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Full title: Early injection of furosemide increases detection rate of local recurrence in prostate cancer patients with biochemical recurrence referred for 68Ga-PSMA-11 PET/CT.

Running title: Furosemide+PSMA PET in prostate cancer.

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ABSTRACT

Purpose: The aim of this study was to assess a) the impact of forced diuresis with early furosemide injection on the detection rate of local recurrence (LR) in prostate cancer (PC) patients with biochemical recurrence (BR) referred for 68Ga-labelled Glu-NH-CO-NH-Lys(Ahx)-HBED-CC (68Ga-PSMA-11) Positron Emission Tomography/Computed Tomography (PET/CT) and b) whether intravenous administration of furosemide shortly after tracer injection increases renal wash-out of 68Ga-PSMA-11 before it binds to the PSMA-receptor with possible influence on biodistribution and intensity of tracer uptake in organs with physiologic tracer accumulation.

Materials and Methods: In a retrospective analysis two different groups with 220 prostate cancer patients each, referred for 68Ga-PSMA-11 PET/CT because of biochemical recurrence after primary therapy, were compared: patients of group one (median prostate specific antigen (PSA): 1.30 ng/ml) receiving no preparation prior to imaging, whereas patients in group two (median PSA: 0.82 ng/ml) were injected with 20 mg furosemide and 500 ml sodium chloride (NaCl 0.9%) immediately after tracer injection. Presence of local recurrence was assessed visually. In addition, intensity of tracer accumulation in organs with physiologic tracer uptake was evaluated standardized uptake value.

Results: The detection rate of lesions judged positive for local recurrence was significantly higher in patients receiving furosemide compared to patients without preparation: 56 cases (25.5%) vs 38 cases (17.3%), respectively (p=0.048). Median maximum standardized uptake values (SUV_{max}) of organs with physiologic uptake of 68Ga-PSMA-11 in group one and two were: urinary bladder (63.0 vs 8.9), kidney (55.6 vs 54.5), liver (9.9 vs 9.4), spleen (11.2 vs 11.9), small bowel (16.2 vs 17.1), parotid gland (19.2 vs 19.6), lacrimal gland (8.9 vs 10.9), blood pool activity (2.2 vs 2.3), muscle (1.0 vs 1.1) and bone (1.6 vs 1.6). Apart from bladder activity, no significant reduction of tracer accumulation was found in the patient group receiving furosemide.

Conclusion: Injection of 20 mg furosemide at the timepoint of radiotracer administration significantly increases the detection rate of local recurrence in prostate cancer patients with biochemical recurrence referred for 68Ga-PSMA-11 PET/CT. As intensity of 68Ga-PSMA-11-uptake in organs with physiologic uptake is not significantly reduced, a negative impact of early furosemide injection on targeting properties and biodistribution of 68Ga-PSMA-11 seems unlikely.

INTRODUCTION

Positron Emission Tomography/Computed Tomography (PET/CT) with radiotracers binding to the prostate specific membrane antigen (PSMA) has become a clinically accepted imaging method in prostate cancer (PC) patients presenting with biochemical recurrence (BR) after primary therapy (*1*–*5*). Several PSMA-ligands currently are used for PET imaging (*6*), of which 68Ga-labelled Glu-NH-CO-NH-Lys(Ahx)-HBED-CC (68Ga-PSMA-11), an inhibitor of the PSMA-receptor, represents one of the most frequently used PSMA tracers worldwide (*7*). Usually, 68Ga-PSMA-11 PET/CT is acquired 60 min post injection (p.i.) (*3*). However, at this time point physiologically high tracer uptake is present in the urinary bladder, which often causes difficulties in the evaluation of anatomical structures surrounding the urinary bladder (*8*–*10*). In particular, local recurrence (LR) may be missed in prostate cancer patients with biochemical recurrence (*11*). In this context PSMA tracers with lower physiologic accumulation in the urinary bladder (e.g. 18F-PSMA-1007) may be advantagous (*12*).

In 68Ga-PSMA-11 PET/CT several techniques can be used to enhance diagnostic certainty in regions adjacent to the urinary bladder. One approach is to perform imaging at a second time point very early after injection of 68Ga-PSMA-11, when tracer accumulation in the urinary bladder is still absent or low (*13*). Early dynamic imaging starting simultaneously with tracer injection, or early static PET exams performed shortly p.i. of tracer have been proven to be helpful in distinguishing malignant PC lesions from urinary bladder activity (*13,14*).

Administration of diuretics is another strategy in order to decrease urinary bladder activity in 68Ga-PSMA-11 PET/CT. In fact, administration of 20 mg furosemide combined with oral hydration of 500 ml water is recommended in the joint EANM and SNMMI procedure guideline for PSMA-ligand PET/CT (*6*). It has been shown that tracer accumulation in the urinary bladder of 68Ga-PSMA-11 but also of 68Ga-PSMA I&T, another PSMA-ligand with predominantely renal excretion, can be reduced with furosemide on PET-scans 60 min p.i., but also on late exams with image acquisition 90 min and 180 min p.i. (*15*–*18*). In a recent study by our group we could demonstrate that intravenous injection of 20 mg furosemide at the time of radiotracer injection followed by an infusion of 500 ml sodium chloride significantly reduces urinary bladder activity (*19*). However, to date no data of a large patient cohort is available, whether reduction of urinary bladder activity achieved by an early furosemide injection also results in a higher detection rate of

LR in PC-patients with BR. In addition, there are concerns that injection of furosemide shortly after tracer administration may cause a relevant renal wash-out of 68Ga-PSMA-11 before it binds to the PSMA-receptor. Therefore, in the present study we investigated whether a) forced diuresis with early furosemide injection has a positive impact on the detection rate of LR in comparison with patients receiving no preparation and b) administration of furosemide simultaneously with tracer injection has a negative influence on intensity of tracer accumulation in organs with physiologic tracer uptake.

MATERIAL AND METHODS

Patient Population

For this retrospective analysis a total of 440 PC patients who were referred to 68Ga-PSMA-11 PET/CT between 11 January 2016 and 25 September 2018 for assessment of BR after definitive primary therapy were extracted from our database. Search for patients in our archive centered on 26 June 2017, when administration of 20 mg furosemide and hydration was indroduced as standard protocol in our clinical routine, following the EANM/SNMMI guideline on PSMA-PET/CT (*6*). The analysis also comprised PET/CT exams of patients partly included in previous publications by our group (*13,19*). In group one (G1) 220 consecutive scans of patients were included who were investigated before that date. Group two (G2) comprised 220 consecutive scans of patients examined after 26 June 2017 who were injected with 20 mg furosemide at the time of tracer administration, followed by intravenous hydration with 500 ml sodium chloride (NaCl 0.9%). Patient characteristics of the two groups are presented in Table 1a and 1b. The study concept was presented to our institutional ethics committee. As the study was designed retrospectively, using data obtained for clinical purposes, formal ethical approval was not deemed necessary by the ethics committee, meeting the legal requirements of our country. Written informed consent was obtained from all patients prior to the exam. All procedures performed in this study were in accordance with the principles of the 1964 declaration of Helsinki and its subsequent amendments (*20*)

Radiopharmaceutical

PSMA-11 (Glu-NH-CO-NH-Lys(Ahx)-HBED-CC; HBED=*N,N'*-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-N, N'-diacetic acid) was obtained from ABX advanced biochemical compounds (Radeberg, Germany) in GMP quality. 68Ga-PSMA-11 was prepared on an automated synthesis module (Modular-Lab PharmTracer; Eckert & Ziegler, Berlin) using a procedure previously described (*14,21*). The radiochemical purity of the final product was >92% as analyzed by reversed phase HPLC analysis.

Imaging Protocol

68Ga-PSMA-11 PET/CT imaging was conducted using a dedicated PET/CT system in time of flight mode (Discovery 690; GE Healthcare, Milwaukee, WI). Patients received a median activity of 154.8 MBq (range: 95.0 – 216.0 MBq). Median injected activity of 68Ga-PSMA-11 did not differ significantly between patients of group one and group two (150.5 MBq vs 156.4 MBq; p=0.605). Median uptake time in group one and two was 67 min (range: 52-101; Q1=60 min; Q3=73 min) and 69 min (range: 45-100; Q1=61 min; Q3=77 min), respectively and differed significantly (p-value: 0.022). A whole-body PET scan (skull vertex to upper thighs) in three-dimensional mode was acquired (emission time: 2 min per bed position with an axial field-of-view of 15.6 cm per bed position). 225 patients (51.1%) received a diagnostic contrast-enhanced CT scan. The contrast-enhanced CT scan parameters using “GE smart mA dose modulation” were: 100 or 120 kVp, 80-450 mA, Noise Index 24, 0.8 s per tube rotation, slice thickness 3.75 mm, and pitch 0.984. A CT scan of the thorax, abdomen and pelvis (shallow breathing) was acquired 40 – 70 sec after injection of contrast agent (60 to 120 ml of Iomeron 400 mg/l, depending on patient body weight), followed by a CT scan of the thorax in deep inhalation. In the remaining 215 patients (48.9%) a low-dose CT scan was performed for attenuation correction of the PET emission data. Low-dose CT was also used for anatomical allocation of lesions with increased uptake found on PET. The low-dose CT scan parameters using “GE smart mA dose modulation” were: 100 kVp, 15-150 mA, Noise index 60, 0.8 s per tube rotation, slice thickness 3.75 mm, and pitch 1.375. Reconstruction was performed with an ordered subset expectation maximization algorithm (OSEM) with 4 iterations/8 subsets. Images were corrected for randoms and scatter.

Image Analysis

All 68Ga-PSMA-11 PET/CT images were analysed with dedicated commercially available software (GE Advance Workstation SW Version AW4.5 02), which allowed the review of PET, CT and fused imaging data in axial, coronal and sagittal slices. PET images were interpreted independently by two board approved nuclear medicine physicians, who were blinded to the method of patient preparation, clinical patient data and results of other exams. In case of patients already included in previous studies, readers were not aware of results of those analysis. If an early static PET scan was performed (*13*), only images 60 min p.i. were assessed. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) diagnostic criteria for 68Ga-PSMA-11 PET/CT reporting in prostate cancer proposed by Eiber et al. (*22*) and consensus criteria for image interpretation defined by Fanti et al. served as a reference for assessment of LR (*8*). Patients were judged either positive or negative for LR. Cases in which a clear distinction between urinary activity and a LR was not possible were classified as equivocal. In case of disagreement between the two readers, images were reevaluated and a final diagnosis was reached in consensus. In addition, intensity of tracer uptake in organs and tissues with physiologic tracer accumulation and lesions judged as LR was measured, using maximum and mean standardized uptake value (SUV_{max} and SUV_{mean}). For SUV-calculations volumes of interest (VOIs) were generated automatically by the software described above with a manually adapted isocontour threshold centered on the organs of interest. Measurements of tracer uptake were performed in the following organs and tissues: Urinary bladder, kidneys, small bowel, liver, spleen, parotid gland, lacrimal gland, blood pool (aortic arch), muscle activity (gluteal region) and bone (thoracic vertebra).

Statistical Analysis

Differences between the two groups (G1: patients without preparation vs. G2: patients receiving furosemide) were evaluated using non-parametric testing procedures. Distributions of continuous variables (baseline characteristics, and SUV_{max} values in various tissues) were compared between groups using Mann-Whitney U tests. Local recurrence detection rates (positive, negative, equivocal) were compared between groups using Fisher's exact tests. All tests of statistical significance were two-sided, and p-values less than 0.05 were considered statistically significant. All analyses were conducted in R, version 3.5.1. (*23*)

RESULTS

In brief, comparison of patient characteristics between both preparation groups revealed a statistically significant difference in patient age, method of definitive treatment prior to the PET exam and T-stage, whereas other parameters listed in detail in Table 1a and 1b did not differ significantly.

With regard to visual evaluation of LR, a statistically significantly higher number of LR could be detected in the patient group that received furosemide compared to patients without preparation, with 56 cases (25.5%) and 38 cases (17.3%) judged positive for LR, respectively (p=0.048). Frequency of equivocal findings in the prostatic fossa was markedly lower in the group with furosemide in comparison with patients without preparation, with 27 (12.3%) vs 37 (16.8%) unclear cases. However, the difference between both groups in this respect did not reach statistical significance (p=0.223). Intensity of tracer uptake in lesions considered as LR did not differ significantly between both groups (p=0.987), showing a median SUV_{max} of 8.1 in group one (range: 3.2-47.9) and 8.4 in group two (range: 3.2-139.0). An overview of these results is also shown in table 2, where a subgroup analysis of patients according to primary treatment is also presented. In addition, prostate specific antigen (PSA)-subgroups were analysed and compared with respect to detection of LR (demonstrated in Figure 1).

Intensity of tracer accumulation in the urinary bladder was significantly higher in patients without preparation compared with the furosemide group, showing a median SUV_{max} of 63.0 and 8.9, respectively (p<0.001). Regarding intensity of physiologic tracer uptake in the remaining predefined organs and tissues no statistically significant difference in median SUV_{max} values could be found between the two groups in the kidneys (55.6 vs 54.5), in the liver (9.9 vs 9.4), in the spleen (11.2 vs 11.9), in the parotid gland (19.2 vs 19.8), blood pool (2.2 vs 2.3) and in the bone (1.6 vs 1.6). Higher SUV_{max} values in the furosemide group in comparison with group one, reaching statistical significance, were measured in the small bowel (17.1 vs 16.2; p=0.040), in the lacrimal gland (10.9 vs 8.9; p<0.001) and in the muscle (1.1 vs 1.0; p=0.001). In total, intensity of physiologic tracer uptake in all organs and tissues investigated (except the urinary bladder) was not reduced significantly in the patient group receiving furosemide compared with the patient group without preparation. A detailed synopsis of SUV-values including SUV_{mean} is given in Table 3a and 3b.

Histologic confirmation of malignant origin of cases judged positive for LR could not be achieved. However, LR could be verified in 50.0% of cases of group one (n=19) and 42.9% of cases of group two (n=24). LR was confirmed either radiologically with a pathologic correlate on diagnostic CT, MRI or transrectal ultrasound (n=33) or on a follow-up 68Ga-PSMA-11 PET/CT scan (n=4) or patients showed a decrease of PSA-values after salvage radiation therapy of the prostatic fossa following PSMA-11 PET/CT (n=6).

In a subgroup analysis of all patients rated positive for LR on 68Ga-PSMA-11 PET/CT (group one: n=38; group two: n=56), LR was the only site of recurrence in 24 cases (63.1%) of group one and in 31 cases (55.4%) of group two. In eight cases of group one (21.1%) and 13 cases of group two (23.2%) PSMA-positive lymph nodes classified as metastases could be detected in addition to LR without sign of metastases to bone or other organs. Two cases of group one (5.3%) and six cases of group two (10.7%) showed a LR and PSMA-positive metastases both to lymph nodes and in the bone. LR and PSMA-positive skeletal metastases without PSMA-positive lymph nodes were present in four cases of group one (10.5%) and six cases of group two (10.7%).

Overall, detection rate of at least one PSMA-positive lesion consistent with recurrent prostate cancer was 60.5% of all patients in group one (n=133) and 66.8% of all patients in group two (n=147), not differing significantly (p=0.198). In group one, PSMA-positive lymph node metastases were detected in 81 cases (36.8%), PSMA-avid skeletal metastases in 34 cases (15.5%) and hematogenous metastases other than bone in four cases (1.8%). In group two, PSMA-positive lymph node metastases were found in 91 cases (41.4%), whereas bone metastases and non skeletal distant metastases were present in 36 cases (16.4%) and five cases (2.3%), respectively.

Patients were also asked whether they felt urinary urgency during the exam, categorizing it as slight, moderate (tolerable) or strong (major discomfort). In group one only nine patients (4.1%) stated urgency, that was described as slight to moderate. In the furosemide group urinary urge during scanning occurred in 93 cases (42.3%), that was classified by the patients in the majority of cases as slight (n=77; 82.8%) and moderate in 16 cases (17.2%). In total, early injection of 20 mg furosemide was tolerated well, no strong urinary urge during the PET-exam was reported and no furosemide-induced adverse reaction was recorded.

DISCUSSION

In 68Ga-PSMA-11 PET/CT, usually conducted 60 min after tracer injection, LR may be overlooked when it is located adjacent to the urinary bladder, mainly due to the masking effect of overlaying urinary bladder activity (*11*). In addition, there are cases in which it is almost impossible to discriminate local recurrence from urinary activity within the urethra or the bladder neck, especially at the site of anastomosis after RP (*8*), as displayed in an example on Figure 2.

Administration of furosemide is recommended in the joint EANM/SNM procedure guideline for 68Ga-PSMA-11 PET/CT (*6*). In a recently published study by our group, we could demonstrate that forced diuresis with 20 mg furosemide, injected simultaneously with the radiotracer, significantly reduces tracer accumulation in the urinary bladder compared with patients receiving no preparation or hydration alone (*19*).

The primary objective of the present study was to investigate whether the afore described furosemide-induced reduction of urinary bladder activity also improves detection rates of LR and enhances diagnostic certainty in the prostate fossa. Indeed, our study revealed a significantly higher number of PSMA-positive LRs in the furosemide group compared to the group of patients without preparation, with 56 and 38 cases judged positive for LR, respectively (25.5% vs 17.3% of patients). The effect of furosemide induced tracer washout of the urinary bladder on detectablity of LR is illustrated on Figure 3. Furthermore, number of equivocal findings in the prostate fossa was lower in patients undergoing forced diuresis in comparison with patients without furosemide, with 27 and 37 unclear cases, respectively (12.3% vs 16.8% of patients). However, the difference in this respect did not reach statistical significance. This may be attributable to the fact that tracer activity does not vanish completely from the urinary routes after furosemide administration, and in a small number of cases a relatively high amount of tracer remains within the bladder and urethra despite forced diuresis (*15,21,24*). Of note, our data suggest that patients after radical prostatectomy (RPE) profit most from furosemide. Number of unclear findings after RPE was significantly lower in the furosemide group and a clear tendency in the positivity rate of LR was found after furosemide, although not reaching statistically significance. In contrast, detection rate of LR in both groups was almost the same in patients who underwent primary radiation therapy without RPE (as presented in Table 2). Our results go in line with the findings of a study conducted by Fennessy et al.,

using a similar preparation protocol with early administration of furosemide (*15*). Authors reported that diagnostic confidence in the pelvic area on 68Ga-PSMA-11 PET/CT could be improved in patients injected with furosemide. However, number of patients in the patient subset with BR was relatively low in this analysis (n=44) and the analysis was probably underpowered to detect a positive effect of the furosemide protocol on detection rates of LR.

There are concerns whether injection of furosemide at the time of radiotracer injection is appropriate. Injection of furosemide early in the uptake phase of the tracer might lead to an increased renal wash-out of 68Ga-PSMA-11 before it binds to PSMA, possibly resulting in a reduced tracer uptake in tumour lesions and in lower sensitivity of the exam. We tried to address this issue by comparing intensity of tracer accumulation in organs and tissues with physiologic 68Ga-PSMA-11 uptake in patients receiving furosemide and patients without preparation. We hypothesized that if a significant increase of renal tracer excretion was induced by early injection of furosemide, it would result in a lower tracer uptake in organs with physiologic uptake. However, our results could clearly show that, apart from urinary bladder, tracer accumulation in all organs and tissues investigated, was not lower in the patient group receiving furosemide compared to the patient group without preparation. Calculated SUV-values are comparable to those of previous studies dealing with biodistribution of 68Ga-PSMA-11 (*7,25,10*). Taken together, our findings can be interpreted as sufficient evidence that adminisitration of furosemide shortly after tracer injection does not have a relevant negative influence on organ distribution of 68Ga-PSMA-11.

A negative impact of early furosemide injection on lesion detectability could not be observed either. Patient based overall detection rate of at least one 68Ga-PSMA-11 avid lesion consistent with recurrent PC was even higher in the group receiving furosemide compared with patients without preparation (66.8% vs 60.5% of cases). In comparison with other studies a somewhat lower overall detection rate in our analysis may be noticed. In a study by Afshar-Oromieh et al. including 1007 PC patients with BR referred for 68Ga-PSMA-11 PET/CT a PET-positivity in 79.5% of patients is described (*1*). In a recently published study by Chevalme et al. on the performance of 68Ga-PSMA-11 PET/CT after a negative or equivocal 18F-fluorocholine PET/CT (including 1084 PC patients with BR), an overall PET positivity rate of 68% of patients was found (*26*), revealing no significant difference between subgroups of patients with furosemide administered at time of tracer injection and patients without furosemide. The

lower percentage of PET-positive patients in our analysis may be due to relatively low PSA-values of patients in both groups (median PSA: 1.3 ng/ml and 0.82 ng/ml, respectively). It is well known that detection efficacy of 68Ga-PSMA-11 PET/CT increases with higher PSA-levels (*1,4*).

Although with the present study we could demonstrate that furosemide administered at the time of tracer injection has a major impact on assessment of LR in PC patients with BR, a debate on the best time point for injection of furosemide in 68Ga-PSMA-11 PET/CT may remain. Applying a biphasic scan protocol, Afshar-Oromieh et al. describe that a reduction of radioactivity in the urinary bladder between scans 1 h p.i. and 3 h p.i. was more intense after injection of furosemide, assuming a better visibility of prostate cancer lesions in the vicinity of the urinary baldder (*17*). Another approach with late furosemide injection is described by Haupt et al. (*16*). Compared with a standard protocol without furosemide and scan acquisition 60 min p.i., a slightly higher detection rate of LR was demonstrated in patients orally hydrated with 1 L of water 30 min p.i. and injected with furosemide 60 min p.i. followed by a single PET-exam 90 min p.i. (LR present in 42.9% of patients with furosemide vs. 42.0% of patients without furosemide). Authors could demonstrate that urinary bladder activity was significantly lower with furosemide as compared with the standard protocol, resulting also in a significantly better contrast between LR and urinary bladder activity. The high percentage of LR in both groups in this study is striking and may be explained by the relatively high overall PSA-levels of patients analysed (39.2% of patients with PSA > 4.0 ng/ml). In a study by Derlin et al. using 68Ga-PSMA I&T, a different PSMA-ligand with high urinary bladder accumulation, authors could show that furosemide injected simultaneously with radiotracer, significantly reduced urinary bladder activity on PET scans 60 min p.i. compared with patients without furosemide, resulting also in a significant improvement in assessment of the prostatic fossa (*18*). However, with respect to evaluation of the prostate bed, best results were obtained with delayed imaging 180 min p.i., performed after oral hydration and injection of furosemide following a PET/CT scan 60 min p.i.

Despite the favourable results of these furosemide protocols, the described procedures require either a longer waiting time for the patients or additional scans. For institutions with high throughput of PET exams and limited camera availability a protocol with an uptake time of only 60 min and a single image acquisition as presented in this study is clearly advantagous.

There are some limitations within this study. Firstly, the data were collected retrospectively. We are aware of the fact that some parameter in the patient population differed significantly between both preparation groups, such as median radiotracer uptake time, number of patients with primary Rt and initial T-stage. We cannot exclude that this heterogeneity may have influenced the results. With respect to median uptake time a difference of two min does, in our view, not have a relevant negative effect on results. In particular, Q1 and Q3 demonstrate that the majority of participants had an uptake time between quite a small time window of 60 min and 77 min. A major drawback of the study is that no histologic verification of lesions rated as LR was performed. Usually, biopsy of PSMA-positive LR is not part of our standard clinical work-up of PC patients with BR. However, interpretation of findings was done by two experienced readers in a standardized way following published guidelines (*8,22*). Therefore, we are strongly convinced that PSMA-positive local findings in the prostate fossa, that were not verified by other imaging modalities or on follow-up, can be regarded as true positive.

CONCLUSION

In PC patients with BR referred for 68Ga-PSMA-11 PET/CT, application of a forced diuresis protocol with 500 ml NaCl 0.9% and 20 mg furosemide, injected simultaneously with the radiotracer, has the potential to significantly increase the detection rate of LRs. Moreover, early injection of furosemide does not seem to have a negative influence on organ distribution of 68Ga-PSMA-11 and does not impair lesion detectability of the exam.

DISCLAIMER

Conflict of interest: The authors declare that they have no conflict of interest.

KEY POINTS

Question: Does intravenous administration of furosemide increase detection rate of local recurrence in prostate cancer patients with biochemical recurrence referred for 68Ga-PSMA-11 PET/CT?

Pertinent findings: In a retrospective analysis of 440 prostate cancer patients undergoing 68Ga-PSMA-11 PET/CT for biochemical recurrence, detection rate of local recurrence is significantly higher in patients injected with 20 mg furosemide at the time point of tracer administration in comparison with patients receiving no furosemide.

Implications for patient care: A more accurate assessment of the prostatic fossa after definitive primary therapy has a major impact on therapeutic management in prostate cancer patients with biochemical recurrence, especially in those patients in whom a salvage radiation therapy is considered.

REFERENCES

1. Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of 68Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. *Eur J Nucl Med Mol Imaging*. 2017;44:1258-1268.

2. Caroli P, Sandler I, Matteucci F, et al. 68Ga-PSMA PET/CT in patients with recurrent prostate cancer after radical treatment: prospective results in 314 patients. *Eur J Nucl Med Mol Imaging*. 2018;45:2035-2044.

3. Fendler WP, Calais J, Eiber M, et al. Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: A prospective single-arm clinical trial. *JAMA Oncol*. 2019;5:856-863.

4. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid 68Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med*. 2015;56:668-674.

5. Ceci F, Uprimny C, Nilica B, et al. 68Ga-PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate? *Eur J Nucl Med Mol Imaging*. 2015;42:1284-1294.

6. Fendler WP, Eiber M, Beheshti M, et al. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. *Eur J Nucl Med Mol Imaging*. 2017;44:1014-1024.

7. Afshar-Oromieh A, Malcher A, Eder M, et al. PET imaging with a (68Ga)Gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. *Eur J Nucl Med Mol Imaging*. 2013;40:486-495.

8. Fanti S, Minozzi S, Morigi JJ, et al. Development of standardized image interpretation for 68Ga-PSMA PET/CT to detect prostate cancer recurrent lesions. *Eur J Nucl Med Mol Imaging*. 2017;44:1622-1635.

9. Afshar-Oromieh A, Haberkorn U, Schlemmer HP, et al. Comparison of PET/CT and PET/MRI hybrid systems using a 68Ga-labelled PSMA ligand for the diagnosis of recurrent prostate cancer: initial experience. *Eur J Nucl Med Mol Imaging*. 2014;41:887-897.

10. 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.

11. Freitag MT, Radtke JP, Afshar-Oromieh A, et al. Local recurrence of prostate cancer after radical prostatectomy is at risk to be missed in 68Ga-PSMA-11-PET of PET/CT and PET/MRI: comparison with mpMRI integrated in simultaneous PET/MRI. *Eur J Nucl Med Mol Imaging*. 2017;44:776-787.

12. Rahbar K, Weckesser M, Ahmadzadehfar H, Schäfers M, Stegger L, Bögemann M. Advantage of 18F-PSMA-1007 over 68Ga-PSMA-11 PET imaging for differentiation of local recurrence vs. urinary tracer excretion. *Eur J Nucl Med Mol Imaging*. 2018;45:1076-1077.

13. Uprimny C, Kroiss AS, Fritz J, et al. Early PET imaging with 68Ga-PSMA-11 increases the detection rate of local recurrence in prostate cancer patients with biochemical recurrence. *Eur J Nucl Med Mol Imaging*. 2017;44:1647-1655.

14. Uprimny C, Kroiss AS, Decristoforo C, et al. Early dynamic imaging in 68Ga-PSMA-11 PET/CT allows discrimination of urinary bladder activity and prostate cancer lesions. *Eur J Nucl Med Mol Imaging*. 2017;44:765-775.

15. Fennessy N, Lee J, Shin J, et al. Frusemide aids diagnostic interpretation of (68Ga)-PSMA positron emission tomography/CT in men with prostate cancer. *J Med Imaging Radiat Oncol*. 2017;61:739-744.

16. Haupt F, Dijkstra L, Alberts I, et al. 68Ga-PSMA-11 PET/CT in patients with recurrent prostate cancer - a modified protocol compared with the common protocol. *Eur J Nucl Med Mol Imaging*. 2020;47:624-631.

17. Afshar-Oromieh A, Sattler LP, Mier W, et al. The clinical impact of additional late PET/CT imaging with 68Ga-PSMA-11 (HBED-CC) in the diagnosis of prostate cancer. *J Nucl Med*. 2017;58:750-755.

18. Derlin T, Weiberg D, Klot C von, et al. 68Ga-PSMA I&T PET/CT for assessment of prostate cancer: evaluation of image quality after forced diuresis and delayed imaging. *Eur Radiol*. 2016;26:4345-4353.

19. Uprimny C, Bayerschmidt S, Kroiss AS, et al. Impact of forced diuresis with furosemide and hydration on the halo artefact and intensity of tracer accumulation in the urinary bladder and kidneys on (68Ga)Ga-PSMA-11-PET/CT in the evaluation of prostate cancer patients. *Eur J Nucl Med Mol Imaging*. 2021;48:123-133.

20. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310:2191-2194.

21. Uprimny C, Kroiss AS, Decristoforo C, et al. 68Ga-PSMA-11 PET/CT in primary staging of prostate cancer: PSA and Gleason score predict the intensity of tracer accumulation in the primary tumour. *Eur J Nucl Med Mol Imaging*. 2017;44:941-949.

22. Eiber M, Herrmann K, Calais J, et al. Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): Proposed miTNM Classification for the interpretation of PSMA-Ligand PET/CT. *J Nucl Med*. 2018;59:469-478.

23. R: A language and environment for statistical computing. Austria, Vienna: R Foundation of Statistical Computing; 2018.

24. Perveen G, Arora G, Damle NA, et al. Can early dynamic Positron Emission Tomography/Computed Tomography obviate the need for postdiuresis image in 68Ga-PSMA-HBED-CC scan for evaluation of prostate adenocarcinoma? *Indian J Nucl Med*. 2018;33:202-208.

25. Prasad V, Steffen IG, Diederichs G, Makowski MR, Wust P, Brenner W. Biodistribution of (68Ga)PSMA-HBED-CC in patients with prostate cancer: Characterization of uptake in normal organs and tumour lesions. *Mol Imaging Biol*. 2016;18:428-436.

26. Chevalme Y-M, Boudali L, Gauthé M, et al. Survey by the French Medicine Agency (ANSM) of the imaging protocol, detection rate, and safety of 68Ga-PSMA-11 PET/CT in the biochemical recurrence of prostate cancer in case of negative or equivocal 18F-fluorocholine PET/CT: 1084 examinations. *Eur J Nucl Med Mol Imaging*. 2021.

Table 1a Patient characteristics and summary of previous treatment in the two different patient preparation groups.

	Age (y) median (range)	PSA (ng/ml) at PET median (range)	PSAdt (months) median (range)	BMI kg/m² median (range)	GFR < 60 ml/min/1.73m² n (%)	ADT at PET n (%)	BR after RPE n (%)	BR after pRt n (%)	BR after RPE + sRT
G1[§]	70 (52-87)	1.30 (0.14-81.09)	6 (0.9-120.2)[†]	25.9 (17.5-57.8)	38 (17.3%)	40 (18.2%)	109 (49.5%)	22 (10.0%)	89 (40.5%)
G2[‖]	72 (44-88)	0.82 (0.10-147.6)	4.7 (1.2-59.1)[‡]	26.0 (18.8-40.8)	34 (15.5%)	46 (20.9%)	116 (52.7%)	40 (18.2%)	64 (29.1%)
p-value*	0.032	0.055	0.417	0.613	0.515	0.809	overall p-value* 0.009		

* p-values from a Mann-Whitney U test (Age, PSA, PSAdt, BMI) and from Fisher's exact tests (GFR, ADT and BR subgroups); [§] no preparation; [‖] injection of 20 mg furosemide and 500 ml NaCl 0.9%; [†] 220 patients, missing data n=171; [‡] 220 patients, missing data n=172;

ADT: Androgen deprivation therapy; BMI: Body mass index; BR: Biochemical recurrence; GFR: Glomerular filtration rate; PSA: Prostate specific antigen; PSAdt: PSA doubling time; RPE: Radical prostatectomy; pRT: Primary radiation therapy; sRT: Salvage radiation therapy;

Table 1b Tumour characteristics in the two different patient preparation groups.

	Gleason score[†]							T-stage[‡]			
	GS 5	**GS 6**	**GS 7a**	**GS 7b**	**GS 8**	**GS 9**	**GS 10**	**T1**	**T2**	**T3**	**T4**
G1[§] n (%)	0 (0.0%)	17 (8.9%)	62 (32.5%)	35 (18.3%)	30 (15.7%)	47 (24.6%)	0 (0.0%)	2 (1.3%)	57 (36.1%)	85 (53.8%)	14 (8.9%)
G2[‖] n (%)	2 (1.0%)	17 (18.1%)	76 (36.2%)	45 (21.4%)	30 (14.3%)	39 (18.6%)	1 (0.5%)	4 (2.4%)	63 (37.3%)	100 (59.2%)	2 (1.2%)
	overall p-value* 0.531							overall p-value* 0.008			

* p-value from Fisher's exact tests; [§] no preparation; [‖] injection of 20 mg furosemide and 500 ml NaCl 0.9%; [†] missing data(G1 n=29; G2 n=10); [‡] missing data(G1 n=62; G2 n=51)

Table 2 Results of visual assessment of local recurrence for main groups and primary therapy subgroups.

	G1§	G2‖	p-value*
Overall, LR positive, n (%)	38 (17.3%)	56 (25.5%)	0.048
Overall, LR negative, n (%)	145 (65.9%)	137 (62.3%)	0.487
Overall, LR equivocal, n (%)	37 (16.8%)	27 (12.3%)	0.223
SUV_{max}, LR positive, median (range)	8.1 (3.2-47.9)	8.4 (3.2-139.0)	0.987
Subgroup pRT, LR positive, n (%)	12 (54.5%)	20 (50.0%)	0.795
Subgroup pRT, LR negative, n (%)	8 (36.4%)	15 (37.5%)	1
Subgroup pRT, LR equivocal, n (%)	2 (9.1%)	5 (12.5%)	1
Subgroup pRPE, LR positive, n (%)	26 (13.1%)	36 (20.0%)	0.095
Subgroup pRPE, LR negative, n (%)	137 (69.2%)	126 (70.0%)	0.911
Subgroup pRPE, LR equivocal, n (%)	35 (17.7%)	18.0 (10.0%)	0.038

* p-values from Fisher's exact tests for frequencies, and from a Mann-Whitney U test for the median SUV_{max} comparison; § no preparation; ‖ injection of 20 mg furosemide and 500 ml NaCl 0.9%;

LR: Local recurrence; pRPE: primary radical prostatectomy; pRT: Primary radiation therapy; SUV_{max}: maximal standardized uptake value

Table 3a Comparison of intensity of tracer accumulation in organs and tissues with physiologic tracer uptake.

	G1§	G2‖	p-value*
SUV_{max} median bladder (range)	63.0 (4.6-350.0)	8.9 (1.7-35.0)	<0.001
SUV_{max} median kidneys (range)	55.6 (7.4-100.9)	54.5 (16.1-94.6)	0.264
SUV_{max} median liver (range)	9.9 (4.5-43.4)	9.4 (3.0-19.5)	0.196
SUV_{max} median spleen (range)	11.2 (4.2-34.0)	11.9 (3.5-23.4)	0.558
SUV_{max} median small bowel (range)	16.2 (4.7-36.9)	17.1 (8.3-51.3)	0.040
SUV_{max} median parotid gland (range)	19.2 (9.1-39.3)	19.8 (10.7-36.0)	0.069
SUV_{max} median lacrimal gland (range)	8.9 (3.0-23.9)	10.9 (2.8-31.9)	<0.001
SUV_{max} median blood pool (range)	2.2 (1.2-4.6)	2.3 (1.2-4.9)	0.649
SUV_{max} median muscle (range)	1.0 (0.5-3.0)	1.1 (0.6-2.2)	0.001
SUV_{max} median bone (range)	1.6 (0.8-3.8)	1.6 (0.8-4.3)	0.564

* p-values from Mann-Whitney U tests; § no preparation; ‖ injection of 20 mg furosemide and 500 ml NaCl 0.9%;

SUV_{max}: maximal standardized uptake value

Table 3b Comparison of intensity of tracer accumulation in organs and tissues with physiologic tracer uptake.

	G1[§]	G2[‖]	p-value*
SUV_{mean} median bladder (range)	41.9 (22.8 - 69.8)	5.3 (3.5 - 7.3)	<0.001
SUV_{mean} median kidneys (range)	34.8 (29.8 - 40.6)	34.1 (27.8 - 40.4)	0.358
SUV_{mean} median liver (range)	5.4 (4.4 - 6.5)	5.2 (4.4 - 6.6)	0.679
SUV_{mean} median spleen (range)	6.5 (5.2 - 8.5)	7.0 (5.8 - 8.3)	0.070
SUV_{mean} median small bowel (range)	9.4 (7.5 - 11.6)	10.0 (8.23 - 12.0)	0.027
SUV_{mean} median parotid gland (range)	12.0 (10.2 - 13.9)	12.4 (10.9 - 15.0)	0.028
SUV_{mean} median lacrimal gland (range)	5.8 (4.4 - 7.2)	7.0 (5.4 - 9.0)	<0.001
SUV_{mean} median blood pool (range)	1.3 (1.1 - 1.5)	1.3 (1.1 - 1.5)	0.990
SUV_{mean} median muscle (range)	0.6 (0.5 - 0.7)	0.6 (0.5 - 0.7)	0.011
SUV_{mean} median bone (range)	0.9 (0.8 - 1.1)	0.9 (0.7 - 1.1)	0.560

* p-values from Mann-Whitney U tests, § no preparation; ‖ injection of 20 mg furosemide and 500 ml NaCl 0.9%;

SUV_{mean}: mean standardized uptake value

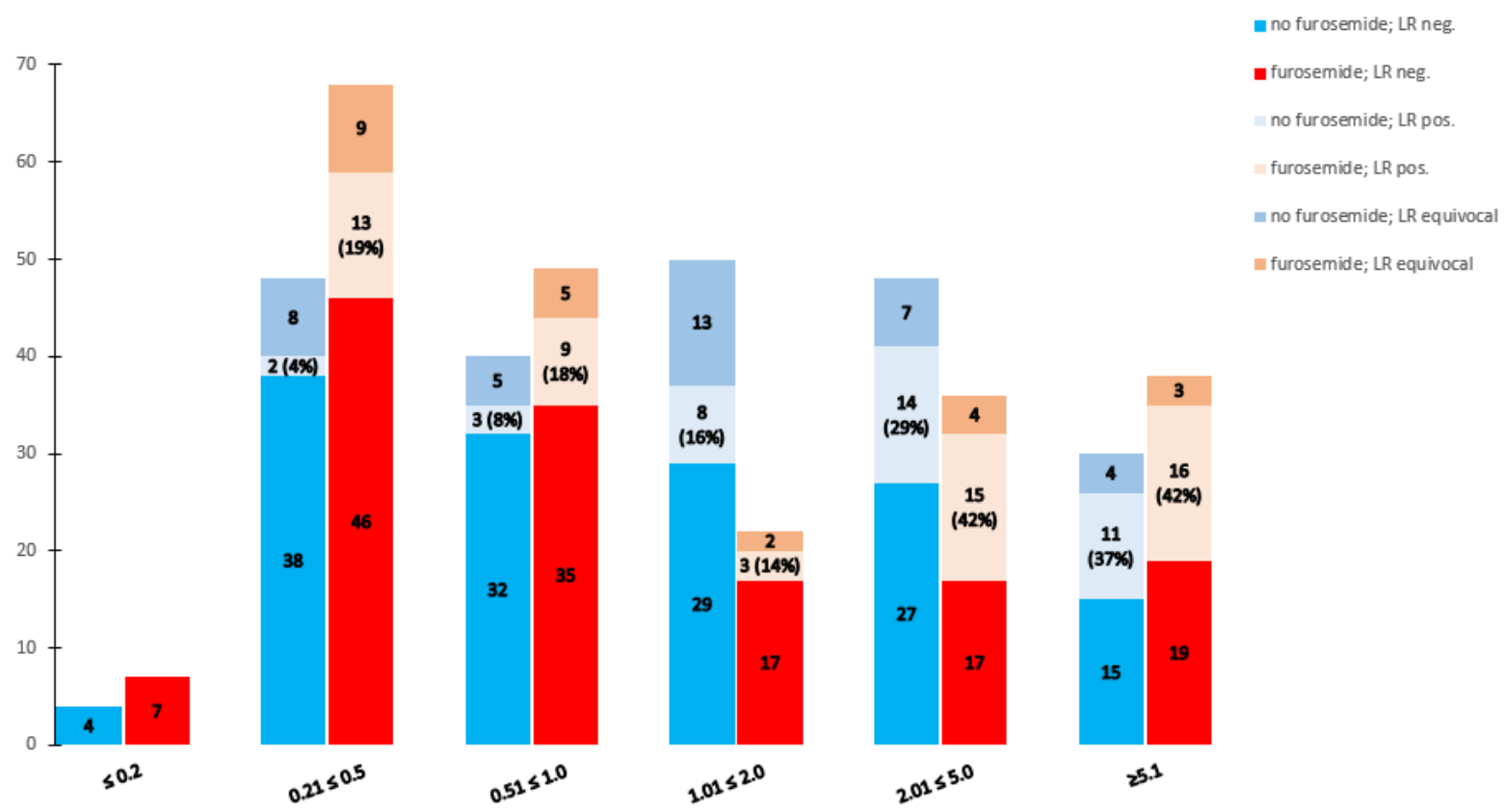

Figure 1 Comparison of number of patients judged positive (pos.), negative (neg.) or equivocal for local recurrence (LR) in relation to PSA level, together with PET-positive rate of local recurrences in each subgroup (%). Group one (no furosemide, blue column); Group two (with furosemide, red column).

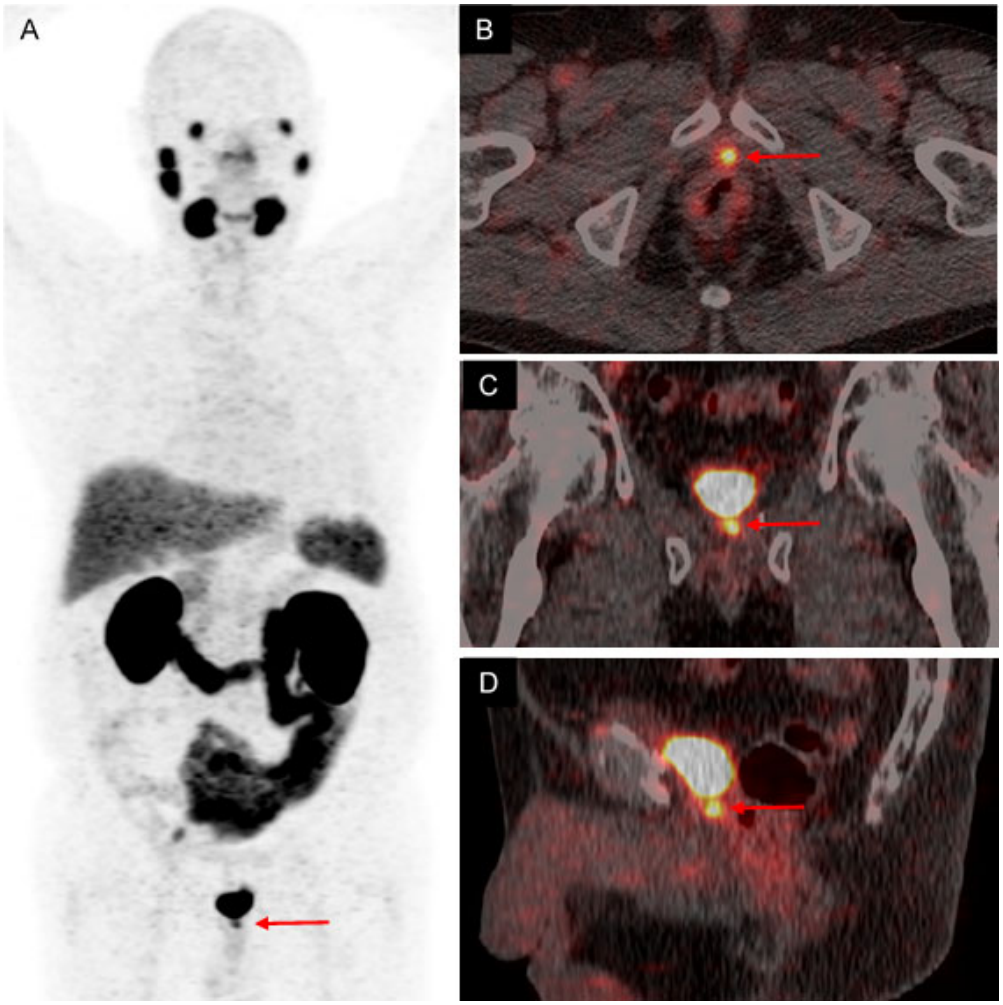

Figure 2 Example of an equivocal finding in the prostate fossa on ^{68}Ga-PSMA-11 PET/CT with maximum intensity projection (A), fused axial (B), fused coronal (C) and fused sagittal (D) slices of a prostate cancer patient with biochemical recurrence after radical prostatectomy and salvage radiation therapy (PSA: 1.34 ng/ml), receiving no preparation prior to imaging. Intense focal uptake is present in the midline at the level of the vesicourethral anastomosis (red arrowhead). A clear distinction between a local recurrence and urinary activity within the urethra is not possible (SUV_{max} of focal uptake in midline: 10.3 and SUV_{max} of urinary bladder: 118.0).

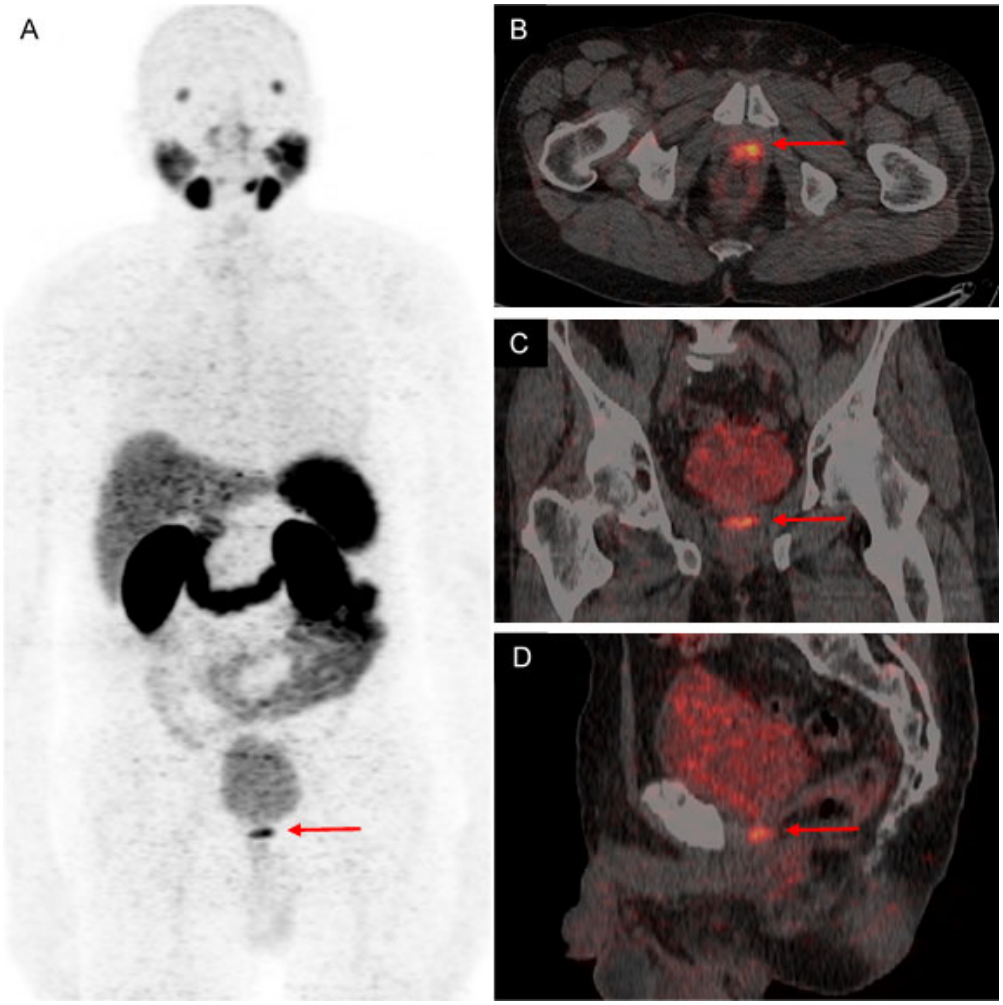

Figure 3 ^{68}Ga-PSMA-11 PET/CT with maximum intensity projection (A), fused axial (B), fused coronal (C) and fused sagittal (D) images of a prostate cancer patient with biochemical recurrence after radical prostatectomy (PSA: 1.18 ng/ml), who received forced diuresis with 20 mg furosemide simultaneously with radiotracer injection. Focal uptake of high intensity with a SUV_{max} of 9.6 is present in the area of the vesicourethral anastomosis (red arrowhead) that can be clearly distinguished from adjacent urinary activity in the bladder (SUV_{max} of 9.4), representing a case consistent with local recurrence. Malignant origin of the finding was confirmed on a subsequent MRI.

GRAPHICAL ABSTRACT