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Detection efficacy of ^{18}F-rhPSMA-7.3 PET/CT and impact on patient management in patients with biochemical recurrence of prostate cancer after radical prostatectomy and prior to potential salvage treatment

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Conflicts of interest:

ME holds patent rights on rhPSMA. ME and WW are consultants for Blue Earth Diagnostics (licensee for rhPSMA). No other potential conflicts of interest relevant to this article exist.

ABSTRACT

Purpose: Radiohybrid prostate-specific membrane antigen (rhPSMA) ligands are a new class of ^{18}F-labeled PSMA-targeting agents. ^{18}F-rhPSMA-7.3 is a lead compound which is currently under investigation in two multicenter phase III trials for PET-imaging. Here, we report the first retrospective data on its detection efficacy and potential impact on clinical management in a homogeneous cohort of patients with biochemical recurrence after radical prostatectomy, and prior to any salvage therapy. **Methods:** 242 patients (median [range] PSA, 0.60 [0.2–60.8] ng/mL) who underwent ^{18}F-rhPSMA-7.3 PET/CT were retrospectively selected from the institutions´ database. Images were re-read by an experienced nuclear medicine physician. Lesion detection rates were stratified by PSA. Further, potential management before and after PET was assessed by an interdisciplinary simulated tumor board and categorized (major vs. minor vs. no therapeutic change). The distribution of management change identified in each PSA subgroup was determined. **Results:** In total, 176/242 (72.7%) patients showed PSMA-ligand positive findings. ^{18}F-rhPSMA-7.3 detection rates were 61.8% (63/102), 67.9% (38/56), 81.1% (30/37) and 95.7% (45/47) for PSA-levels of 0.2–<0.5 ng/mL, 0.5–<1 ng/mL, 1–<2 ng/mL and ≥2 ng/mL, respectively. ^{18}F-rhPSMA-7.3 PET/CT revealed local recurrence, pelvic lymph node metastases, retroperitoneal lymph nodes metastases, supradiaphragmatic lymph nodes, bone metastases, and visceral metastases in 48.8% (n=118), 28.9% (n=70), 6.6% (n=16), 1.2% (n=3), 13.2% (n=32) and 1.2% (n=3) of patients, respectively. Notably, bone lesions were identified in 8.8% of patients (9/102) with PSA <0.5 ng/mL. Results from the interdisciplinary simulated tumor board indicated change of therapeutic management in 153/242 patients (63.2%) with 54/242 (22.3%) considered major and 99/242 (40.9%) minor, respectively. ^{18}F-rhPSMA-7.3 PET/CT did not prompt any therapeutic changes in 64/242 patients (26.4%). **Conclusion:** ^{18}F-rhPSMA-7.3 PET offers high detection efficacy in patients with biochemical recurrence after radical prostatectomy, and prior to potential salvage therapy, and results in a

potential change in treatment plans in nearly 2/3 of patients. **Keywords:** Biochemical recurrence; hybrid imaging; positron emission tomography; prostate cancer; prostate-specific membrane antigen.

INTRODUCTION Prostate cancer relapse following curative-intent primary therapy remains a considerable clinical challenge with up to one-third of patients experiencing biochemical recurrent disease (*1,2*). The utility of conventional imaging as well as PET imaging using e.g. ^{11}C-choline or ^{18}F-FDG for the localization of recurrence is limited, especially in patients with low prostate specific antigen (PSA) levels (*3*). Several studies have already proven the high impact of prostate-specific membrane antigen (PSMA) targeted radiopharmaceuticals on the clinical management of prostate cancer patients (*4-6*). ^{68}Ga-PSMA-11 PET has been extensively assessed in multiple retrospective and prospective studies and is already recommended in various guidelines as the preferred imaging tool to localize recurrent disease (*7-11*). Along with improved detection efficacy in comparison to conventional imaging and PET e.g. using ^{11}C-choline, the impact of ^{68}Ga-PSMA-11 PET on the management of prostate cancer patients has been assessed in several studies (*12-15*). A recent meta-analysis investigating the impact of PSMA-ligand PET on the management of primary or recurrent disease reported management changes in approximately half of patients, but found considerable heterogeneity among trials depending on PSA-level, PET positivity, and type of change definition (*16*). Further, a recent prospective trial in recurrent prostate cancer patients reported management changes in more than half of patients (*17*).

Recently, promising ^{18}F-labelled PSMA-ligands (e.g. ^{18}F-DCFPyL, ^{18}F-PSMA-1007, ^{18}F-rhPSMA-7) have been developed employing the superior nuclear properties of ^{18}F resulting in potential logistic and economic advantages (*18-20*). Radiohybrid (rh) PSMA ligands form a novel class of radiopharmaceuticals which can either be labeled with ^{18}F or with radiometals (e.g. ^{68}Ga, ^{177}Lu or ^{225}Ac) offering unique options for both imaging and theranostic applications (*21*). ^{18}F-rhPSMA-7 has already been assessed in staging and restaging of prostate cancer patients demonstrating high detection rates (*22,23*). ^{18}F-rhPSMA-7 consists of four stereoisomers (^{18}F-rhPSMA-7.1−7.4) and preclinical data comparing all four isomers in tumor-

bearing mice identified rhPSMA-7.3 as the preferred isomer given its pharmacokinetics, high tumor accumulation and low uptake in kidneys (Wurzer et al submitted JNM). Thus, single isomer rhPSMA-7.3 has been evaluated in a phase I study (NCT03995888) of biodistribution and internal dosimetry in both healthy individuals and patients with prostate cancer. Further, its diagnostic performance in newly diagnosed intermediate-to-high-risk prostate cancer and suspected disease recurrence is being investigated in two currently enrolling multicenter phase III studies (NCT04186819, NCT04186845).

Therefore, the aim of this retrospective analysis is to assess the detection efficacy of ^{18}F-rhPSMA-7.3 PET/CT and its impact on patient management in a highly selected homogenous series of patients with biochemical recurrence after radical prostatectomy but prior to potential salvage treatment.

MATERIALS AND METHODS

Patients In total, 242 patients with biochemical recurrence of prostate cancer who underwent clinically indicated ^{18}F-rhPSMA-7.3 PET/computed tomography (CT) between September 2018 and October 2019 at our institution were reviewed retrospectively. Only patients who had undergone primary radical prostatectomy with curative intent were included. Patients with any documented salvage therapy (e.g. radiation therapy or salvage surgery) or the use of androgen deprivation therapy (ADT) after radical prostatectomy were excluded from the analysis. Patients had a median age of 72 years, a median pre-scan PSA level of 0.6 ng/mL. For details please see Table 1.

All patients gave written informed consent for the procedure. All reported investigations were conducted in accordance with the Helsinki Declaration and with national regulations. The retrospective analysis was approved by the local Ethics Committee (permit 99/19). The

administration of ^{18}F-rhPSMA-7.3 complied with The German Medicinal Products Act, AMG §13 2b, and the responsible regulatory body (Government of Oberbayern).

Synthesis of ^{18}F-rhPSMA-7.3 and Imaging Protocol ^{18}F-rhPSMA-7.3 was synthesized as described previously (Wurzer et al submitted). A median activity of 332 MBq of ^{18}F-rhPSMA-7.3 (mean 336±43, range 206–454 MBq) was administered by intravenous bolus a median of 73 (mean 75±11 range 58–117) minutes prior to scanning.

All patients underwent ^{18}F-rhPSMA-7.3 PET/CT on a Biograph mCT flow scanner (Siemens Medical Solutions, Erlangen, Germany). A diagnostic CT scan was performed in the portal venous phase 80 seconds after intravenous injection of contrast agent (Imeron 300) followed by the PET scan. All patients received diluted oral contrast (300 mg Telebrix) and 40 mg furosemide. All PET scans were acquired in 3D mode with an acquisition time of 1.1 mm/second. Emission data were corrected for randoms, dead time, scatter, and attenuation and were 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 PET images were reviewed by a board-certified nuclear medicine physician (I.R.) with 8 years of experience in reading oncological images. All lesions suspicious for recurrent prostate cancer were noted. Any focal tracer uptake higher than blood pool activity and not associated with physiological uptake was considered suspicious for malignancy. Typical pitfalls in PSMA-ligand PET-imaging such as low-to-moderate PSMA expression associated with osteoblastic changes or in ganglia were taken into account (*24*). For lesion assessment the Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria were used (*25*). All lesions suspicious for recurrent prostate cancer were noted and grouped into prostate bed, pelvic nodes, extrapelvic nodes, bone metastases, and visceral metastasis using the miTNM framework.

Assessment of potential impact of ^{18}F-rhPSMA-7.3 PET/CT on Patient Management A simulated interdisciplinary tumor board was carried out to assess potential management before and after ^{18}F-rhPSMA-7.3 PET/CT. Therapeutic decisions in the simulated interdisciplinary tumor board where mainly based on national and international guidelines (e.g. German S3 Guideline on Prostate Cancer, the Guideline on Prostate Cancer of the European Association of Urology) (*26,27*). Since the category of oligometastatic PC is still insufficiently represented in the guidelines, some therapeutic decisions were also individual decisions considering e.g. recently published results on salvage lymph node dissection/PSMA radioguided surgery (*28-32*). The tumor board consisted of an uro-oncologist (T.H.), a radiation oncologist (K.S.) and a nuclear medicine physician experienced in oncological imaging (I.R.). First, all available clinical information (T- and N-stage, initial PSA (iPSA) at time of diagnosis, PSA nadir, time from radical prostatectomy to biochemical recurrence, PSA-level), but not results from ^{18}F-rhPSMA-7.3 PET/CT were presented. Based on all clinical information available, tumor board members were asked their currently intended potential management in consensus. There was also the possibility that no potential baseline management plan could be defined by tumor board members based on clinical information.

In the second step, the presence and localization of recurrent disease in ^{18}F-rhPSMA-7.3 PET/CT was demonstrated by a nuclear medicine physician. Then, tumor board members were asked to indicate post-PET management. Therapeutic management was grouped into five major modality groups: (A) radiation therapy (RT) (local RT of the prostatic bed, RT to pelvine lymphatic drainage, stereotactic body radiotherapy (SBRT)), (B) surgery (salvage lymphadenectomy (SLND), (C) systemic therapy (e.g. ADT), hormone chemotherapy (HCTx)), (D) multimodal therapy (a combination of RT/surgery and systemic treatment) and (E) no therapy (e.g. active surveillance and follow-up). Finally, therapeutic change was categorized as major change, minor change or no change. Intramodality change was considered

as minor change, while intermodality changes were considered major changes, with the exception of ADT added to or removed from local therapy, which was considered a minor change. Furthermore, ≥2 minor changes were considered a major change as well as a switch of systemic treatment (i.e. modality abiraterone/enzalutamide to chemotherapy), addition of radiation to M1-Lesions and addition of second-generation androgen receptor inhibitors (SGARIs), such as apalutamide, to systemic treatment. A detailed description of category changes can be found in Table 2.

Statistical Analysis The detection rate of presumed recurrence sites was plotted against the baseline PSA value for both the patient-level recurrence (number of patients with at least one positive finding) and for regional levels according to miTNM classification. Mann–Whitney U test was used to evaluate differences in PSA values between groups with and without pathological uptakes. Proportions of management change (major vs. minor change, no change) were determined. Further, potential change in management is illustrated using a Sankey diagram that show the selected therapies in relation to previous treatments with and without PET information. All tests were two-sided and used a significance level of α=5%. Statistical analyses were conducted with MedCalc software (version 13.2.0, 2014; MedCalc, Ostend, Belgium).

RESULTS

^{18}F-rhPSMA-7.3 Detection Efficacy

Detection Rate. Of the 242 patients, 176 (72.7%) showed one or more localized area suspicious for recurrent prostate cancer in ^{18}F-rhPSMA-7.3 PET. The detection efficacy of ^{18}F-rhPSMA-7.3 PET/CT positively correlated with PSA levels. It was 61.8% (63/102; 95% CI: 0.52–0.71), 67.9% (38/56; 95% CI: 0.55– 0.79), 81.1% (30/37; 95% CI: 0.66–0.91) and 95.7% (45/47; 95% CI: 0.86–0.99) for PSA levels of 0.2–<0.5 ng/mL, 0.5–<1 ng/mL, 1–<2 ng/mL and ≥2 ng/mL, respectively (Figure 1 A). The mean PSA level was significantly ($p< 0.0001$) lower among

patients with negative ^{18}F-rhPSMA-7.3 PET/CT (0.61±0.68 ng/mL) compared with ^{18}F-rhPSMA-7.3-positive patients (2.77±6.88 ng/mL).

Lesion Location. Lesion localization in ^{18}F-rhPSMA-7.3 PET/CT based on the miTNM classification system is shown in Figure 1B. Local recurrence in the prostate bed ranged from 39.2% at PSA 0.2–<0.5 ng/mL to 61.7% at PSA ≥2 ng/mL, while pelvic lymph node metastases were present in 20.6% at PSA 0.2–<0.5 ng/mL and increased to 53.2% of patients at PSA ≥2 ng/mL. While extrapelvic lymph node metastases were rare (<5%) at PSA levels 0.2–<0.5 ng/mL, 17% of patients with a PSA ≥2 ng/mL presented with positive retroperitoneal and/or supradiaphragmatic lymph nodes. ^{18}F-rhPSMA-7.3-avid bone metastases were present even in 8.8% of patients in early biochemical recurrent disease with a PSA 0.2–<0.5 ng/mL increasing to 29.8% in patients with PSA levels ≥2 ng/mL. Visceral metastases were absent or low in all PSA levels as only 4.3% of patients with a PSA ≥2 ng/mL showed visceral metastases. Further, the number of regions being involved broadly increased with increasing PSA levels with >1 region being involved in nearly half of the patients (44.4%) with a PSA ≥2 ng/mL compared with only 16% of patients with a PSA 0.2–<0.5 ng/mL.

Impact on Patient Management Compared with the initial plan, therapeutic management was changed by the simulated tumor board in 153/242 patients (63.2%) after results from ^{18}F-rhPSMA-7.3 PET/CT were presented. In detail, the potential management change was considered major in 22.3% (n=54) and minor in 40.9% (n=99), respectively. No change of therapeutic management was stated in 26.4% (n=64) after ^{18}F-rhPSMA-7.3 PET/CT. In 10.3% (n=25) of patients, no baseline management plan could be assessed. All 25 of these patients presented with a PSA value of ≥3 ng/mL at the time of ^{18}F-rhPSMA-7.3 PET/CT and tumor board members decided that no potential management could be defined as additional imaging is recommended prior to treatment planning. Figure 2 visualizes the potential management before and after ^{18}F-rhPSMA-7.3 PET/CT. Potential management change after ^{18}F-rhPSMA-

7.3 PET/CT stratified by PSA value can be seen in Figure 3. Here, the number of patients with a potential management change after ^{18}F-rhPSMA-7.3 PET/CT was already high (60.7%) in the patient subgroup with a PSA 0.2–<0.5 ng/mL and consistently increased to 67.9% and 86.5% in patients with a PSA 0.5–<1 ng/mL and PSA ≥2 ng/mL, respectively.

Management change according to lesion localization is presented in Table 3. The presence of a local recurrence resulted only in a minor change of management in a majority of patients (67.8%; 80/118) while the presence of pelvic lymph node metastases and either extra-pelvic lymph node, bone or visceral metastases induced a major change of treatment in 67.1% (47/70) and 66.7% (36/54) of patients, respectively. Figure 4 presents patient examples with minor and major therapeutic changes of management.

DISCUSSION In this retrospective analysis, investigating a large cohort of patients with biochemical recurrence of prostate cancer after prostatectomy and prior to potential salvage therapy, ^{18}F-rhPSMA-7.3 PET/CT detected and localized prostate cancer highly effectively in 72.3% of patients. Consistent with other PET tracers, the detection rate of ^{18}F-rhPSMA-7.3 increases with PSA level (61.8% in patients with a PSA 0.2–<0.5 ng/mL rising to 95.7% in patients with a PSA level of ≥2 ng/mL, respectively) (22-24). Of note, the detection rate in this study is lower in comparison to our previously published data on the diastereomeric mixture of ^{18}F-rhPSMA-7 in biochemical recurrent prostate cancer after radical prostatectomy (62%, 68% and 81% vs. 71%, 86% and 86% in ^{18}F-rhPSMA-7.3 and ^{18}F-rhPSMA-7 at PSA levels of 0.2–<0.5 ng/mL, 0.5–<1 ng/mL, 1–<2 ng/mL and ≥2 ng/mL, respectively) (*22*). This is most likely explained by inclusion of only patients without prior salvage therapy or ADT compared to 26% and 40% of patients who have been on ADT in the 6 months preceding the PET or had external radiation after radical prostatectomy using ^{18}F-rhPSMA-7. The latter cohort can be regarded as slightly more advanced in the course of biochemical recurrence, potentially leading to higher detection rates. Therefore, direct comparison between these datasets is not feasible. Nevertheless, based on the data from both retrospective analyses, the high detection rates of ^{18}F-rhPSMA-7 and -7.3 are very likely similar.

Recent data suggest that ^{18}F-labeled PSMA-ligands with low urinary excretion (e.g. ^{18}F-PSMA-1007 and ^{18}F-rhPSMA-7.3) can achieve higher detection rates than reported for ^{68}Ga-labelled PSMA-ligands. Our data provide further evidence for this hypothesis, in particular given the results for patients with PSA levels <0.5 ng/mL. In our study, the detection rate for local recurrence was 39% for ^{18}F-rhPSMA-7.3 in comparison to only 20% reported in a recently published study in 272 patients undergoing ^{68}Ga-PSMA-11-imaging (*33*).

Accurate localization of disease is crucial in the management of patients with biochemical recurrence of prostate cancer, as focal salvage therapies need accurate target

delineation. On the other hand, the presence of distant metastases may trigger additional or alternative systemic therapy (*10*). Therefore, the updated EAU guidelines recommend PSMA PET, if available, in patients experiencing biochemical recurrence after radical prostatectomy when the results might influence subsequent treatment decisions (*10*). The results of our study demonstrate that after ^{18}F-rhPSMA-7.3 PET/CT, potential therapeutic management was changed in 153/242 patients (63.2%) compared to an initial treatment strategy strategy based on clinical characteristics. This is in line with a recently published prospective study by Fendler, et al., with a change in intended management in more than two-thirds of patients undergoing ^{68}Ga-PSMA-11 PET for localization of biochemically recurrent prostate cancer (*17*). Several other studies have demonstrated the potential of ^{68}Ga-PSMA-11 to influence the future management of these patients, with the detection of lymph nodes and distant metastases having the highest impact on patient management (*16,34,35*). Similarly, in our study, patients with the presence of either pelvic or extra-pelvic lymph node metastases, bone metastases or visceral metastases in ^{18}F-rhPSMA-7.3 PET resulted in a major treatment change in about 2/3 of the patients. Contrary, minor management changes were observed predominantly in patients with local recurrence and in a limited number of patients with pelvic lymph node metastases. The high number of potential management changes derived from our simulated tumor board provide further data – in this case, based on the application of ^{18}F-rhPSMA-7.3 PET/CT – outlining the high value of PSMA-ligand PET imaging in early biochemical recurrence of prostate cancer.

After evaluation of tumor extent and localization with ^{18}F-rhPSMA-7.3- PET/CT, modern local therapies with either local salvage surgery or local stereotactic body radiotherapy according to our virtual tumor board was possible in 17 (7%) and 15 patients (6%), respectively, while in three patients active surveillance was possible instead of local radiation therapy. This is in line with a recently published meta-analysis of Han et al. including fifteen studies with

1163 patients showing that imaging with PSMA-ligand PET has shifted the percentage of patients receiving systemic treatments in favor of local treatments (*16*).

There are several limitations to our study. First, intended management before and after ^{18}F-rhPSMA-7.3 PET/CT was assessed hypothetically, as part of a simulated tumor board, and no information on actual implemented management change was available due to the retrospective character of this analysis including patients from different external and internal referrers where treatment approaches might be different. Thus, more prospective evaluations are still needed to prove the overall benefit of these management changes in patients. Second, a rigorous validation of PSMA-ligand positive lesions by (immuno-)histopathology was not performed, although the very high positive predictive value for PSMA-ligand PET considering known limitations/pitfalls has been shown in several studies (*36-38*). Only a subset of 17 patients underwent salvage PSMA-radioguided surgery and in the region of all ^{18}F-rhPSMA-7.3 PET-positive lesions lymph node metastases and/or local recurrences were confirmed histopathologically. Further, concise follow-up imaging was not available for lesion validation in most patients. However, in the case of PSMA-ligand uptake in the bone without any clear correlate not only CT but also more importantly on MRI, it has to be assumed that the uptake is non prostate cancer related as currently MRI is regarded as the gold standard for the detection of bone metastases. However, lesion characterization depends also on the number of lesions and the clinical context as a single PSMA-ligand positive bone lesion (especially in the ribs) without any morphological correlate in a patient presenting with a very early biochemical recurrence would mostly be considered as unspecific benign PSMA-ligand uptake, while a patient presenting with multiple PSMA-ligand positive bone lesions in the context of a clearly increased PSA-level would rather be interpreted als malignant resulting in a potential major change of management.

Third, results of conventional imaging modalities (e.g. computed tomography or bone scan) were not incorporated in intended management before ^{18}F-rhPSMA-7.3 PET as availability was limited and inhomogeneous. Neverthess, it is appropriate to perform a simulated tumor board acknowledging clinical characteristics of the patient as conventional (non-PSMA-PET) imaging lacks the potential to effectively detect early biochemical recurrence (*3*).

Further, clinical information on PSA nadir and number of resected lymph nodes at primary lymphadenectomy was available for only a minority of patients. Thus, it remains unknown whether all patients achieved an undetectable PSA nadir after radical prostatectomy, potentially influencing intended management before ^{18}F-rhPSMA-7.3 PET. Further, an extended pelvic lymph node dissection during primary surgery was not performed in all patients potentially influencing intended management before ^{18}F-rhPSMA-7.3 PET (e.g. towards a more extended radiation therapy of the lymphatic drainage).

CONCLUSIONS In this large population of patients with recurrent prostate cancer following radical prostatectomy and prior to any potential salvage therapy, ^{18}F-rhPSMA-7.3 PET/CT offers high detection rates at least equal to those reported for ^{68}Ga-PSMA-11. Incorporation of the ^{18}F-rhPSMA-7.3 PET/CT results into simulated clinical decision-making led to a change of management in nearly two-thirds of the patients, potentially paving the way to personalized medicine.

KEY POINTS:

Question: What is the detection efficacy and the potential impact on therapeutic management of novel ^{18}F-rhPSMA-7.3 isomer PET in patients with biochemical recurrent prostate cancer after radical prostatectomy prior salvage therapy?

Pertinent findings: ^{18}F-rhPSMA-7.3 PET/CT offers high detection efficacy in biochemically recurrent prostate cancer, at least equal to data published for ^{68}Ga-PSMA-11, and resulted in potential therapeutic management change in a substantial number of patients.

Implication for patient care: ^{18}F-rhPSMA-7.3 is a novel and effective PET agent for imaging of recurrent prostate cancer resulting in a potential management change in approximately two-thirds of the patients

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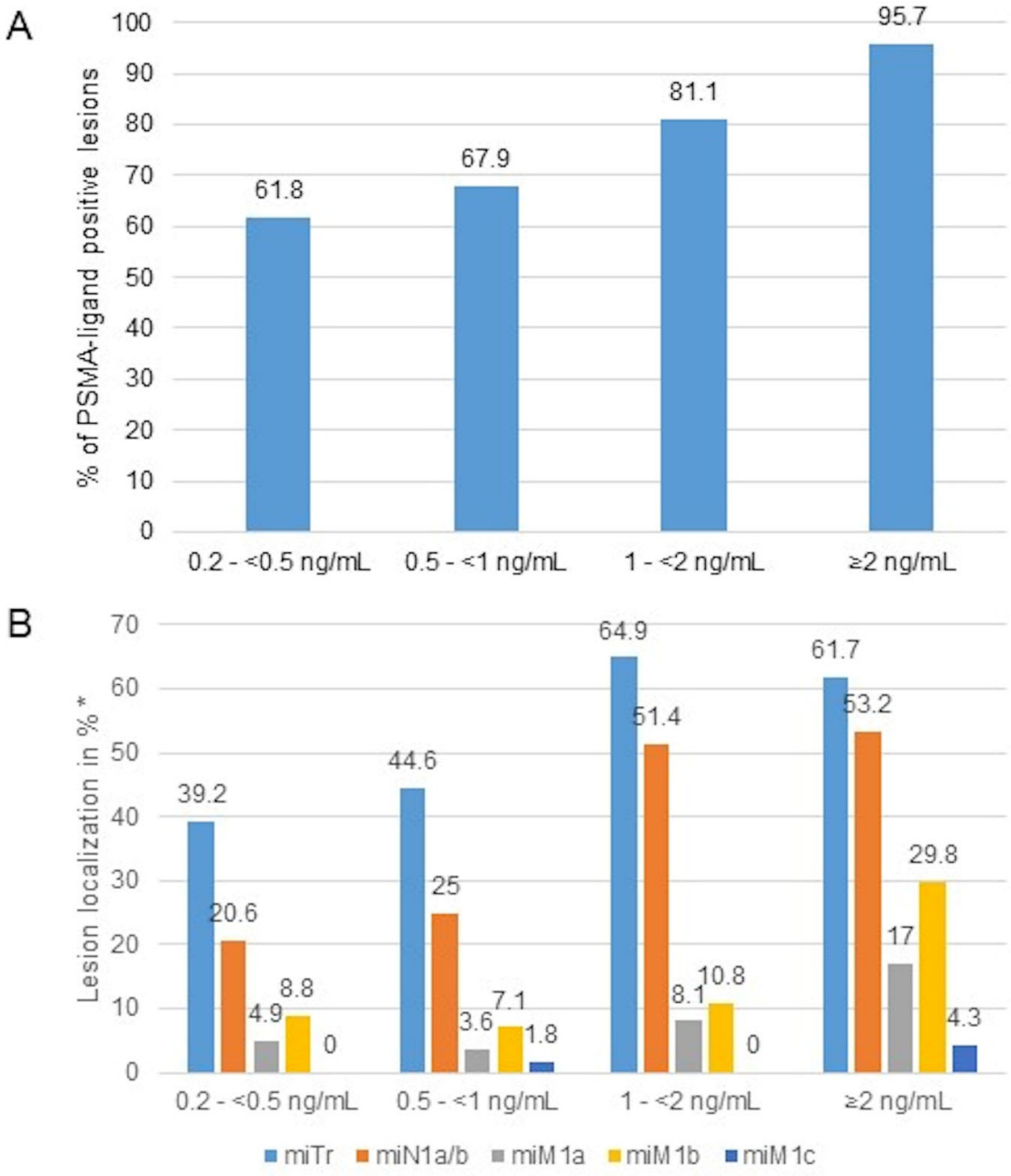
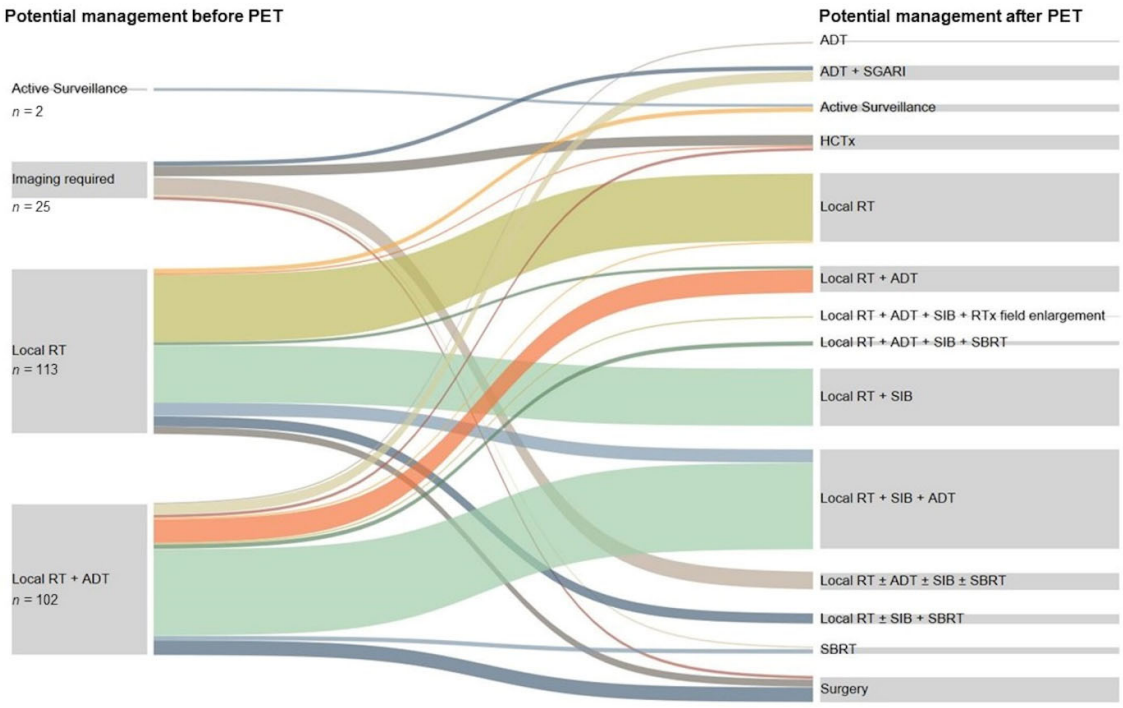
Figure 1: Overall detection rate of ^{18}F-rhPSMA-7.3 PET stratified by PSA value (A) and lesion localization using the miTNM classification stratified by PSA value (B)



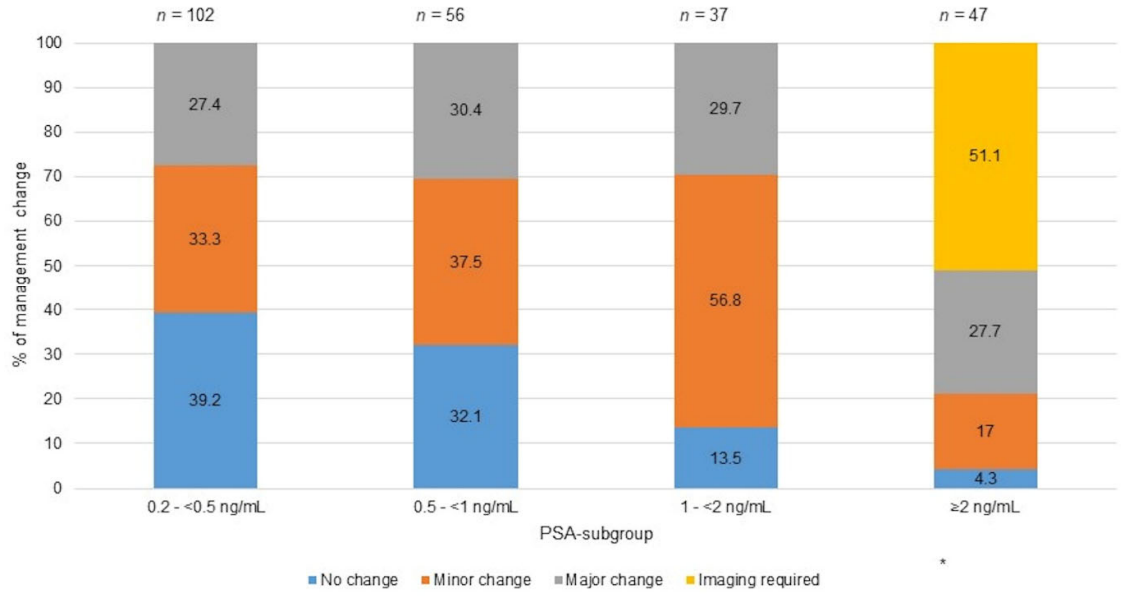
miTr: presence of local recurrence after radical prostatectomy, miN1a/b: single or multiple positive regional lymph nodes, miM1a: extrapelvic lymph nodes, miM1b: bone metastases, miM1c: other distant metastases; * multiple metastatic regions within one patient possible

Figure 2: Sankey diagram for pre- to post-PET change of potential management (n=242)



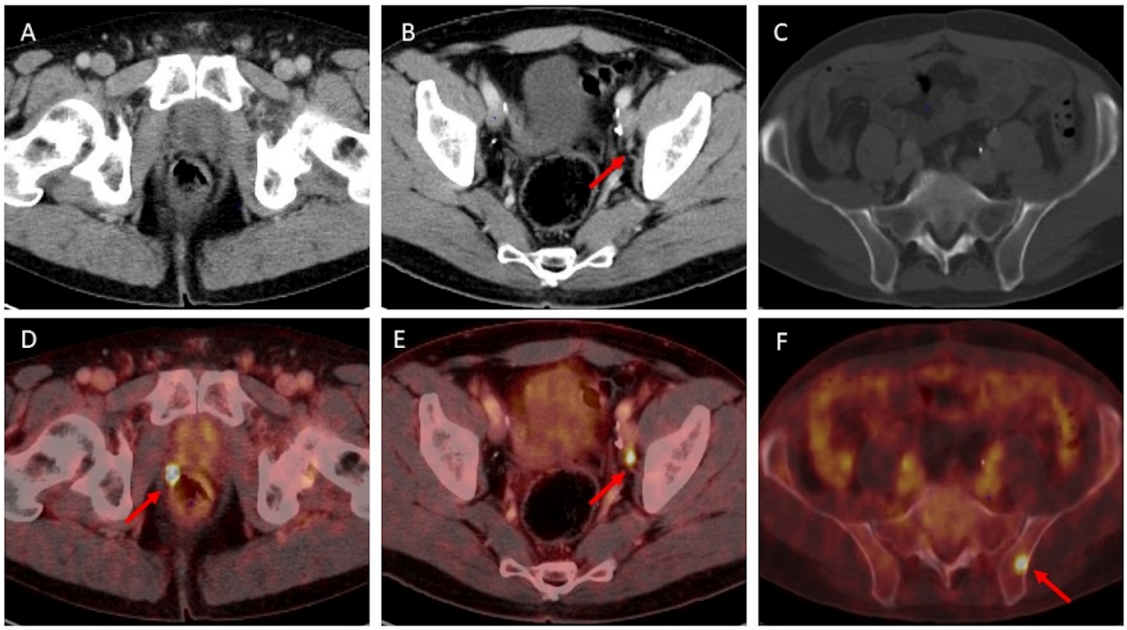
HCTx hormone chemotherapy, RT radiation therapy, SIB Simultaneous integrated boost, SBRT stereotactic body radiotherapy, ADT androgen depriviation therapy, SGARI second-generation androgen receptor inhibitor

Figure 3: Potential management change after PSMA PET stratified by PSA value



* In patients with no assessment feasible, tumor board members suggested additional imaging prior to management decision

Figure 4:



Examples of individual minor and major therapeutic change in patients with biochemical recurrence after radical prostatectomy undergoing ^{18}F-rhPSMA-7.3- PET/CT examination:

A, D 70-year-old patient (PSA-level at time of PET 0.49 ng/mL) with ^{18}F-rhPSMA-7.3-ligand uptake in the right prostatic bed (B, red arrow) without clear morphological correlate on corresponding CT)). Therapeutic management was changed from radiation therapy of the prostatic bed to radiation therapy of the prostatic bed with simultaneous integrated boost being considered a minor change.

B, E: 57-year-old patient presenting with biochemical recurrence (PSA leve,l 1.0 ng/mL) 7 years after radical prostatectomy (T2c, N0, Grade Group 8, iPSA 4,5 ng/mL). Fused ^{18}F-rhPSMA-7.3-PET/CT shows focal PSMA-ligand uptake in a unsuspicious lymph node (axial diameter 5 mm) adjacent to the left external iliac artery suspicious for singular lymph node metastasis. Therapeutic management was changed from radiation therapy of the prostatic bed and additional short-term androgen depriviation therapy to salvage lamphadectomy (major change) as individual treatment concept.

C, F: 62-year-old patient presenting with biochemical recurrence (PSA level, 0.3 ng/mL) 1.5 years after radical prostatectomy (T3a, N0, Grade Group 9, iPSA 7.0 ng/mL). Fused ^{18}F-rhPSMA-7.3-PET/CT shows focal PSMA-ligand uptake in the left iliac bone without unequivocal morphological correlate. Therapeutic management was considered a major change (change from androgen depriviation therapy to stereotactic body radiation therapy of the singular bone metastasis).

Table 1: Patient characteristics

Characteristics		*n* = 242 (%)
Age at PET in years, median (range)		72 (44-86)
ISUP Grade Group, n (%)	I	14 (5.7%)
	II	69 (28.5%)
	III	52 (21.5%)
	IV	27 (11.2%)
	V	38 (15.7%)
	Unknown	42 (17.4%)
Pathologic Primary Tumor Staging (pT)	pT2	95 (39.3%)
	pT3	111 (45.9%)
	pT4	3 (1.2%)
	Unknown	33 (13.6%)
Pathologic regional lymph node staging (pN)	pN0	151 (62.4%)
	pN1	36 (14.9%)
	pNx	55 (22.7%)
Positive Margin	R0	136 (56.2%)
	R1	44 (18.2%)
	Unknown	62 (25.6%)
Initial PSA-value in ng/ml, median (range)		10.5 (3-177)
Time between surgery and PET in months, median (range)		50 (3-1437)
Last PSA value prior PET in ng/ml, median (range)		0.60 (0.2-60.8)
Injected activity in MBq, median (range)		332 (206-454)
Uptake time in min, median (range		73 (58-117)

* PSA value obtained within the 4 weeks preceding the ^{18}F-rhPSMA-7 PET examination

Table 2: Post-PET Management Pathway Category Details (n=242)

Potential management before PSMA PET	**Potential management after PSMA PET**	**Change category**	**N (%)**
Active Surveillance	Active Surveillance	No change	2 (1%)
Local RT	Local RT	No change	46 (19%)
(prostatic bed)	+ SIB	Minor	39(16%)
	+ SIB + ADT	Major	9 (5%)
	+ ADT	Minor	2 (1%))
	Surgery	Major	5 (2%)
	SBRT ± SIB	Major	7 (3%)
	HCTx	Major	1 (0%)
	Active surveillance	Major	3 (1%)
Local RT + ADT	Local RT + ADT	No change	16 (7%)
	+SIB	Minor	59 (24%)
	Only local RT	Minor	1 (0%)
	Only ADT	Major	1 (0%)
	+ SIB + RTx field enlargement	Major	1 (0%)
	SBRT	Major	3 (1%)
	+ SIB + SBRT	Major	3 (1%)
	Surgery	Major	10 (4%)
	ADT + SGARI	Major	7 (3%)
	HCTx	Major	2 (1%)
No therapy without prior imaging possible	HCTx	n.a.	7 (3%)
	ADT + SGARI	n.a	3 (1%)
	SBRT	n.a	1 (0%)
	Local RT± ADT±SIB±SBRT	n.a	12 (5%)
	Surgery	n.a	2 (1%)

HCTx hormone chemotherapy, RT radiation therapy, SIB Simultaneous integrated boost, SBRT stereotactic body radiotherapy, ADT androgen depriviation therapy, SGARI second-generation androgen receptor inhibitor

Table 3: Potential Management change according to lesion localization

No. and localization of Suspicious lesions	Restaging Necessary*	Major change	Minor change	No change
Local recurrence (n=118)	15	22	80	1
Pelvic LNM (n=70)	12	47	10	1
Retroperitoneal LNM (n=16)	5	11	-	-
Supradiaphragmatic LNM (n=3)	1	1	-	1
Bone metastases (n=32)	8	23	-	1
Visceral metastases (n=3)	2	1	-	-

* no therapy decision could be defined by the simulated tumor board members without additioal imaging