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The clinical impact of additional late PET/CT imaging with ^{68}Ga-PSMA-11 (HBED-CC) in the diagnosis of prostate cancer

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Conflicts of interest none

Purpose: While Positron Emission Tomography/Computed Tomography (PET/CT) with ^{68}Ga-PSMA-11 in the diagnosis of prostate cancer (PCa) is routinely performed at 1h post injection (p.i.), later scans may be beneficial since most lesions present with higher uptake and contrast. This evaluation aimed to investigate the clinical impact of additional late ^{68}Ga-PSMA-11-PET/CT.

Methods: Between 2011 and 2016, 112 patients with PCa who received early (at 1h p.i.) and late (at 3h p.i.) ^{68}Ga-PSMA-11-PET/CT scans were retrospectively evaluated. The late scans were conducted in order to clarify unclear findings in early scans or to increase the probability of tumor detection in case of negative early scans. All patients were asked to drink 1 liter of water between early and late scans. In addition, 20 of them received 20 milligram furosemide prior to late scans. Tumor detection and radioactivity concentration within the urinary bladder were analyzed in both scans. The maximum standardized uptake value (SUVmax) and contrast of 149 tumor lesions were measured in 69 patients with pathological findings.

Results: Overall, 134 lesions characteristic for PCa in 57 patients clearly presented at 1h p.i. and 147 lesions in 68 patients at 3h p.i.. Forty-three patients showed no pathological findings. Eight patients (7.1%) showed one unclear finding in early scans which could be clarified as characteristic for PCa at 3h p.i.. Four patients (3.6%) presented with one lesion characteristic for PCa at 3h p.i. only. Twelve patients (10.7%) presented with 12 possible PCa lesions at 1h p.i., which, however, could not be confirmed as PCa in late scans. Two patients presented with one lesion characteristic for PCa at 1h p.i. which became invisible at 3h p.i. due to low contrast. At 3h p.i., 62.4% of the lesions demonstrated higher SUVmax and 65.1% higher contrast compared to 1h p.i. Patients with furosemide presented with lower SUV and radioactivity concentration within the urinary bladder.

Conclusion:

^{68}Ga-PSMA-11-PET/CT at 3h p.i. showed most lesions characteristic for PCa with higher uptake and contrast. In addition, the radioactivity signal within the urinary bladder was lower at 3h p.i., especially when furosemide was applied. Consequently, scans at 3h p.i. detected more tumor lesions than 1h p.i..

Prostate cancer (PCa) is the most frequent malignant tumor in men *(1,2)*. After initial curative therapy, mainly by surgery or radiation, biochemical recurrence is frequent in men with high-risk disease. At this stage, searching for tumor lesions is challenging for conventional imaging modalities such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) due to frequently unsatisfying sensitivity and specificity. Since the invention and clinical introduction of ^{68}Ga-PSMA-11 ("HBED-CC"), imaging with Positron Emission Tomography (PET) using ^{68}Ga-PSMA-11 has rapidly spread. ^{68}Ga-PSMA-11 is a small molecule inhibitor of the Prostate-Specific Membrane Antigen (PSMA), a transmembranous enzyme which is significantly overexpressed in most adenocarcinomas of the prostate gland. The first publications indicated that this novel method is significantly superior compared to other methods used for the detection of recurrent PCa *(3–6)*. Later publications and a meta-analysis confirmed these findings *(7–9)*.
Positron Emission Tomography/Computed Tomography (PET/CT) with ^{68}Ga-PSMA-11 is routinely conducted 1h after the injection (p.i.) of the tracer according to its first described clinical set-up *(3)*. However, the same article already demonstrated that late images conducted at 3h p.i. show the majority of PCa lesions with higher contrast due to an ongoing decrease of the background signal and increase of tracer uptake in the majority of PCa lesions which was confirmed by other publications *(10,11)*. All three listed publications are based on bi- or multiphasic scans which were planned in advance. However, the impact of additional late scans which were not planned in advance but initiated after the regular scans (1h p.i.) in order to clarify unclear findings has not yet been investigated.
At our institute, additional late scans have been subsequently used to increase the detection rate of PCa lesions with ^{68}Ga-PSMA-11-PET in men with unclear findings 1h p.i.. This manuscript addresses the issue of what can be expected from late ^{68}Ga-PSMA-11-PET/CT imaging in case of unclear findings or negative scans conducted at 1h p.i.

MATERIALS AND METHODS

Out of 887 patients with PCa referred for ^{68}Ga-PSMA-11-PET/CT between 2011 and February 2016, 149 patients (16.8%) received scans, both, at 1h and 3h p.i.. In the majority of the patients (n=107) recurrent disease was suspected. In 5 cases, PET/CT was conducted before initiation of local therapy to exclude metastases after PCa was confirmed by biopsy.
The first 37 of the above-mentioned 149 patients were part of a previous publication *(3)* and were excluded from the current analysis as these patients were planned in advance to be scanned at 1h and 3h p.i.. The difference between the before-mentioned publication and the

current evaluation is that the late scans of the current evaluation were not planned prior to the first scan at 1h p.i. but were arranged thereafter in order to clarify unclear findings or to increase the probability of tumor detection in case of negative early scans.
It needs to be pointed out that like other imaging modalities, many cases remain which show no pathologic findings in ^{68}Ga-PSMA-11-PET/CT at 1h p.i.. However, the workload in clinical routine does not allow to conduct additional late scans in every of these cases. As a retrospective analysis, it remains impossible to reconstruct the particular situations in which the decision was made to conduct an additional late scan in ^{68}Ga-PSMA-11 PET/CT.

The patients' characteristics are presented in Table 1. 39 patients of the present evaluation have also been part of a previous publication, which, however, exclusively analyzed the "regular" scans conducted at 1h p.i. *(5)*. The authors therefore believe that these patients had to be included in the present evaluation instead of being excluded. Their inclusion improves the data quality and significantly strengthens the conclusions.

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 our national regulations. This evaluation was approved by the ethics committee of the Heidelberg University (permit S-321/2012).

All patients received regular whole body PET scans (from head to upper parts of the legs) at 1h p.i.. Thirty of the scans at 3h p.i. consisted of whole-body, 17 of them of abdomen and pelvis and 65 of them of the pelvis only.
Both, regular scans at 1h p.i. and late scans at 3h p.i. were analyzed with regard to tumor detection. Amongst all lesions visually considered characteristic for PCa, we selected 149 representative lesions for radiotracer uptake analysis measured as maximum standardized uptake value (SUVmax). Tumor contrast was measured by subtracting the SUVmean of the background from the SUVmax of tumor lesions. As background, we selected gluteal musculature. Any visible PCa lesion of a patient was counted and analyzed unless they had more than 10 lesions (5 patients). In such a case a maximum of 10 lesions were analyzed after a random selection. This kind of selection avoids an overestimation of SUV values in the patients' cohort as otherwise dominant lesions would be preferentially selected.

Radiotracer

^{68}Ga-PSMA-11 was produced as previously described *(5,12)*. Briefly: $^{68}Ga^{3+}$ was obtained from a ^{68}Ge/^{68}Ga radionuclide generator and used for radiolabelling of PSMA-11. The ^{68}Ga-PSMA-11 solution was applied to the patients via an intravenous bolus injection (mean of 207 ± 78 MBq, range 40-345 MBq). The targeted dose was 2MBq per kilogram. Variation of injected radiotracer activity was caused by the short physical half-life of ^{68}Ga (68 min), variable elution efficiencies resulting during the lifetime of the ^{68}Ge/^{68}Ga generator and unexpected delays in clinical routine. A previous study demonstrated that PCa lesions can present with high contrast at 3h p.i. despite such low amounts of tracer *(3)*. Low amounts of injected tracer cause a high background "noise" in late images. However, the favorable pharmacokinetics of ^{68}Ga-PSMA-11 (increase of uptake over time in a majority of lesions) compensates for this disadvantage.

Imaging

The patients of this evaluation were investigated with two different scanners. A Biograph-6 PET/CT scanner was used until August 2015 and was replaced by a Biograph mCT Flow scanner (both scanners made by Siemens, Erlangen, Germany). The two different PET/CT-scanners were cross-calibrated.

With regard to the Biograph-6 PET/CT, the scan protocol (1h p.i.: whole-body and 3h p.i.: whole body or part-body) was as described previously *(5)*. For each bed position a 4 min acquisition time was used for both scans (1h and 3h p.i.). With regard to the Biograph mCT Flow scanner, a non-contrast-enhanced CT scan was performed (1h p.i.: whole-body and 3h p.i.: whole body or part-body) using the following parameters: slice thickness of 5 mm, increment of 3-4 mm, soft tissue reconstruction kernel, Care Dose. Immediately after CT scanning, a PET scan was acquired in 3-D (matrix 200x200) in Flow Motion with 0,7cm/min (for both scans at 1h and 3h p.i.). The emission data were corrected for randoms, scatter and decay. Reconstruction was conducted with an ordered subset expectation maximization algorithm with 2 iterations/21 subsets and Gauss-filtered to a transaxial resolution of 5 mm at full-width at half-maximum. Attenuation correction was performed using the low-dose non-enhanced CT data. PET and CT were performed using the same protocol for every patient on a Biograph mCT Flow scanner (Siemens, Erlangen, Germany).

Between early and late scans, all patients were asked to drink 1 liter of water. Twenty patients received additionally 20mg of furosemide prior to late scans. None of the patients received furosemide prior to early scans. Diuretics were given per physician's choice. As a retrospective

analysis, we cannot reconstruct the particular situations in which the decision was made to apply furosemide.

Image evaluation

Two experienced physicians of Nuclear Medicine with eleven and six years of clinical experience (first and second author) read all data sets independently and resolved any disagreements by consensus.

Lesions that were visually considered as suggestive for PCa were counted and analyzed with respect to their localization (local relapses, lymph node, bone and soft tissue metastases) and to their SUVmax. For calculation of the SUV, circular regions of interest were drawn around areas with focally increased uptake in transaxial slices and automatically adapted to a three-dimensional volume of interest at a 70% isocontour as previously described *(5)*.

SUVmax in scans at 3h p.i. were compared to those at 1h p.i. and defined as increasing, decreasing or stable with intensity changes of >10%, < -10% or between -10% and +10% respectively.

Furthermore, the SUVmean and SUVmax of the urinary bladders 1h and 3h p.i. were measured as well as the average radioactivity concentration in Becquerel per milliliter (Bq/ml) within the urinary bladder. In addition, the area around the urinary bladder was visually analyzed for the presence (=1) or absence (=0) of the “Halo artifact”, an artifact caused by extinction of the PET signal as described previously for a hybrid PET/MRI scanner *(13)*.

Statistical analysis

SUV values of the tumor lesions at 1 and 3 hours p.i. were compared using a Two-Sided Wilcoxon-Signed-Rank test. The same test was also used to evaluate differences concerning the radioactivity signal within the urinary bladder between the groups with and without furosemide. In addition, mathematical differences between 1h p.i. and 3h p.i. were calculated within each group. Thereafter, the results from these calculations were compared between the two groups. In this case, a Two-Sided Mann-Whitney-Test was used. A p value of <0.05 was considered statistically significant.

RESULTS

Overall, 134 lesions characteristic for PCa in 57 patients clearly presented at 1h p.i. and 147 lesions in 68 patients at 3h p.i.. Forty-three patients showed no pathological findings in both scans. As presented by Fig. 1 and 2, eight of the 112 patients (7.1%) showed one unclear finding in early scans which could be clarified as characteristic for PCa at 3h p.i.. Four patients (3.6%) with a non-pathologic scan at 1h p.i. presented with one lesion characteristic for PCa at 3h p.i.. Twelve patients (10.7%) presented with 12 possible PCa lesions at 1h p.i., which, however, could not be confirmed as PCa in late scans (Fig. 3); amongst them were 7 patients who presented exclusively with one of the mentioned lesions. Two patients presented with one lesion characteristic for PCa at 1h p.i. which became invisible at 3h p.i. due to a decrease of uptake and contrast (Fig. 4). No unclear lesions were found when analyzing all scans conducted at 3h p.i..

Amongst all 149 lesions visually considered typical for PCa, 63 were defined as lymph node (LN) metastases, 43 as bone metastases, 16 as primary PCa, 14 as local relapses and 13 as soft tissue/organ metastases. Overall, 62.4% of the PCa lesions (n=93) demonstrated higher (>+10%) SUVmax values at 3h p.i. (Fig. 2), 13.4% (n=20) lower (<-10%) and 24.2% (n=36) stable (between -10% and +10%, respectively) SUVmax values compared to 1h p.i.. The higher SUVmax at 3h p.i was statistically significant (p<0.001).
In addition, 65.1% of the PCa lesions (n=97) demonstrated higher (>+10%) contrast at 3h p.i., 14.1% n=21) lower (<-10%) and 20.8% (n=31) stable (between -10% and +10%, respectively) contrast compared to 1h p.i.. The higher contrast at 3h p.i was also statistically significant (p<0.001).

In 8 of all 69 patients with pathological PET/CT (11.6%), lesions with decreasing uptake between 1h and 3h p.i. were simultaneously present with lesions demonstrating an increasing uptake. In 6 patients (8.7%), lesions with decreasing uptake were present exclusively.

Supplementary Figure 1 is representative for the advantages of a lower radioactivity signal within the urinary bladder. The average radioactivity within the urinary bladder at 1h and 3h) are presented in table 2. In addition, mathematical differences between 1h p.i. and 3h p.i. were calculated within each group (with and without furosemide). Thereafter, the results from these calculations were compared between the group with hydration only and that with hydration

+ furosemide. The results were as follows: p=0.014 for SUVmean, p=0.031 for SUVmax and p=0.092 for Bql/ml.

In none of the 112 patients a “Halo artifact” was observed around the urinary bladder, neither at 1h nor at 3h p.i..

DISCUSSION

In the first ^{68}Ga-PSMA-11-PET/CT study the uptake of PCa lesions was analyzed at 1h and 3h p.i. in 37 patients revealing that in the majority of PCa metastases the uptake and contrast were more intense at 3h p. i. *(3)*. However, as all tumor lesions presented with good contrast already at 1h p.i., ^{68}Ga-PSMA-11-PET/CT is routinely performed at 1h p.i.. In small patient cohorts, PSMA-11 and different other PSMA-ligands demonstrated to be taken up in PCa lesions increasingly over time *(14–16)*. The current analysis in a larger patient cohort confirmed this observation.

In contrast to other published studies, the current manuscript specifically focuses on additional late scans which were not planned prior to the first (“regular”) scans. This manuscript therefore addresses the issue of what can be expected from late imaging in case of unclear findings or negative scans conducted at 1h p.i.. As far as the authors know, such data have never been published before.

The here presented results demonstrate that ^{68}Ga-PSMA-11 at 3h p.i. is a powerful method to confirm findings of “regular scans” at 1h p.i., to find new PCa lesions or to clarify unclear findings. With regard to detection rates and lesion visibility, ^{68}Ga-PSMA-11-PET/CT at 3h p.i. showed to be superior compared to scans at 1h p.i.. These results confirm the findings of a previous study in which 3h p.i. appeared to be the best imaging timing for ^{68}Ga-PSMA-11-PET/CT *(10)*. In addition, no unclear findings were detected at 3h p.i.. This result, however, needs to be interpreted with caution as the scanned area at 3h p.i. was smaller in the majority of patients compared to the scan area at 1h p.i.

Diuretics were given per physician's choice prior to the late scans. Due to these possibly biased decisions regarding the administration of diuretics, a statistical lesion-based analysis under consideration of diuretics is not appropriate. However, our results demonstrate that the reduction of SUV values and radioactivity within the urinary bladder between 1h and 3h p.i. was

more intense in patients who received diuretics. This fact is known from other imaging modalities such as PET imaging with FDG or DOTA-conjugates. One can assume that the lower the PET signal of the urinary tract, the higher the visibility of adjacent PCa lesions. In this context, hydration and diuretics can help to optimize the visibility of PCa lesions in those regions. The routine administration of diuretics is controversial due to their side effects, though. Recently, a manuscript was published showing the positive effects of diuretics on the assessment of prostate region when using the PSMA-ligand ^{68}Ga-PSMA I&T for PET/CT *(17)*.

Our results demonstrate that in more than 12% of the patients referred to ^{68}Ga-PSMA-11 PET/CT, an additional late scan was conducted by the responsible physicians in order to clarify unclear findings of regular scans at 1h p.i.. These additional scans were not planned prior to the arrival of the patients at our PET center. As a consequence, such scans disturb the clinical routine, consume time and further resources. This is an important aspect for a modern health care system which continuously pushes the boundaries of efficacy. In addition, reimbursement issues for additional scans raise questions. At least, the patients need to be informed about the additional costs in an appropriate time prior to the additional scans. Therefore, the question remains if a procedure exists which provides the best possible information available by ^{68}Ga-PSMA-11-PET/CT at a single time. According to our experiences and the presented results, a ^{68}Ga-PSMA-11-PET/CT at 3h p.i. following a sufficient hydration with at least 1 liter of water and the administration of diuretics appears to be the best option to increase the probability of a pathologic PET scan. In this context, hydration and diuretics administration should not be admitted too early as we believe that both would excrete portions of the tracer before it had enough time to interact with the PSMA receptor. We believe that hydration may be started at 2h p.i. followed by diuretics 20-30 minutes later. Still, later images, e.g. at 4h p.i., can show an increase of tumor uptake and therefore help to clarify unclear lesions *(10)*. However, with increasing time intervals between tracer administration and imaging the injected activity and, therefore, the count rate and image quality become more and more important. Quantification analysis can become instable at images conducted at 5h p.i. due to low count rates remaining after 5 half-lifes, especially when tracer amounts of 150-200 MBq are administered *(10)*.

Without doubt, the longer waiting time is a disadvantage of the suggested procedure compared to scans conducted at 1h p.i.. The amount of activity after radiolabelling may also be limiting. However, the higher diagnostic outcome may justify the longer waiting time and further actions to reduce the signal of the urinary bladder and ureters, especially for patients with low PSA levels and, therefore, expected reduced tumor detection rates. In case of a negative single scan at 3h p.i. despite a biochemical relapse of PCa, we recommend waiting until a further PSA

elevation and plan a bi-phasic ^{68}Ga-PSMA-11-PET/CT at 1h and 3h p.i. including hydration and furosemide administration as described before.

In accordance with previous publications *(3,11)*, a minority of PCa lesions showed a decreased uptake in late images. Such lesions often occur simultaneously with lesions demonstrating an increasing uptake with time. In a few number of patients, decreasing lesions occur exclusively. With the exception of two lesions, all PCa lesions which presented with a lower uptake at 3h p.i. compared to 1h p.i. were still clearly visible at 3h p.i..
While the reasons for a decrease of uptake remain unclear, we speculate that some lesions show reduced internalization rate of the PSMA-ligand. Further studies are mandatory to analyze this observation.

In none of the patients, an artifact caused by extinction of the PET signal around the urinary bladder (called “Halo artifact” by the authors) was observed. This artifact was reported when using ^{68}Ga-PSMA-11 in a PET/MRI hybrid system *(13)*. The “Halo artifact” can cause reduced tumor visibility, thereby leading to false negative results *(13)*. The scatter correction of the PET/MRI hybrid system is suggested to cause or influence the mentioned artifact. After the first description of this artifact, some colleagues argued that an extinction artifact around the urinary bladder is also present in PET/CT. However, as described above, we could not observe such an artifact when using the above-mentioned scanners. Further improvements of the manufacturer are mandatory to reduce the “Halo artifact” in PET/CT or PET/MRI scanners.

Our retrospective analysis shows typical limitations compared to prospective studies: probably biased decisions regarding the conduction and area of additional late scans as well as the administration of diuretics. However, our data reflect the daily clinical routine and every center conducting ^{68}Ga-PSMA-PET/CT faces similar conditions. Regarding the area of the late scans, most were conducted from pelvis or abdomen and pelvis. Therefore, additional PCa lesions outside these areas cannot be excluded. On the other hand, it is unlikely that PCa lesions exist outside these areas without the existence of lesions in the pelvis or abdomen, especially in patient cohorts with low PSA values such as the current cohort. We therefore believe that - in case of negative whole-body PET scan - additional late scans can be focused on pelvis and abdomen, especially in patients with low PSA values.
One additional limitation of the here presented analysis is the lack of a standard reference in terms of systematic histopathological investigations of PET-positive lesions. However, since ^{68}Ga-PSMA-11-PET/CT was introduced, the results prove the excellent specificity of this

compound indicating that any uptake of ^{68}Ga-PSMA-11 above local background in CT- or MR-morphological visible lesions of PCa-patients should be regarded as highly suspicious for PCa *(5,6,18,19)*.

CONCLUSION

PET/CT with ^{68}Ga-PSMA-11 at 3h p.i. is a valuable method to clarify unclear findings of “regular scans” conducted at 1h p.i. or to find new PCa lesions as the majority of PCa lesions present with higher uptake and contrast in late scans. With regard to detection rates and lesion visibility, ^{68}Ga-PSMA-11-PET/CT at 3h p.i. was superior compared to scans at 1h p.i. Hydration and diuretics shortly before the scans at 3h p.i. are recommended as they can help to better distinguish between urinary bladder and adjacent PCa lesions.

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FIGURES

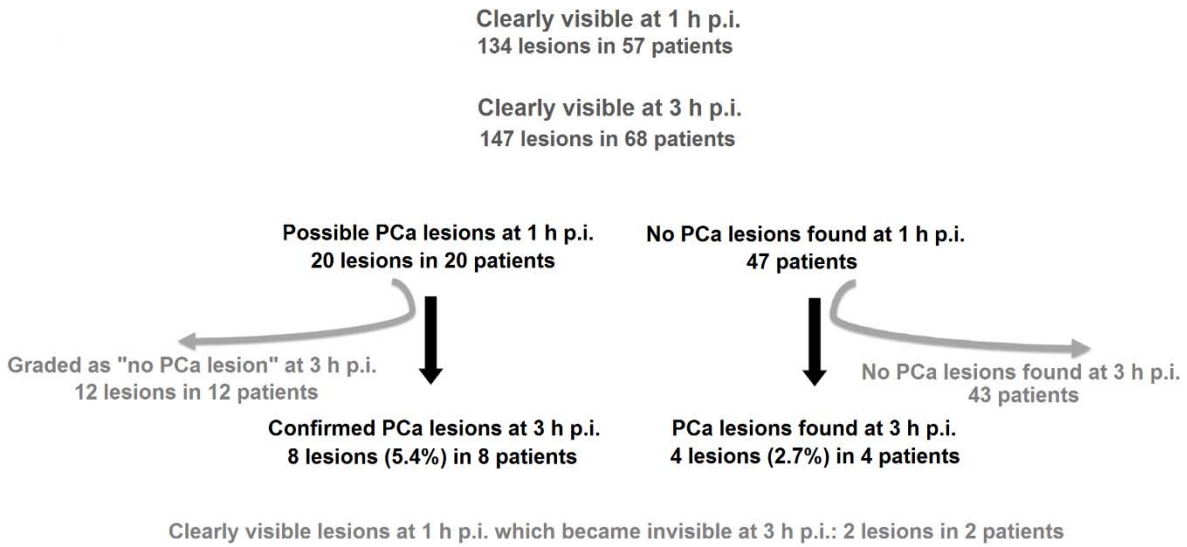


FIGURE 1. ^{68}Ga-PSMA-11-PET/CT at 3h p.i. helped to clarify unclear lesions found at "regular scans" 1h p.i. and detected new PCa lesions. Included in this figure are two lesions characteristic for PCa at 1h p.i. which, however, became invisible at 3h p.i. due to a decrease of uptake and contrast. Lesion-percentages are related to all lesions characteristic for PCa detected in both scans (n=149).

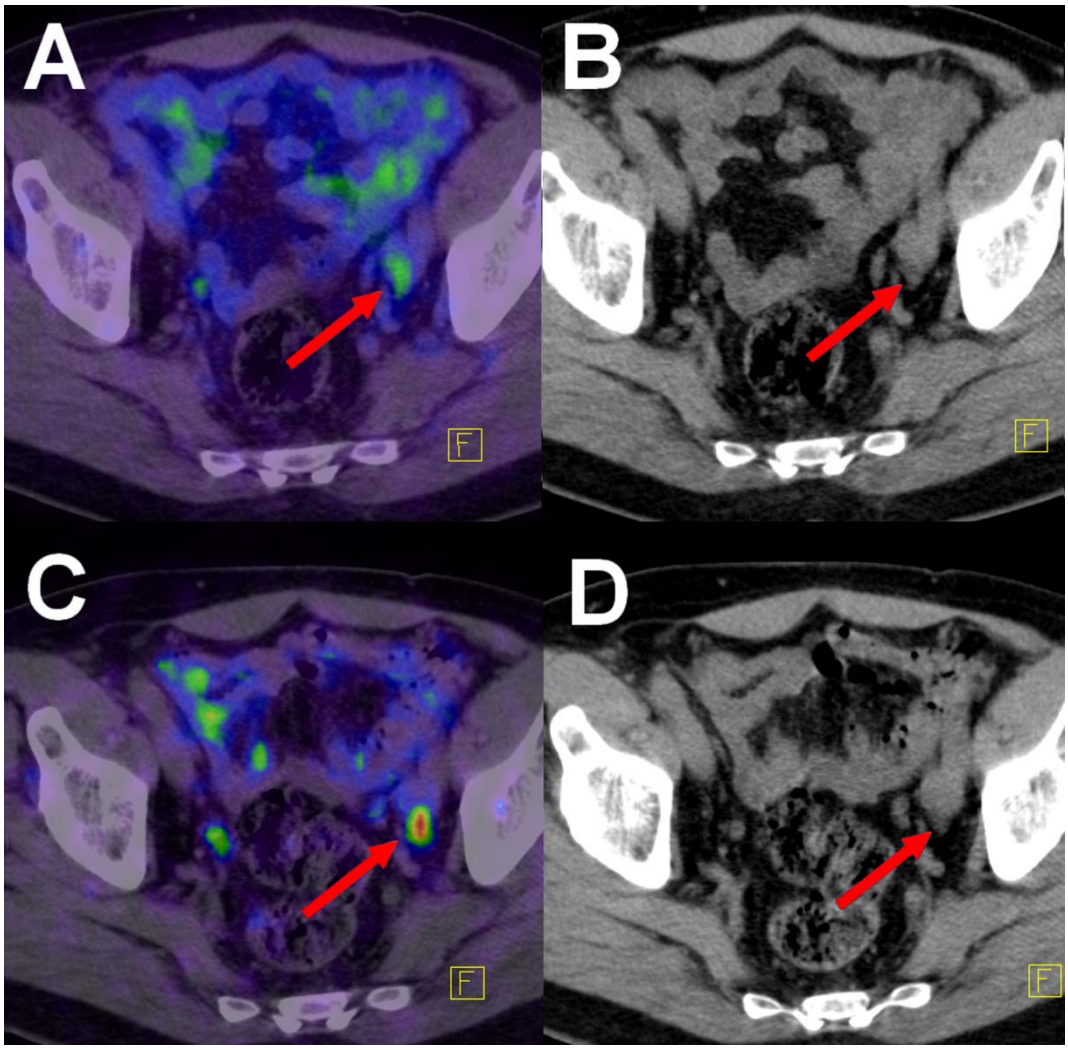


FIGURE 2. The majority of PCa lesions present with higher uptake and contrast at 3h p.i. compared to 1h p.i. Red arrows point to a LN metastasis adjacent to the intestines which was clearly visible at 3h p.i. (C-D) (SUVmax 5.7). At 1h p.i. (A-B) the slight uptake (SUVmax 2.2) was thought to be related to the background signal of the intestines as also visible in the upper parts of the sub-image A. A: fusion of PET and CT at 1h p.i., B: low dose CT at 1h p.i., C: fusion of PET and CT at 3h p.i., D: low dose CT at 3h p.i.

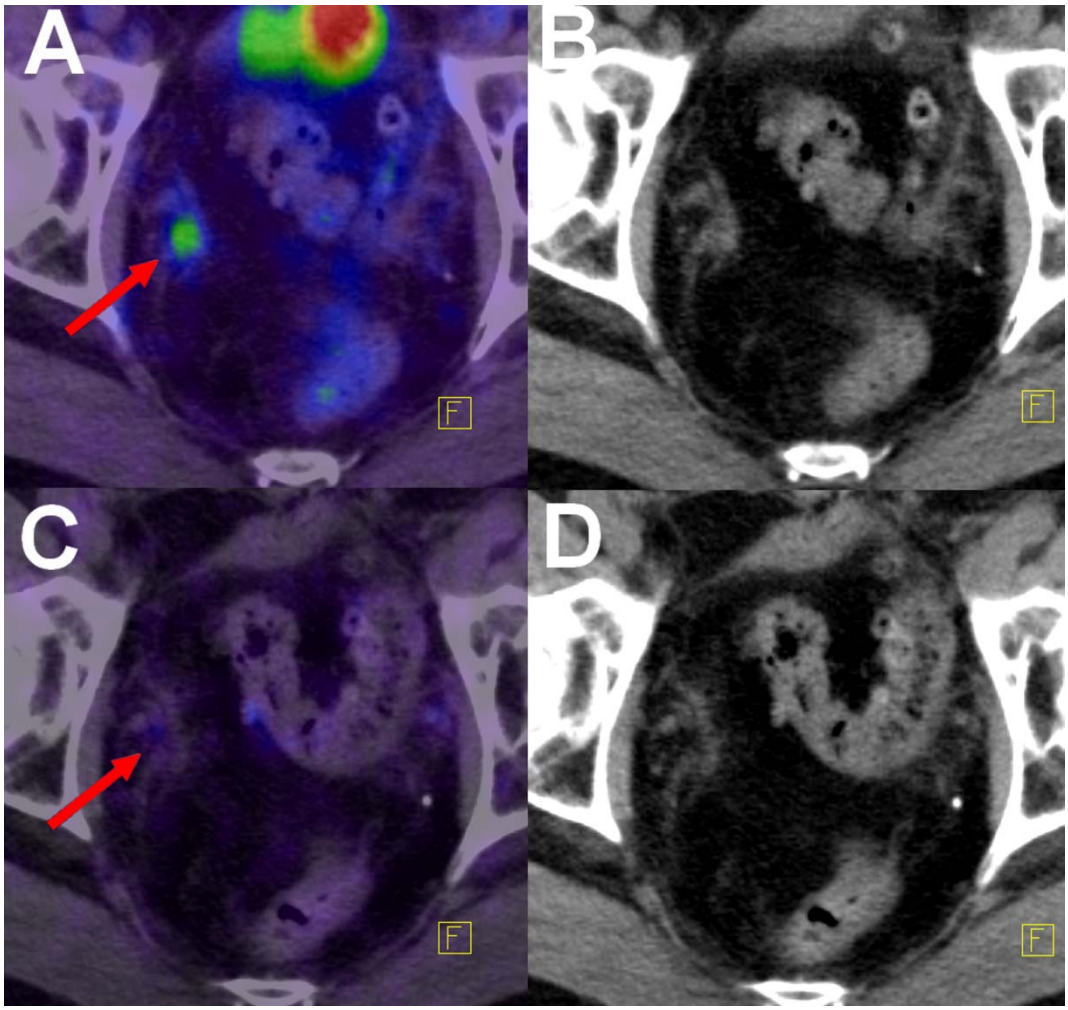


FIGURE 3. ^{68}Ga-PSMA-11-PET/CT of a patient at 1h p.i. (A, B) and at 3h p.i. (C, D). Red arrows point to an unclear finding in scans at 1h p.i. demonstrating a slight focal uptake without a clear morphological correlation in the CT scan. Late scans demonstrated no pathological uptake and still no morphological correlation in the CT scan. The slight uptake was therefore thought to be related to the background signal of the intestines. A: fusion of PET and CT at 1h p.i., B: low dose CT at 1h p.i., C: fusion of PET and CT at 3h p.i., D: low dose CT at 3h p.i..

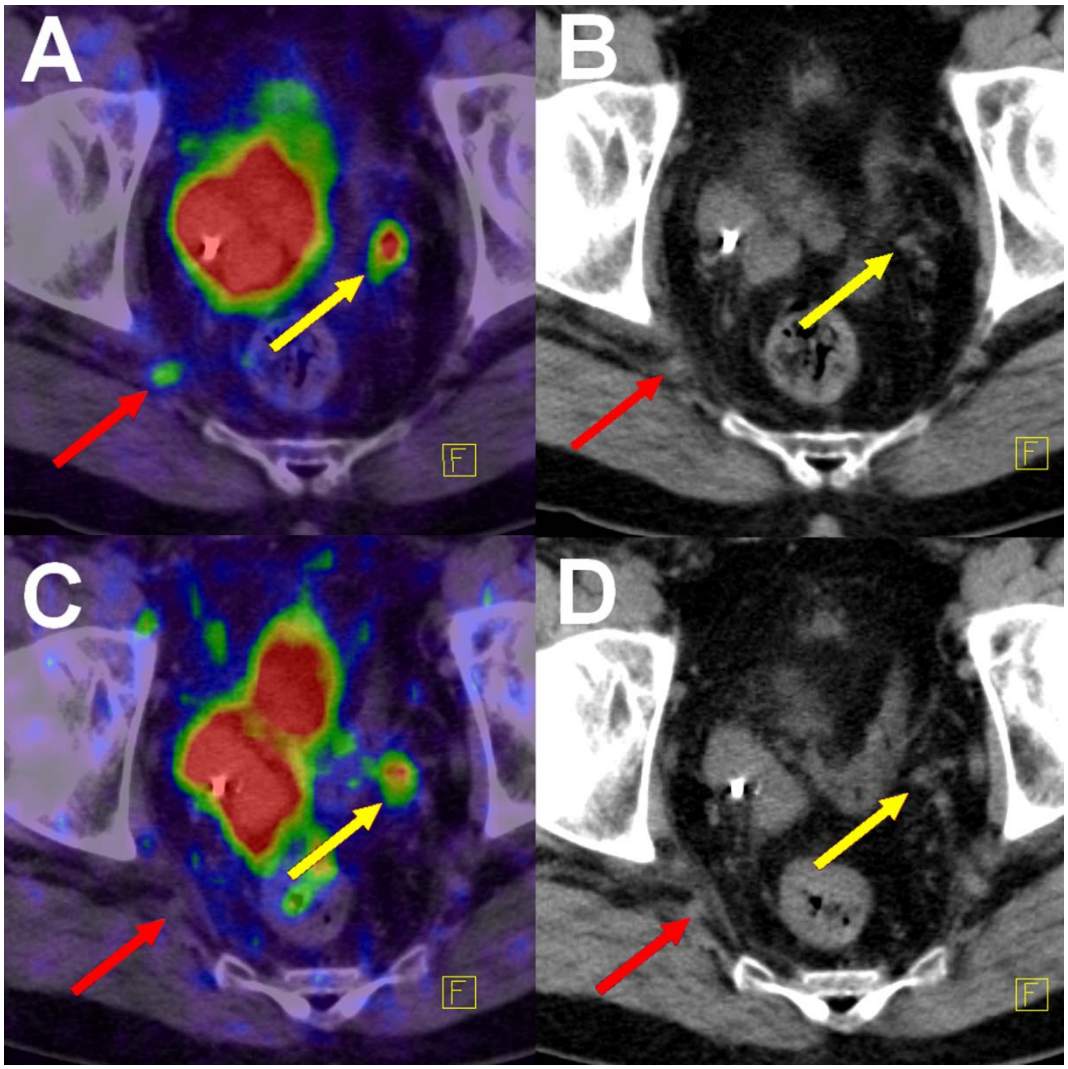


FIGURE 4. ^{68}Ga-PSMA-11-PET/CT of a patient at 1h p.i. (A, B) and at 3h p.i. (C, D). Red arrows point to a lesion (LN) characteristic for PCa in early images which, however, became invisible in late scans. Another LN metastasis (yellow arrows) presented also with decreasing uptake and contrast in late scans (SUVmax: 5.0 at 1h p.i. and 3.5 at 3h p.i., contrast: 4.7 at 1h p.i. and 3.3 at 3h p.i.). A: fusion of PET and CT at 1h p.i., B: low dose CT at 1h p.i., C: fusion of PET and CT at 3h p.i., D: low dose CT at 3h p.i..

TABLE 1. Characteristics of all patients investigated in this study (n=112).

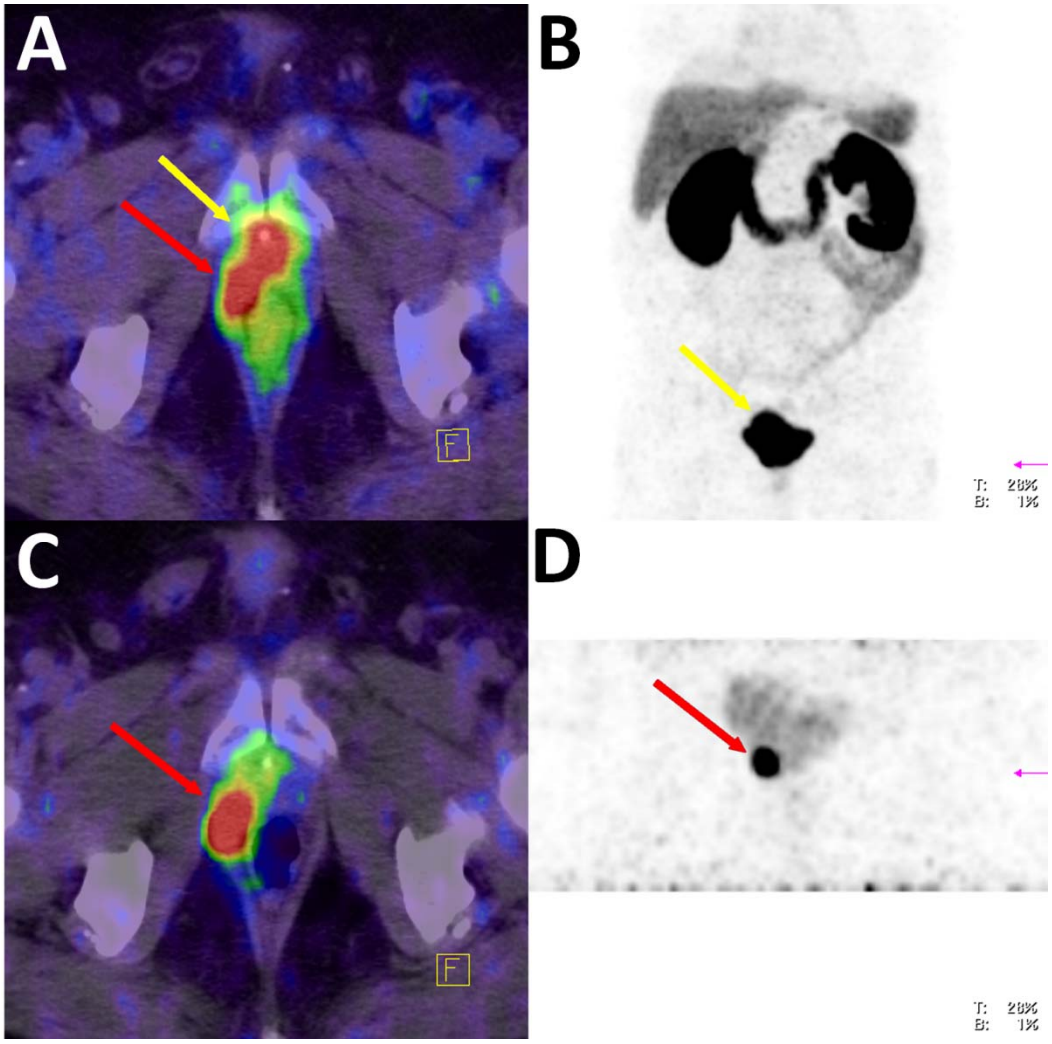
	Age (y)	Tracer (MBq)	GSC	PSA at PET	PET 1 (min. p.i.)	PET 2 (min. p.i.)
Mean	69.8	207	7.5	6.39	65	185
SD	7.8	78	1.1	17.94	8	17
Range	42-87	40-345	5-10	0.01-176.0	52-83	154-213
Median	71	207	7	2.28	61	182

	Prostatectomy	Radiation Therapy	ADT	Primary Tumor without Therapy
	89	50	39	5

TABLE 2. SUV and radioactivity concentration within the urinary bladder at 1h and 3h p.i. and associated p-values.

	With hydration (n=92)		
	Bq/ml	**SUVmean**	**SUVmax**
1h p.i.	37,345 ± 48,237	31.6 ± 31.8	50.9 ± 52.0
3h p.i.	9,875 ± 11,181	27.5 ± 28.3	43.5 ± 43.8
1h vs. 3h p.i.	-73.6% (p<0.001)	-13.1% (p=0.644)	-14.5% (p=0.734)
	With hydration + Furosemide (n=20)		
	Bq/ml	**SUVmean**	**SUVmax**
1h p.i.	50,102 ± 63,771	38.5 ± 40.3	60.2 ± 64.6
3h p.i.	5,006 ± 4,862	13.0 ± 13.2	22.1 ± 20.6
1h vs. 3h p.i.	-90% (p<0.001)	-66.1% (p=0.008)	-63.3% (p=0.017)

SUPPLEMENTARY MATERIALS



Supplementary Figure 1. ^{68}Ga-PSMA-11-PET/CT of a patient at 1h p.i. (A, B) and at 3h p.i. (C, D). Red arrows point to a local recurrence which could be clearly distinguished from the urinary bladder (yellow arrows) at 3h only (hydration + 20mg furosemide). A: fusion of PET and CT at 1h p.i., B: MIP of the PET/CT at 1h p.i., C: fusion of PET and CT at 3h p.i., D: MIP of the PET/CT at 3h p.i..