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ORIGINAL ARTICLE

^{68}Ga-PSMA-11 PET/CT in patients with recurrent prostate cancer—a modified protocol compared with the common protocol

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Abstract

Purpose ^{68}Ga-PSMA-11 PET/CT is commonly performed at 1 h post injection (p.i.). However, various publications have demonstrated that most prostate cancer (PC) lesions exhibit higher contrast at later imaging. The aim of this study was to compare the "common" protocol of ^{68}Ga-PSMA-11 PET/CT with a modified protocol.

Methods In 2017, we used the following scanning protocol for ^{68}Ga-PSMA-11 PET/CT in patients with recurrent PC: acquisition at 1 h p.i. without further preparations. From 2018, all scans were conducted at 1.5 h p.i. In addition, patients were orally hydrated with 1 L of water 0.5 h p.i. and were injected with 20 mg of furosemide 1 h p.i. Both protocols including 112 patients (2017) and 156 (modified protocol in 2018) were retrospectively compared. Rates of pathologic scans, maximum standardized uptake values (SUVmax), and tumor contrast (ratio lesion-SUVmax/background-SUVmean) as well as average standardized uptake values (SUVmean) of urinary bladder were analyzed.

Results Both tumor contrast and tracer uptake were significantly ($p < 0.001$) higher in the novel protocol. Although statistically not significant, the rates of pathologic scans were also higher in the modified protocol: 76.3% vs. 68.8% for all PSA values including 38.9% vs. 25.0% for PSA < 0.5 ng/ml and 60.0% vs. 56.7% for PSA > 0.5–≤ 2.0 ng/ml. Average SUVmean of the urinary bladder was significantly ($p < 0.001$) lower with the modified protocol.

Conclusions The modified protocol, which includes a combination of delayed image acquisition at 1.5 h p.i., hydration, and furosemide resulted in higher tumor contrast and seems to have the potential to increase the rates of pathological scans, especially at low PSA levels.

Keywords Prostate cancer · PET/CT · PSMA · Prostate-specific membrane antigen · ^{68}Ga-PSMA-11 · Furosemide · Hydration · Protocol

Introduction

Prostate cancer (PC) is the most frequently occurring cancer in men, for whom it is the second leading cause of cancer-related death. It accounts for approximately 1/5 of all male cancer cases. Accurate staging, particularly at early stages of biochemical recurrence of PC represent a significant challenge, and in particular for conventional imaging modalities, which

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often have limited sensitivity and specificity [1–3]. Furthermore, accurate staging is essential for stratification of patients into various treatment modalities.

It is in this context that prostate-specific membrane antigen (PSMA)-ligand PET/CT, especially with ^{68}Ga-PSMA-11, has gained significant attention. Following its first clinical use in 2011 [4], it has rapidly become the investigation of choice in recurrent PC. PSMA-ligand PET/CT was found to be superior compared with conventional imaging methods for the detection of PC recurrence [1–6]. PSMA, a transmembrane enzyme, is highly overexpressed in most adenocarcinomas of the prostate [7]. Besides PC lesions, PSMA is expressed in various benign tissues and in the neovasculature of multiple malignant tumors [7, 8]. In preclinical studies, it was shown that higher Gleason Scores (GSC) correlate with higher expression levels of PSMA [7, 9, 10].

According to its first described clinical setup [4], PET/CT with ^{68}Ga-PSMA-11 is conventionally conducted at 1 h post injection (p.i.) [11]. However, several publications have shown that despite the short half-life of ^{68}Ga, the signal to background ratio in PC lesions increases in later scans due to increasing tracer uptake in the majority of PC lesions coupled with ongoing decrease of the background signal [4, 12, 13].

In order to improve the detection of local tumor recurrence adjacent to the urinary bladder, guidelines emphasize the use of diuretics such as furosemide, which reduces the activity concentration in the urinary bladder [11].

With these information in mind, we modified our imaging protocol by including the routine application of diuretics, oral hydration, and a later acquisition time. In this study, we compare the results of this modified protocol with that of the usually used protocol.

Materials and methods

Patients and inclusion criteria

Three hundred twenty-three patients with PC were scanned with [^{68}Ga]Ga-PSMA-11 PET/CT at our department between February 2017 and October 2018 for biochemically recurrent PC. Since it is known that long-term androgen deprivation therapy (ADT) can result in unpredictable scanning results, and therefore influencing the detection of lesions on PSMA-PET/CT scans [14], we excluded those patients who were treated by ADT within the last 6 months before the PET/CT (n = 55). The rest of the patients (n = 268; 112 for 2017 and 156 for 2018) were included in the presented retrospective analysis. For all patients who were scanned twice (n = 14), only the first scan was included in the study. Characteristics of all patients are summarized in Table 1.

Radiotracer

^{68}Ga-PSMA-11 was produced as previously described [6, 15]. Briefly, $^{68}Ga^{3+}$ was obtained from a ^{68}Ge/^{68}Ga radionuclide generator and used for radiolabeling of PSMA-11. The ^{68}Ga-PSMA-11 solution was applied to the patients via an intravenous bolus injection (mean of 197.6 ± 19.1 MBq, range 104–235 MBq). The targeted dose was 3 MBq per kilogram.

Imaging

The patients of this evaluation were investigated with two Biograph mCT PET/CT scanners (Siemens, Erlangen, Germany) which were cross-calibrated.

The “common” (2017) protocol is shown in Fig. 1a. In brief, 1 h post iv administration of ^{68}Ga-PSMA-11, a non-contrast-enhanced CT scan from pelvis to vertex was performed using the following parameters: slice thickness of 5 mm; increment of 3.0 mm; soft tissue reconstruction kernel; maximum of 120 keV and 90 mAs by applying CARE kV and CARE Dose. Immediately after CT scanning, a whole body PET (pelvis to vertex) was acquired in 3D (matrix 200 × 200) with a zoom factor of 1. For each bed position (16.2 cm, overlapping scale 4.2 cm), a 2 min acquisition time with a 15.5 cm field of view (FOV) was used. The emission data were corrected for randoms, scatter, and decay. Reconstruction was conducted with an ordered subset expectation maximization algorithm (OSEM) with 4 iterations/21 subsets and Gaussian-filtered to a transaxial resolution of 5 mm at FWHM (full width at half maximum). Attenuation correction was performed using the low dose non-enhanced computed tomography data. Image analysis was performed using an appropriate workstation and software (SyngoVia; Siemens, Erlangen, Germany).

The modified (2018) protocol is shown in Fig. 1b. In this case, 30 min post iv administration of ^{68}Ga-PSMA-11, the patients were asked to drink 1 L of water. A dose of 20 mg of iv furosemide was administered 1 h after the tracer. PET/CT scans were acquired 1.5 h after tracer administration with the same technique as described for the “common” protocol. None of the patients was furosemide contraindicated.

Image analysis

Two board-certified specialists in Nuclear medicine with 5 and 14 years of clinical experience (first and last author) read all data sets together and resolved any disagreements by consensus. Lesions that were visually considered as suggestive for PC were counted and analyzed with respect to their localization (local relapses, lymph node, and bone and soft tissue metastases) as well as to their maximum standardized uptake values (SUVmax). SUVmax was measured by drawing circular regions of interest around areas with focally increased uptake in transaxial slices

Table 1 Patients characteristics

Parameter	2017	2018
Age (years) (mean/standard deviation/range/median)	70/7/46–86/71	70/7/50–87/71
GSC (mean/standard deviation/range/median)	7/1/5–10/7	8/1/5–9/7
PSA (ng/ml) (mean standard deviation/range/median)	5.6/10.5/0.1–92.0/25	1402/54.0/0.1–478.0/28
Initial therapy	73 × RP	88 × RP
	27 × RP + adj. Rx	39 × RP + adj. Rx
	11 × Rx	29 × Rx
Injected activity (mean/standard deviation/range/median)	196.1/20.6/120–235/201	196.3/19.9/104–222/200

Rx radiation therapy of the prostate or prostate fossa, *GSC* Gleason score, *RP* radical prostatectomy, *adj.* adjuvant

and automatically adapted to a three-dimensional volume of interest at a 40% isocontour. Any uptake of ^{68}Ga-PSMA-11 above local background in lesions morphologically visible was considered PC. A maximum of five lesions per patient were randomly selected, counted, and analyzed, thus avoiding overrepresentation of patients with large numbers of metastatic lesions, which could bias our small cohort.

Tumor to background contrast was determined by dividing the SUVmax of tumor lesions by the SUVmean of gluteal musculature (for background).

In addition, the SUVmean of the urinary bladder was measured with a volume of interest (40% isocontour) which included approximately the bladder boundaries visible in the CT scan. For local tumors of the prostatic fossa, a contrast between tumor SUVmax and bladder SUVmean was additionally calculated by dividing the SUVmax of local tumor lesions by the SUVmean of the urinary bladder.

Statistical analysis

A two-tailed Fisher's exact test was used in order to compare the rate of pathologic PSMA-PET/CT in both groups. Significance of differences between PC lesions in the 2017 and 2018 group with regard to SUVmax and lesion type (local recurrence, lymph node, and bone and soft tissue metastases) were compared using a two-tailed Mann-Whitney U test. The same test was also used to evaluate differences concerning the radioactivity signal within the urinary bladder and the tumor contrast between the groups. A p value of < 0.05 was considered statistically significant.

Results

Pathologic PSMA PET/CT scans

Comparing the "common" (2017) with the modified (2018) protocol, the rate of positive (pathologic) PET/CT scans was observed to increase from 68.8% to 76.3% in total (Fig. 2). Sub-analyses for different PSA levels showed the biggest differences between the two protocols mainly at low PSA levels as also presented by Fig. 2. PSA-cohorts were as follows: up to 0.5 ng/ml ($n = 20$ in 2017 and $n = 18$ in 2018), > 0.5–≤ 2.0 ($n = 30$ in 2017 and $n = 45$ in 2018), > 2.0–≤ 4.0 ($n = 19$ in

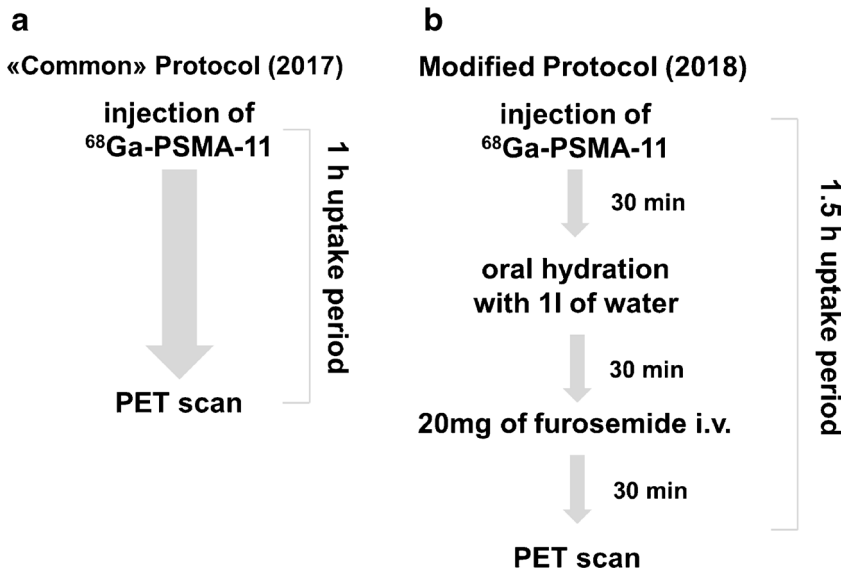

Fig. 1 Visualization of the "common" PET/CT protocol (2017) (**a**) and the modified protocol (2018) (**b**)

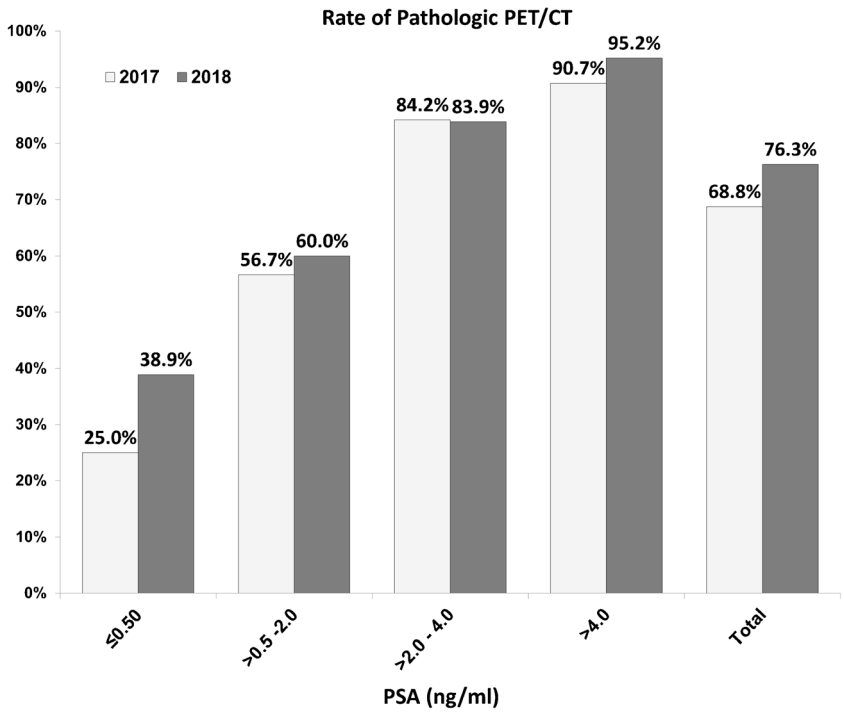

Fig. 2 The rate of pathologic PET/CT scans by the "common" and the modified protocol in the different PSA-cohorts up to 0.5 ng/ml (n = 20 in 2017 and n = 18 in 2018), > 0.5–≤ 2.0 ng/ml (n = 30 in 2017 and n = 45 in 2018), > 2.0–≤ 4.0 ng/ml (n = 19 in 2017 and n = 31 in 2018), and > 4.0 ng/ml (n = 43 in 2017 and n = 62 in 2018). Although the rates of pathologic scans were higher in almost all PSA-subgroups, the differences were statistically not significant, including the group with the lowest PSA.

2017 and n = 31 in 2018), and > 4.0 (n = 43 in 2017 and n = 62 in 2018). Although the rates of pathologic scans were higher in almost all PSA-subgroups as demonstrated by Fig. 2, the differences were statistically not significant according to a two-tailed Fisher's exact test: p = 0.489 for PSA < 0.5 ng/ml; p = 0.814 for PSA 0.51–2.0 ng/ml; p = 1.0 for PSA 2.01–4.0 ng/ml; p = 0.228 for PSA > 4.01 ng/ml; and p = 0.161 for all patients.

PC lesions

In our cohort, 178 lesions indicative for PC from 112 patients with the "common" protocol and 289 lesions indicative for PC from 156 patients with the modified protocol were further analyzed. Lesion characteristics are summarized in Table 2.

The overall tumor SUVmax (16.8 ± 16.0 vs. 13.0 ± 12.15) as well as tumor contrast (to the gluteal musculature; 58.3 ± 61.6 vs. 36.4 ± 35.2) were significantly (p = 0.004 and p < 0.001, respectively) higher in the modified protocol (Fig. 3). Also, the contrast of local recurrent lesions (to the urinary bladder; 3.0 ± 2.9 vs. 0.8 ± 1.2) was significantly (p < 0.001) higher in the modified protocol (Figs. 3 and 4).

Urinary bladder activity

As demonstrated by Fig. 3, bladder activity was significantly lower (p < 0.001) in the modified (2018) protocol in comparison with the "common" (2017) protocol (SUVmean 6.0 ± 3.5 vs. 34.7 ± 25.6). In the modified protocol the contrast of the local recurrent PC lesions increased significantly in

Table 2 Number of lesions classified as pathologic (for PC) in ^{68}Ga-PSMA-11 PET/CT, a maximum of five lesions were analyzed per patient

Lesions	2017			2018		
	Number	SUVmax ± SD	Contrast* ± SD	Number	SUVmax ± SD	Contrast* ± SD
Total	178	13.0 ± 12.2	36.4 ± 35.2	289	16.8 ± 16.0	58.3 ± 61.6
Local relapse	48	15.2 ± 13.5	39.1 ± 31.5	67	17.0 ± 16.1	59.3 ± 62.3
Lymph node metastases	84	13.5 ± 12.7	40.1 ± 41.2	162	17.1 ± 16.1	59.4 ± 62.4
Bone metastases	42	9.6 ± 8.8	26.2 ± 24.3	59	16.8 ± 16.0	58.3 ± 61.8
Soft tissue metastases	4	9.8 ± 8.7	26.8 ± 24.2	1	8.5	28.3
	Number	SUVmax ± SD	Contrast** ± SD	Number	SUVmax ± SD	Contrast** ± SD
Local relapse	48	15.2 ± 13.5	0.8 ± 1.2	67	16.5 ± 16.1	3.0 ± 2.9

*contrast was calculated by dividing the SUVmax of PC lesion by the SUVmean of the gluteal musculature as the general background; ** for local relapses the contrast was additionally calculated by dividing the SUVmax of the local PC lesion by the SUVmean of the urinary bladder

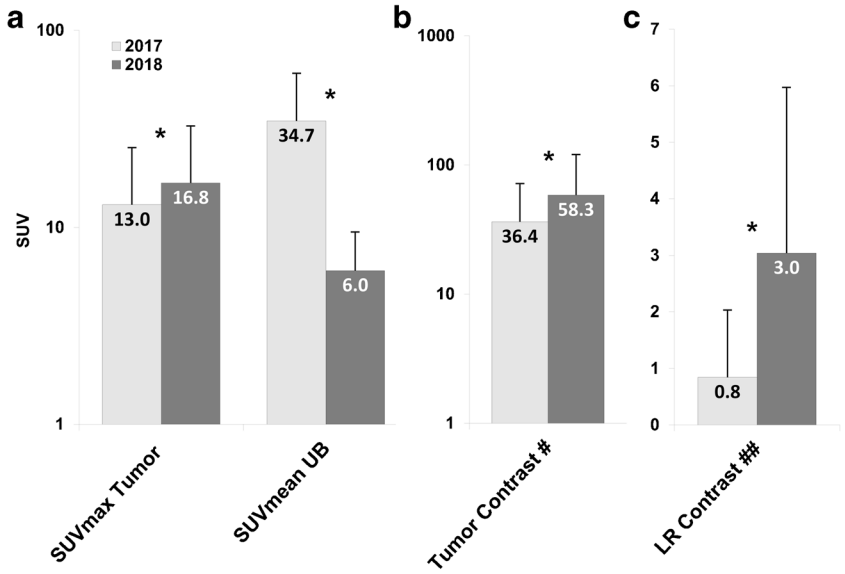

Fig. 3 (A) Tumor SUVmax and SUVmean of the urinary bladder. (B) Tumor contrast. (C) Local recurrent PC contrast calculated as SUVmax of tumor divided by the SUVmean of urinary bladder. Left bars represent the "common" protocol (2017, light gray), right bars the modified protocol (2018, dark gray). Indicators represent standard deviations. LR, local relapses of PC; UB, urinary bladder; BG, background, which was the gluteal musculature. The number sign represents the contrast that was calculated by dividing the SUVmax of PC lesion by the SUVmean of the gluteal musculature as the general background. The two number signs represent local relapses; the contrast was additionally calculated by dividing the SUVmax of the local PC lesion by the SUVmean of the urinary bladder. The asterisk indicates statistically significant differences ($p < 0.05$).

comparison with the "common" protocol (3.0 ± 2.9 vs. 0.8 ± 1.2). Examples of the higher visualization of local relapses after diuretics and hydration are shown in Fig. 4 and 5.

Background activity

Background activity, measured as the SUVmean in the gluteal musculature, was significantly reduced ($p < 0.001$) by the modified protocol (SUVmean 0.38 ± 0.08 vs. 0.30 ± 0.08).

Discussion

According to its first clinical setup, ^{68}Ga-PSMA-11 PET is routinely conducted at 1 h p.i. [4]. However, several publications have shown that late image acquisition has advantages over scans conducted at 1 h p.i. For instance, scans at 3 h p.i. have demonstrated significantly higher tracer uptake and contrast in the majority of PC lesions due to the favorable pharmacokinetics of ^{68}Ga-PSMA-11 [4, 12, 13, 16].

However, to our best knowledge, no center conducts routinely scans later than 1 h p.i. We speculate that the relatively short half-life of ^{68}Ga might be one of the reasons why clinicians show a cautious behavior to conduct scans later than 1 h p.i. despite the abovementioned advantages.

Another strategy to improve the sensitivity of ^{68}Ga-PSMA-11 PET/CT is the administration of diuretics, which can help to reduce the activity concentration in the urinary bladder thereby improving the chance to detect adjacent PC lesions.

With all abovementioned information in mind, we modified our institutional ^{68}Ga-PSMA-11 PET/CT protocol in 2018 by hydrating the patients, applying routinely furosemide, and conducting scans at 90 min p.i. as described in detail in the materials and methods section. In this manuscript, we present the performance of this modified protocol and compare the results with those of the "common" protocol, thereby providing information as to the optimal protocol for ^{68}Ga-PSMA-11 PET/CT. To the best knowledge of the authors, there are no previous studies that address this question.

As demonstrated by Fig. 3, the later acquisition time showed PC lesions with significantly higher tracer uptake. In addition, the general background signal (gluteal musculature) was significantly lower in the modified protocol. The combination of higher tumor uptake and lower background signal resulted in significantly higher tumor contrast in the modified protocol. In addition, hydration and diuretics lead to a significantly lower signal within the urinary bladder thereby strongly improving the ratio between the signal in local recurrences and the signal within the urinary bladder. Interestingly, this ratio was less than 1.0 in the common protocol (namely 0.8), which means that the average signal within the bladder was higher than the average signal of the local relapses. However, as demonstrated by Fig. 3C, the ratio was clearly turned in the favor of local relapses by the novel protocol.

The novel protocol resulted in higher rates of pathologic scans in almost all PSA-subgroups (Fig. 2) with the highest benefit in early stages of recurrent disease. Although the mentioned higher rates were not statistically significant in any of

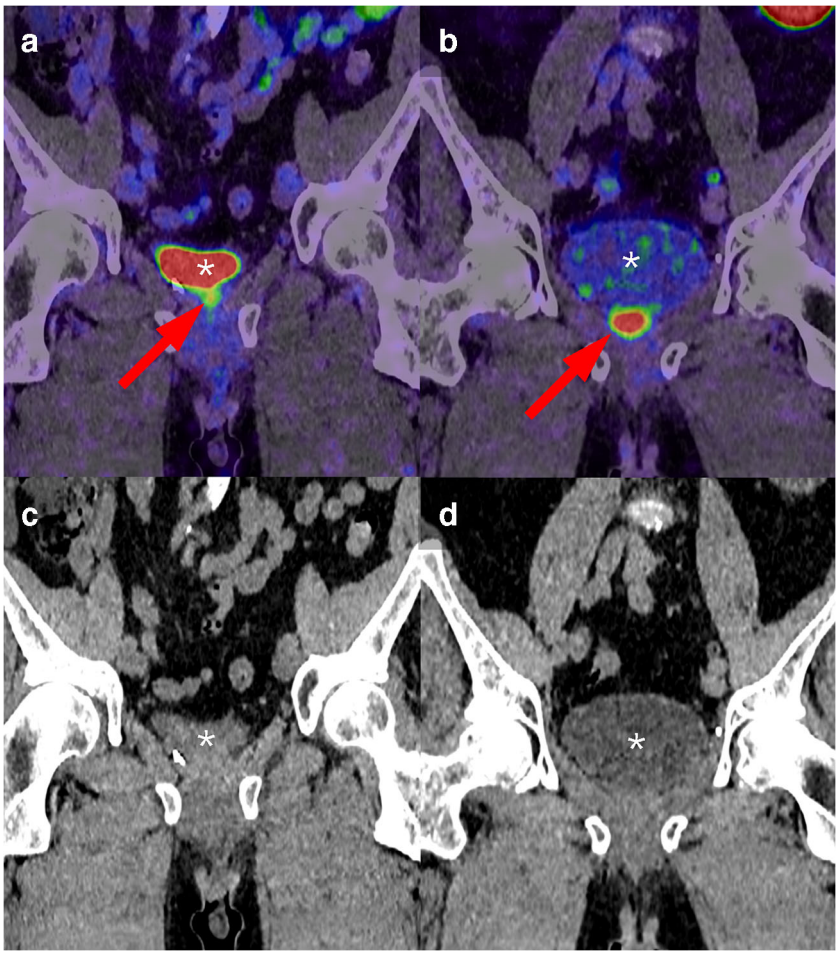

Fig. 4 ^{68}Ga-PSMA-11 PET/CT fused coronal images (A and B) and CT images (C and D) of two different patients, one scanned with the "common" protocol (A and C) and one with the modified protocol (B and D). Red arrows indicate local tumor recurrence in the prostate lodge, adjacent to the urinary bladder (*). (Tumor SUVmax to urinary bladder SUVmean ratio was 0.3 in the patient with the old protocol and was 7.8 in the patient with the modified protocol). The color scale belongs to both scans. The local relapse in A + C was proved by biopsy and treated with external beam radiation therapy. Thereafter, PSA turned from 0.53 ng/ml to 0.011 ng/ml.

the PSA-subgroups, one can assume that a considerable number of patients benefit from the modified protocol. Due to the nature of our matched-pair analysis with no head-to-head comparison, it was not possible to analyze whether the mentioned higher contrast of PC lesions resulted in higher detection rates including that of local relapses. However, we assume that the requirements for a higher detection rate were set by the novel protocol.

Interestingly, our rates of pathologic scans in different PSA-subgroups were lower in the "common" protocol when compared to previous studies [6, 17, 18]. We propose that the reason for this difference is the exclusion of patients undergoing ADT from our study. Previous publications showed that patients with an ongoing ADT more often presented with a pathologic ^{68}Ga-PSMA-11 PET/CT [6, 18]. However, in these publications the authors discussed that this higher rate may not be associated with molecular mechanism such as increase of PSMA-expression but to the fact that ADT is usually commenced in higher tumor stages [14]. In 2018, it was shown on the other hand, that long-term androgen deprivation therapy (ADT) has a significantly negative impact on PC lesion detection and makes the results of the PET quite unpredictable [14]. With the latter publication in mind, we correctly anticipated that the rate of pathologic scans in our current study would be lower by excluding ADT patients. When our results are compared with the study of Caroli et al. [19], who—to our best knowledge—features the largest cohort for recurrent PC patients without the influence of an ADT scanned with ^{68}Ga-PSMA-11 PET/CT at 1 h p.i., the rate of pathologic scans with our modified protocol is higher in the total patients cohort (76% vs. 62.7%) as well as in the group with a PSA value < 0.5 ng/ml (38.9% vs. 29.4%) which is the most challenging subgroup. This indicates that our modified protocol seems advantageous compared to the "common" protocol.

By analyzing the scans, we subjectively did not notice relevant differences regarding the image quality despite the longer decay of ^{68}Ga in the modified protocol. A direct analysis of the image quality was therefore not performed.

There are several shortcomings to this study. Firstly, it is a retrospective analysis whose findings require prospective studies for confirmation, ideally in a study design, which contrasts the two protocols in a direct head-to-head comparison. Although we mitigated this weakness of our study by allocating the patients into different

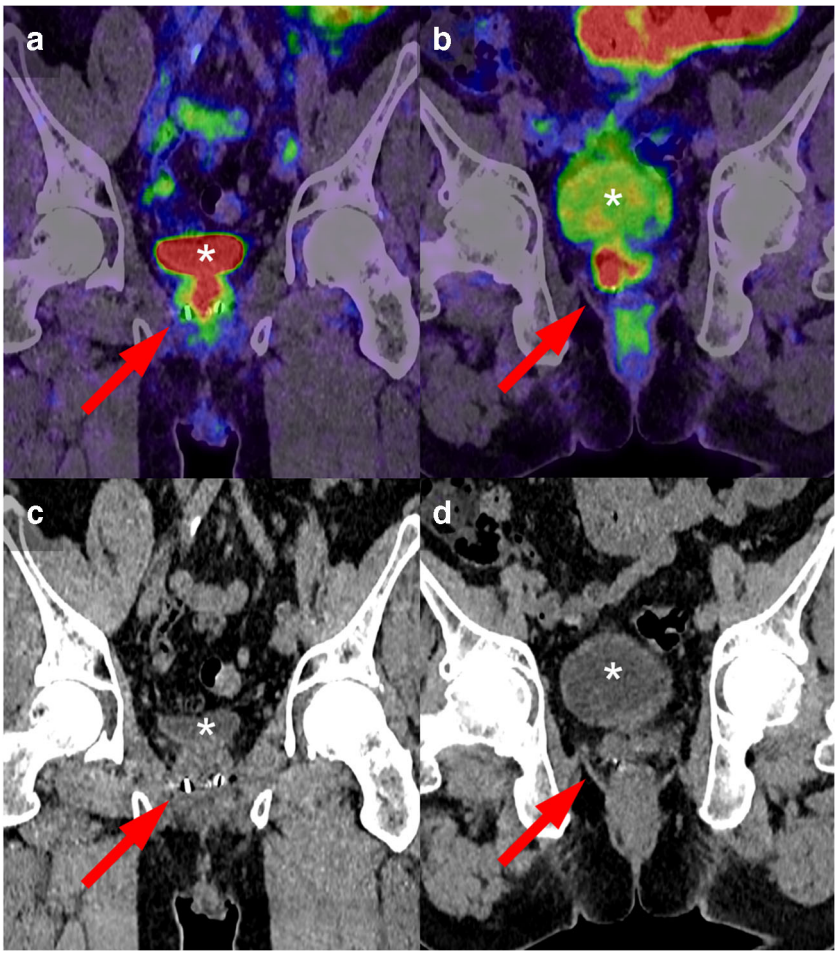

Fig. 5 Another example of ^{68}Ga-PSMA-11 PET/CT fused coronal images (A and B) and CT images (C and D) of two different patients, one scanned with the "common" protocol (A and C) and one with the modified protocol (B and D). Red arrows indicate local tumor recurrence in the prostate lodge, adjacent to the urinary bladder (*). (Tumor SUVmax to urinary bladder SUVmean ratio was 0.1 in the patient with the old protocol and was 5.0 in the patient with the modified protocol). The color scale belongs to both scans.

PSA-subgroups, we concede that a properly designed head-to-head comparison is clearly preferable. However, considering our results, we wonder if a head-to-head comparison, which would expose the vast majority of patients to additional, unnecessary radiation for the clinical benefit of few percent of patients, would be ethical. In addition, sub-analyses including other clinical factors such as initial tumor stage, previous treatments, PSA doubling time, and Gleason Score would be desirable. However, besides the fact that so far only PSA and ADT have shown a positive association with the probability of a pathologic PSMA-PET in studies including bigger cohorts [18, 20], the number of the patients included in our study is too low for such sub-analyses.

Without doubt, the data of our study need to be interpreted with great caution. For instance, the higher rate of pathologic scans can be related to the fact that two different cohorts were compared. Nevertheless, despite all mentioned weaknesses, we argue that given both the nature of our results, coupled with a multitude of evidence in favor of diuretics and later imaging, we posit that the use of our imaging protocol seems to have a greater potential of a higher detectability of PC lesions.

Conclusion

The combination of longer tumor uptake time, oral hydration, and diuresis improved the tumor contrast and seems to have the potential to increase the rate of pathologic ^{68}Ga-PSMA-11 PET/CT in a few percent of patients. This advantage was shown to be most favorable at low PSA values.

Compliance with ethical standards

Ethical approval All patients published in this manuscript signed a written informed consent form for the purpose of anonymized evaluation and publication of their data. This evaluation was approved by the ethics committee of the University of Bern (KEK-Nr. 2018-00299).

Conflicts of interest The authors declare that they have no conflict of interest.

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