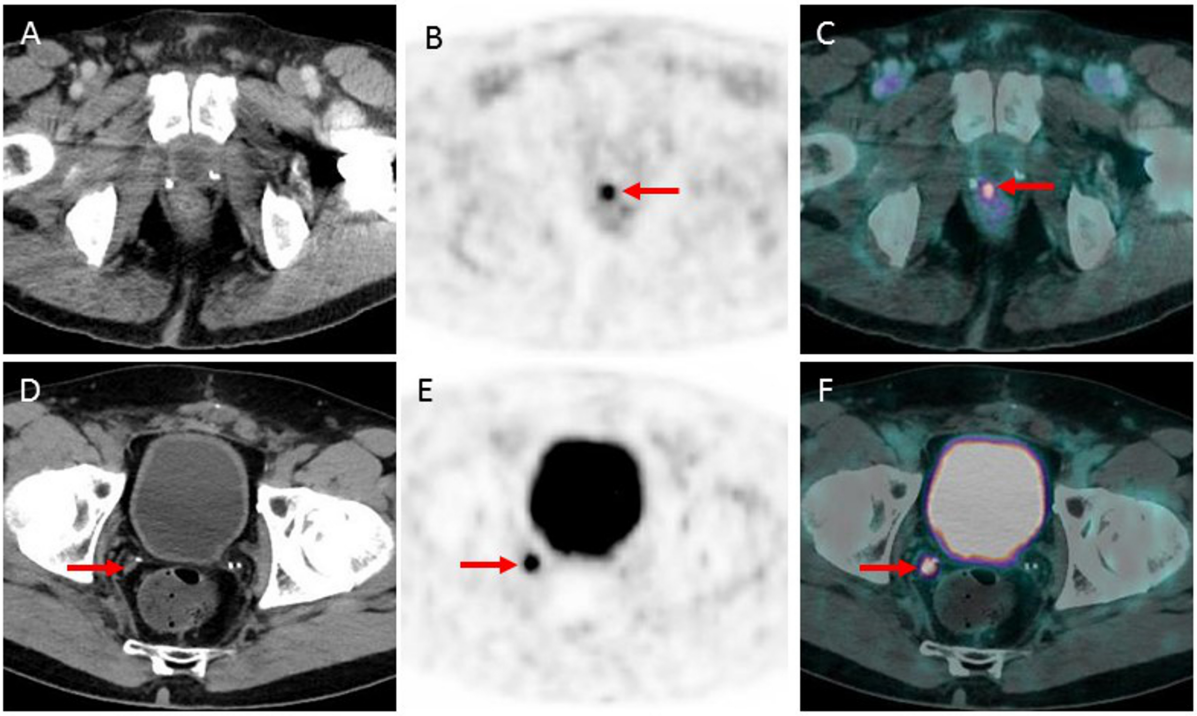
	^{68}Ga-PSMA-11 PET		**^{18}F-PSMA-1007 PET**	
	No. of patients	**No. of lesions**	**No. of patients**	**No. of lesions**
Total No. of pitfall lesions	34/102 (33.3%)	52	88/102 (86.3%)	245
Unspecific LN total	14/102 (13.7%)	22/52 (42.3%)	40/102 (39.2)	77/245 (31.4%)
- inguinal		2		18
- mediastinal		9		24
- hilar		8		17
- axillary		3		18
Ganglia total	12/102 (11.8%)	15/52 (28.8%)	68/102 (66.7%)	106/245 (43.3%)
- cervical		8		33
- coeliac		7		64
- sacral		0		9
Bone total	15/102 (14.7%)	14/52 (26.9%)	49/102 (48.0%)	58/245 (23.7%)
- fracture		2		3
- degeneration		3		13
- unclear		3		6
- unspecific bone uptake		6		36
Others total	1/102 (1.0%)	1/52 (1.9%)	4/102 (3.9%)	4/245 (1.6%)
- unspecific uptake soft tissue lesion*		1		2
- unclear°		-		2

* unspecific uptake subcutaneous (n=2) and in an adenoma of the adrenal gland (n=1)

° unclear uptake in the mamma (n=1) and the kidney(n=1)

Table 4: Localization of unspecific uptake in bone lesions in ^{18}F-PSMA-1007 PET and ^{68}Ga-PSMA-11 PET

Localization	**^{18}F-PSMA-1007 PET/CT**	**^{68}Ga-PSMA-11 PET**
Total no.	36	6
SUVmax	5.5±1.4 (range 3.6-10.9)	4.6±1.6 (range 3.0-7.5)
ribs	21	3
spine	5	2
pelvis	5	1
scapula	2	-
sternum	2	-
femur	1	-



Supplemental FIGURE 1:

A-C: ^{18}F-PSMA-1007 PET/CT examination of a prostate cancer patient (Gleason score 7, T2, N0) with biochemical recurrence (PSA 0.33 ng/ml) after radical prostatectomy. Axial PET and fused ^{18}F-PSMA-1007 PET/CT show a focal PSMA-ligand uptake in the prostate bed (B, C red arrow) with no morphological correlate on CT images (A).

D-F: ^{68}Ga-PSMA-11 PET/CT examination of a local recurrent prostate cancer patient (Gleason score 7, T2, N0, PSA 1.0 ng/ml) after radical prostatectomy with focal PSMA-ligand uptake (E, F red arrow). On corresponding CT images a small soft tissue lesion can be observed (D, red arrow). Note, relatively high uptake of ^{68}Ga-PSMA-11 in the urinary bladder.

Table 1 Supplemental: Comparison of SUV mean of lesions attributed to recurrent PC and benign origin in ^{18}F-PSMA-1007 PET and ^{68}Ga-PSMA-11 PET according to their localization and origin.

	Median SUVmax (range)	
	^{68}Ga-PSMA-11 PET	**^{18}F-PSMA-1007 PET**
Lesions attributed to benign origin		
Total	4.4 (2.8-7.5)	5.3 (3.0-42.7)*
Unspecific LN		
- inguinal	4.5 (3.6-6.7)	5.1 (3.0- 7.5)
- axillary/mediastinal/hilar	4.1 (3.9-4.2)	4.9 (3.8- 14.9)
Ganglia		
- cervical	3.9 (3.3-4.8)	5.3 (3.1-10.7)*
- coeliac	5.2 (4.2-7.0)	5.4 (3.1-26.6)
- sacral	none	4.2 (4.0-7.9)
Bone	4.5 (2.8-7.5)	5.4 (3.6-12.4)*
Others	n.e.	
Lesions attributed to recurrent PC		
Total	9.9 (3.3-112.5)	9.4 (2.7-234.4)
Local recurrence	7.5 (3.3-48.2)	6.0 (2.7-34.8)
Lymph node metastases		
- abdomino-pelvic	10.8 (3.6-112.5)	12.6 (3.4-234.4)
- supradiaphragmatic	13.8 (4.7-80.5)	7.5 (3.3-159.9)
Bone metastases	10.6 (3.6-35.4)	15.2 (3.4-110.6)
Other metastases	7.4 (5.7-8.5)	17.3 (5.6-31.4)

* indicates a significant difference $p<0.05$

n.e.: non evaluable due to small sample size