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Combination of forced diuresis with additional late imaging in ^{68}Ga-PSMA-11 PET/CT – effects on lesion visibility and radiotracer uptake

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ABSTRACT **(word count: 350/350)**

Purpose: Renal excretion of some prostate specific membrane antigen (PSMA)-ligands and consequently increased bladder activity can obscure locally relapsing prostate cancer (PC) lesions in PSMA-PET/CT. Furthermore, additional late imaging in PSMA-PET/CT provides a useful method to clarify uncertain findings. The aim of this retrospective study was to investigate a modified imaging protocol combining late additional imaging with hydration and forced diuresis in individuals undergoing additional late scanning for uncertain lesions or low PSA.

Methods: We compared two protocols: one group of patients undergoing ^{68}Ga-PSMA-11-PET/CT were examined at 90 min p.i. with 1L oral hydration beginning at 30min p.i. and 20mg of Furosemide i.v. at 1h p.i. followed by additional late imaging at 2.5h p.i. without further preparation ("old" protocol). A second group received the same procedure as before, with an additional 0.5L oral hydration and 10mg of Furosemide i.v. 30min before the late imaging. 132 patients (76 "old" protocol, 56 "new" protocol) were examined with respect to urinary bladder activity (SUVmean), PC-lesion uptake (SUVmax) and lesion contrast (tumor-SUVmax÷bladder-SUVmean for local relapses and tumor-SUVmax÷gluteal-musculature-SUVmean for non-local PC lesions).

Results: Bladder activity was significantly greater for the "old" protocol in the late scans compared to the "new" protocol (ratio of bladder activity (2.5h÷1.5h): 2.33±1.17 vs. 1.37±0.50, $p<0.0001$). Increased tumor SUVmax and contrast was seen at 2.5h compared to 1.5h ($p<0.0001$ "old"; $p=0.02$ "new"). Increased bladder activity for the "old" protocol resulted in decreased lesion-to-bladder contrast, which was not the case for the "new" protocol. Tumor-to-background ratios increased at late imaging for both protocols, but the increase was significantly lower for the "new" protocol. For the "old" protocol, comparing the 1.5h to 2.5h acquisitions, 4 lesions in 4 patients (4/76=5.2% of the cohort) were visible at the post-diuresis 1.5h acquisition, but not visible at 2.5h, having been obscured as a result of the higher bladder activity. In the new protocol, 2/56 (3.6%) of patients had lesions visible only at late imaging and two had lesions which could be better discriminated at late imaging.

Conclusion: Although the combination of diuretics and hydration can be a useful method to increase the visualization and detectability of locally recurrent PC in standard [^{68}Ga]Ga-PSMA-11-PET/CT, their effects do not sufficiently continue into additional late imaging. Additional diuresis and hydration is recommended to improve visibility, detection and diagnostic certainty of local recurrences.

Keywords: Prostate cancer, PET/CT, Positron emission tomography, PSMA, Prostate-specific membrane antigen, local recurrence, detectability, Furosemide, diuresis

INTRODUCTION

^{68}Ga-PSMA-11 PET/CT has become the examination of choice in recurrent prostate cancer with excellent tumor-to-background contrast and high sensitivity (*1*). However, ^{68}Ga-PSMA-11, in common with other PSMA-radioligands such as ^{18}F-DCFPyl, undergoes predominantly renal excretion (*2,3*). Activity in the urinary bladder can obscure locally recurrent lesions which are at risk to be missed (*4*). PET/MRI and PET/CT are vulnerable to halo-artefact with large activity concentrations in the urinary bladder (*5,6*), although this can be minimized by adequate scatter correction. Novel radiotracers which undergo biliary excretion have been introduced, which when labelled with ^{18}F combine the advantages of cyclotron production of the radiotracer and improved availability, longer half-life and reduced bladder activity (*7,8*).

Despite nearly a decade of routine use, the optimal examination protocol for PSMA radiotracers remains elusive with only generic guidance available (*9*). PET/CT with 68Ga-PSMA-11 is commonly performed at 1h post-injection (p.i.). However, a number of publications show an increase in tracer uptake for a majority of PC lesions over time (*2,10-13*). Later acquisition of images, or additional late imaging can improve lesion visibility and aid in the discrimination between non-PC related tracer uptake (*12*).

A number of publications report the utility of forced diuresis as a means of mitigating urinary bladder activity and improves diagnostic certainty for lesions in proximity to the bladder and ureters (*14*). The extant guidelines recommend application of Furosemide either shortly before or after administration of ^{68}Ga-PSMA-11 (*9*), although early co-application of radiotracer and diuretic is associated with degraded image quality at delayed imaging (*15*). Instead, later application is associated with improved lesion detection and reduced bladder activity (*16*). In cases of uncertain findings, later imaging may afford a better discrimination between pathological and non-pathological causes of tracer-uptake; the majority of tumor lesions exhibit increasing PSMA-ligand uptake, whereas ganglia or inflammatory lymph nodes usually do not (*17,18*). Whereas

previous studies examine the optimal imaging time point for ^{68}Ga-PSMA-11 (*19*) with increased lesion detection when combining later imaging (at 90 min p.i. compared to 60min p.i.) with diuresis (*20*), there are no publications which systematically address the issue of dual-time point imaging and forced diuresis. Furthermore, no studies report the influence of diuresis on tumor uptake, which this study aims to address.

MATERIALS AND METHODS

In this retrospective analysis, we investigated 132 individuals who, having been referred to our centre for biochemically recurrent PC between 10/2018 and 10/2019, underwent [^{68}Ga]Ga-PSMA-11-PET/CT including additional late imaging. The cantonal ethics committee approved this retrospective study (KEK-Nr. 2020-00162) and the requirement to obtain informed consent was waived. The study was performed in accordance with the declaration of Helsinki. Since 2018, our institutional protocol was to perform PET/CT with ^{68}Ga-PSMA-11 at 90 min p.i. with 20mg of i.v. Furosemide at 60 min p.i. with 1L of water per os beginning at 30 min p.i. Additional late scans were acquired at 2.5h p.i. in cases of low PSA (<2.0 ng/mL) or in cases where uncertain lesions were identified on the whole-body PET, as previously published (*10*). In the 2018 “old” protocol, this late imaging was performed without any further preparation and is as previously published (*20*). Noting higher bladder activity at late imaging compared to the regular scans, our protocol changed in April 2019 to include additional Furosemide (10mg i.v.) at 2h p.i. with 0.5L water per os prior to late imaging at 2.5h p.i. The two examination protocols are as outlined in fig. 1. We therefore included 76 consecutive patients who were examined under the protocol prior to April 2019 (“old” protocol (*20*)) and compare them with 56 patients consecutive patients who underwent scanning under the “new” protocol (since April 2019 until October 2019 when we switched to the routine use of a ^{18}F-PSMA-tracer). Patient details including details of prior treatments for both cohorts, Gleason Score and prostate specific antigen level (PSA) are as outlined in Table 1.

Radiotracer

^{68}Ga-PSMA-11 was produced as previously described (*21,22*). The radiotracer was given by intravenous bolus injection with a body weight adjusted dose of 2-3 MBq/Kg as standard.

Imaging

All patients received regular whole-body PET scans (from head to the thighs) at 1.5h p.i. Additional late imaging was performed at 2.5h p.i. Hydration and forced diuresis for both groups is as outlined in fig. 1. Patients were requested to void the bladder immediately prior to all imaging. Both scans at 1.5h and 2.5h p.i. were analysed for pathological lesions characteristic for PC in addition to the activity concentration in the urinary bladder. Our PET and CT protocol parameters were as previously published (*23*).

Image Evaluation

Image analysis was performed using an appropriate workstation and software (SyngoVia; Siemens, Erlangen, Germany). Two experienced physicians (first and second authors) read each dataset in a consensus read. Clinical details and demographics were available. Scans were noted for the presence of pathological lesions (including local recurrence, lymph nodes and bone/organ metastases) on the whole-body scan, and cases where these lesions were not visible on either early or late imaging. For calculation of tracer uptake, circular regions of interest were drawn for locally recurring lesions around areas in the prostatic fossa with focally increased uptake in transaxial slices and automatically adapted to a three-dimensional volume of interest (VOI) at a 40% isocontour as previously described (*21*). Care was taken to check the VOI in transverse, coronal and sagittal slices to avoid inclusion of the bladder. Likewise, VOI were drawn around the bladder using the same method, with care to ensure only the anatomical bladder on CT imaging was included. Background uptake was measured as standard using a 1cm^3 VOI in the left gluteal muscle as previously published (*18*).

Statistical Analysis

Bladder (and background gluteal) tracer activity was measured by obtaining the SUVmean (the variable with the lowest coefficient of variation (*2*)). Lesion activity was determined by convention as SUVmax. Uptake for the bladder, gluteal musculature and PC lesions were compared at 1.5h and 2.5h by means of the paired Student's t-test; a two-tailed p-value of <0.05 was considered statistically significant. Comparisons between protocols for changes in bladder activity was calculated by the unpaired Welch's t-test (for unequal sample size). The binomial test was used to determine the statistical significance in detection frequency at standard and late imaging. Statistical analyses were performed using SPSS (IBM Vers. 25) and R (Vers. 4.0.2).

Clinical Follow-Up

Lesions rated as pathological or benign were confirmed by composite reference standard as previously published (*23*) (histology where available, correlative MRI imaging or post-salvage radiotherapy fall in PSA following targeted therapy).

RESULTS

Patient Tolerability

All patients were clerked as institutional standard by a physician prior to the examination to exclude contraindications to forced diuresis by Furosemide (e.g. sulphonamide allergy). Patients tolerated both protocols equally well, and no examples of scanner contamination through urinary incontinence were encountered. We find the application of Furosemide and oral hydration to be a simple maneuver and was easily integrated into clinical routine.

Changes in Bladder Activity

Greater urinary activity was seen in the “old” protocol at 2.5h (7.01±9.03 SUV at 1.5h versus 13.42±9.38 SUV at 2.5h) than in the “new” protocol (11.04±12.5 SUV at 1.5h versus 12.39±13.36 SUV at 2.5h) and is shown in fig. 2. The dimensionless ratio between bladder activity at 2.5h÷1.5h was significantly higher ($p<0.0001$) for the old protocol (2.33±1.17) than for the new protocol (1.37±0.50).

Changes in Lesion Activity and Tumor to Background Ratio

For both the “old” and “new” protocols, a significant increase in SUVmax for all pathological lesions was noted from 1.5h p.i. to 2.5h p.i. (“old” 5.98 vs. 7.78 2.5h; “new” 4.27 vs. 4.98 2.5h, $p<0.0001$ “old”, $p=0.02$ “new”). Similarly, tumor to background ratio (TBR) for all pathological lesions (with respect to the gluteal musculature) was higher at 2.5h compared to 1.5h (“old” 55.80 vs. 91.39; “new” 41.88 vs. 55.96; $p<0.0001$ for both, see fig. 3). Comparing the ratio of the TBR at 2.5h to 1.5h p.i., the mean increase for the “old” protocol was higher than for the “new” protocol (1.72±0.56 vs. 1.49±0.62, $p=0.013$, see fig. 4).

Lesion Detectability

Overall, 71% of patients in the “new” and 70% in the “old” have a positive scan (at least one pathological lesion). Comparing the 1.5h to 2.5h acquisitions, for the “old” protocol, four patients (4/76=5.2% of the patient cohort) had four lesions which were visible at the post-diuresis 1.5h acquisition, but not visible at 2.5h, having been obscured as a result of the higher bladder activity. Example images are shown in fig. 5. Furthermore, for the “old” protocol, the lesion SUVmax at 2.5h in two cases corresponded almost exactly with the urinary bladder activity. As confirmation, follow up to composite standard revealed that two of the patients had subsequent fall in PSA following directed radiotherapy, one had correlative MRI findings and one had PSA fall following systemic therapy.

For the “new” protocol, two patients had additional locally recurrent lesions that could only be visualized at 2.5h, owing to increasing tracer uptake. Correlative imaging (composite standard) was available as confirmation of these two lesions. A further two patients had lesions which were more clearly visualized at late imaging, delivering greater diagnostic certainty (example patient image in supplementary fig. 1).

DISCUSSION

In this study, we compare two examination protocols that seek to combine mitigation for increased bladder activity through forced diuresis and additional late imaging. We find that forced diuresis prior to acquisition of images at 1.5 h p.i. gives good results, with resultant low bladder activities and high lesion TBR. Concordant with numerous studies reporting improved lesion detection and visibility at additional late imaging (*2,10-13*), we also find improved pathological lesion TBR with higher SUVmax for a majority of pathological lesions at additional late imaging. In two patients, additional later imaging combined with repeated diuresis revealed two lesions that were not visible at early imaging. In two patients, two lesions were revealed with greater clarity.

Although Furosemide has a prompt onset of diuresis, its biological half-life is as long as two hours (*24*). However, our data show this residual effect does not sufficiently continue into additional late imaging. In keeping with previous work suggesting that locally recurrent lesions are at risk to be missed with high bladder activity (*25*), we find that in the “old” protocol, 4/76 patients (5.3%) had lesions that were obscured by increased bladder activity at additional late imaging. Comparing locally recurrent tumor uptake to the local bladder activity confirms this, with lower lesion-to-bladder contrast at late imaging for the “old” protocol. In contrast, for the “new” protocol including additional Furosemide at late imaging, no reduction in lesion-to-bladder contrast was observed, with all PC lesions clearly visible at both early and late imaging.

Numerous publications report the utility of forced diuresis to mitigate against accumulation of bladder activity (*26*). Alternatives, such as the application of intravenous mannitol have been less well studied (*27*). The current guidelines for PSMA-imaging endorse application of Furosemide to mitigate against activity in the ureters in ^{68}Ga-PSMA-11 PET/CT (*9*), although application "shortly before or after administration" of the radiopharmaceutical is recommended. Judicious timing of diuresis is essential: Derlin et al. compare two protocols with early (concomitant application with radiotracer) and late (100 min p.i.) diuresis. Whereas the early protocol resulted in reduced image quality and increased bladder activity, this was not the case for late application (*15*). Likewise, Wondergem et al. advocate application of diuretic shortly prior to imaging with ^{18}F-DCFPyL (*6*). Piron et al. publish results for an optimized protocol for ^{18}F-PSMA-11 with Furosemide application 30 min p.i. (*28*). The wide variation in protocols and recommendations serves to highlight that the issue remains far from settled and a myriad of protocols advocate both early and dynamic imaging (*29-32*).

We find no publications reporting the influence of forced diuresis on radiotracer uptake: noting the pharmacodynamics of PSMA-radioligands, which show increasing radiotracer uptake over time, we posit that forced diuresis might reduce the amount of radiotracer available during this uptake phase; this pharmacokinetic consideration would favor later application compared to early diuresis (*10,19*). In keeping with this hypothesis, Derlin et al. found reduced image quality following early application of diuretic, although no data for lesion radiotracer uptake were reported (*15*). Early application of the diuretic could result in rapid elimination of the radiotracer during the uptake phase, resulting in reduced lesion uptake. Indeed, our findings suggest that additional diuresis prior to late imaging results in a lower increase in TBR than was observed in the "old" protocol. Any protocol must therefore find the optimal balance between improved TBR at later imaging versus the short physical half-life of the radiotracer along with accumulation of bladder activity and the ease with which any protocol can be integrated into a busy clinic. Similarly, Furosemide should be given at a time point where its prompt onset of diuresis has maximum

effect; application shortly before or after the radiopharmaceutical is not commensurate with its well-known pharmacodynamics, and is exemplified by our finding that its diuretic effects do not continue into additional late imaging. Application of Furosemide with or shortly after the radiotracer, as recommended by the guidelines (*9*), is therefore unlikely to result in satisfactory reduction in bladder activity if imaging is performed at 1h p.i.

Instead, we find our "new" protocol be a reasonable balance between these myriad competing demands. A larger dose of Furosemide (i.e. 20mg prior to additional late imaging) is unlikely to be of additional benefit and Uprimny et al. found no benefit of 40mg Furosemide compared to 20mg Furosemide at imaging 60min p.i. (*33*).

Our results may also find application in PET/MRI (*34*) Owing to the halo-artefact (*35,36*) optimal reduction in urinary activity is necessary, although the longer examination times encountered in pelvic MRI may necessitate a urinary catheter to be placed if forced diuresis shortly before image acquisition is used. Our findings also place new radiotracers into important context. Recently, PSMA-radioligands undergoing biliary or hepatic excretion have been introduced, such as ^{18}F-PSMA-1007 and ^{18}F-rh-PSMA-7 (*8,37*). These cyclotron-produced radiotracers have improved availability and simplify logistical supply-chains owing to a longer half-life. Other theoretical advantages include a lower positron energy, which may improve imaging resolution (*7,37*). However, the principle clinical advantage of such radiotracers is their low rate of urinary excretion in the first 2 hours p.i., with consequent reduction in bladder activity (*38*). Nevertheless, our data provide insight into the magnitude of any effect size that can be anticipated because of this reportedly favorable pharmacokinetic property. Only a small number of lesions directly contiguous with the bladder or ureter are likely to be obscured and large patient cohorts would be required to demonstrate this small effect size with adequate power. Neither a matched pair comparison nor a head-to-head study found any increased detection rate for these new radiotracers (*39,40*), although lower specificity has been observed for ^{18}F-PSMA-11 (*39*). In contrast, we find that Furosemide offers a low cost, well tolerated and easily performed maneuver

to reduce urinary activity. Ideally, such protocols would be integrated into any studies comparing tracers undergoing renal extraction affording a fair comparison with respect to bladder activity, and consideration must be given to the timing of diuresis when reporting semi-quantitative parameters such as lesion SUV.

We note several weaknesses with our study. Firstly, our data are collected retrospectively, and prospective trials are required to confirm the optimum protocol. In-keeping with previously published studies (*41*), we sought to establish the utility of our protocol and its effects on urinary bladder activity and lesion uptake. Therefore, the two patients cohorts do not need to be similar with regard to clinical data since these data do not influence the urinary excretion of the tracer. Applied activity was given according to the same weight adapted dose regime. Despite slightly greater mean absolute dose of radiopharmaceutical applied in the “new” protocol, lower bladder activities were seen when compared to the “old” protocol (see fig. 2) meaning that applied activity did not act as a confounder. Lesions classified as pathological and where discrepancy between the late and early images were noted were confirmed at follow-up by composite standard. TBR was slightly higher for the “old” protocol compared to the “new” protocol and both early and late imaging, reflecting possible underlying differences in patients in these two non-matched cohorts.

CONCLUSION

Performing ^{68}Ga-PSMA-11 PET/CT at 1.5h p.i. with application of 20mg of Furosemide half an hour prior to imaging yields good results with excellent TBR and low bladder activity. However, the effect of Furosemide does not sufficiently last into additional late imaging, where increased bladder activity due to diminishing Furosemide efficacy can obscure locally recurrent lesions. To overcome this limitation of the additional late scans, additional Furosemide prior to late imaging provides a useful method to increase the contrast of tumor lesions adjacent to the urinary bladder,

allowing for better discrimination of lesions, and in a small number of cases, revealing lesions that were not visible at early imaging. However, additional diuresis for late scans can results in lower increases in tumor radiotracer uptake at late imaging, suggesting that the dose and timing of diuresis can influence the radiotracer's pharmacodynamics.

***Competing interests*:** All authors declare that they have no conflict of interest

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KEY POINTS

QUESTION: Does additional late imaging combined with hydration and diuresis improve local recurrence visibility in ^{68}Ga-PSMA-11 PET/CT?

PERTINENT FINDINGS: Additional late imaging without Furosemide is associated with high bladder activity that obscures locally recurrent lesions. The addition of Furosemide and hydration results in lower bladder activity, allowing better discrimination of lesions. In two cases, lesions were revealed at late imaging which were not visible at early imaging.

IMPLICATIONS FOR PATIENT CARE: Later application of Furosemide 30min prior to imaging is recommended. Additional late imaging should be performed with additional diuresis and hydration.

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TABLES AND FIGURES

Table 1. Patient characteristics (PSA – Prostate Specific Antigen, TNM – Tumor Stage (IUCC, 8th Edition). Previous treatment: OP = radical prostatectomy, RT = radiotherapy, OP+RT = combined prostatectomy and radiotherapy, Chemo = chemotherapy, Unknown = lost to follow up/details unavailable.

Parameter	2018 Protocol (old) n=76	2019 Protocol (new) n=56
Age (years ± SD)	67.9 ±6.7	69.2 ± 6.3
Tracer (MBq ± SD)	216.9 ± 35.7	243.7 ± 39.5
Gleason Score (Median, Range)	7 (6-10)	7 (6-9)
PSA (ng/ml Mean, Median ± SD)	11.5, 1.1 ± 32.7	7.6, 0.5 ± 45.6
TNM (Median, range)	T (3, 1-4) N (0, 0-1) M (0, 0-1)	T (3, 1-4) N (0, 0-1) M (0, 0-1)
Previous Treatment	OP =50; RT = 10; OP+RT = 8; Chemo= 1, Unknown = 7	OP = 49; RT=2; OP+RT=2; Chemo = 1; Unknown = 2

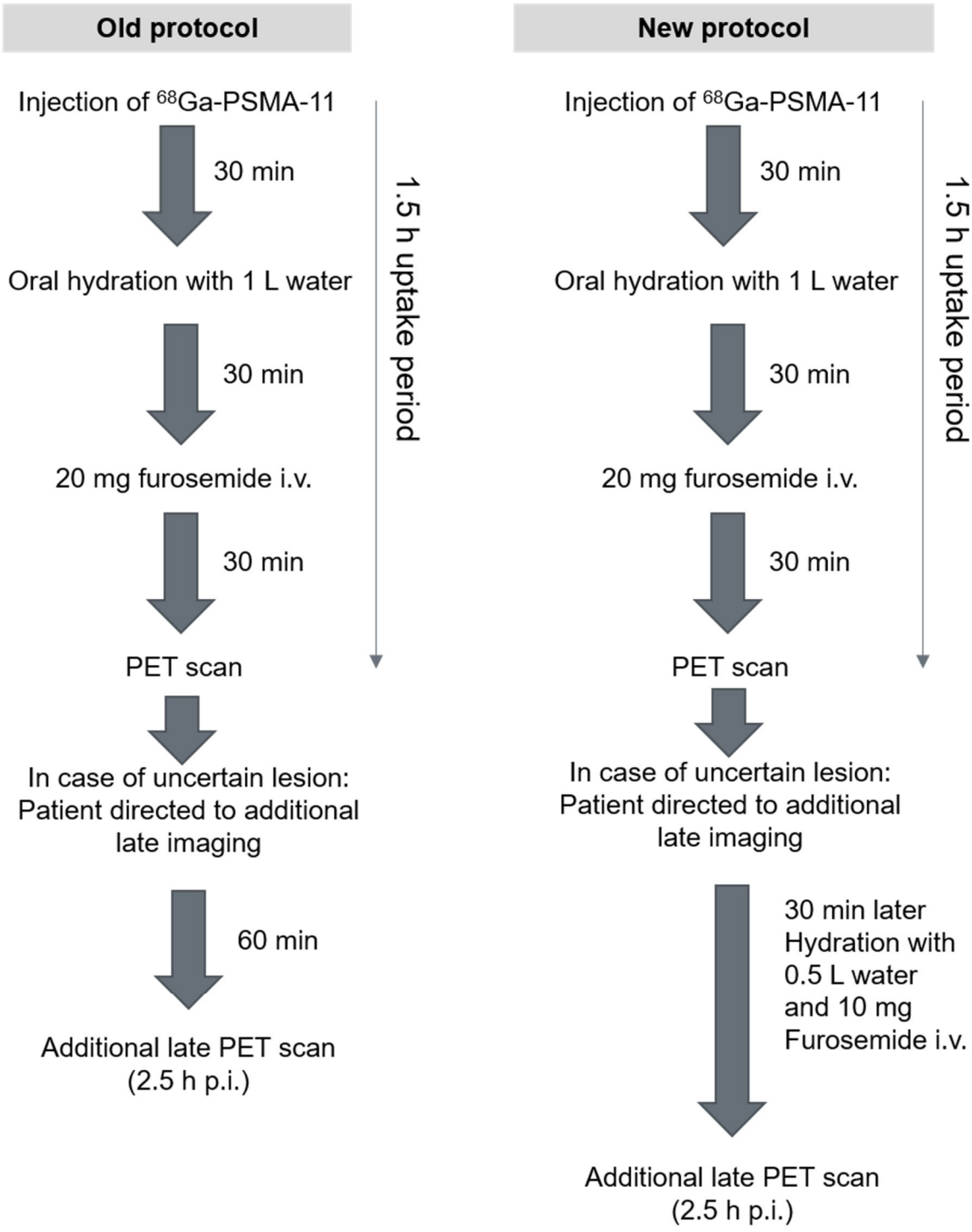

Fig. 1. Comparison of the "old" 2018 protocol and "new" 2019 protocol

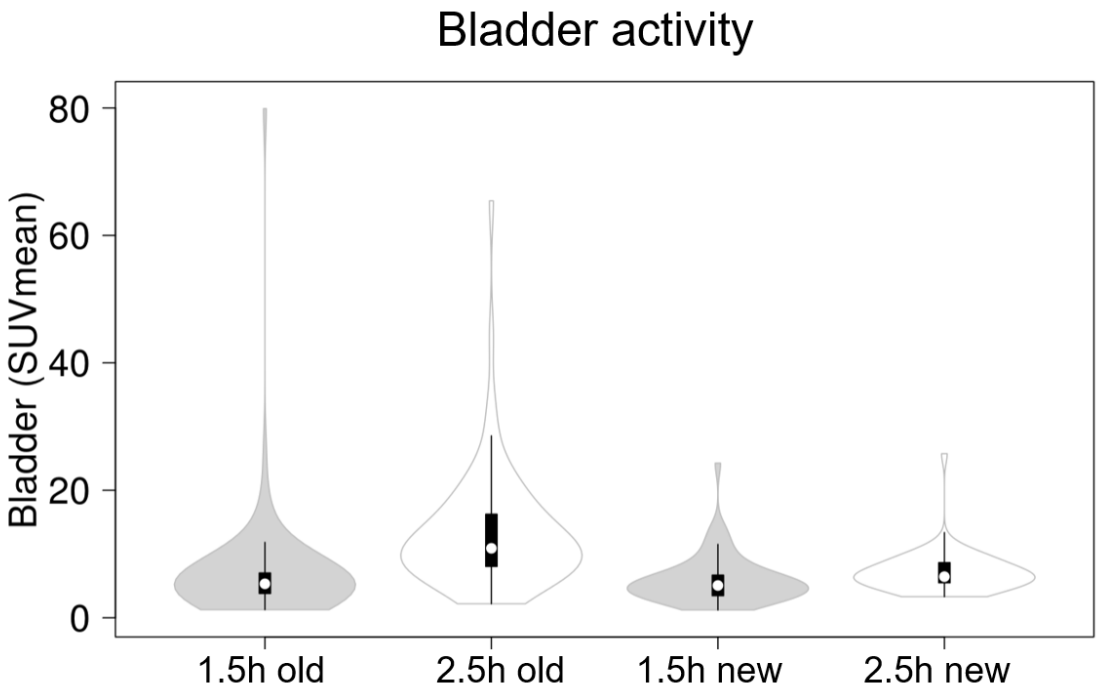

Fig. 2. Violin plots showing urinary bladder SUV for the “old” and “new” protocols. Whereas an increase in bladder SUVmean is seen for the old protocol, this is not the case in the new protocol.

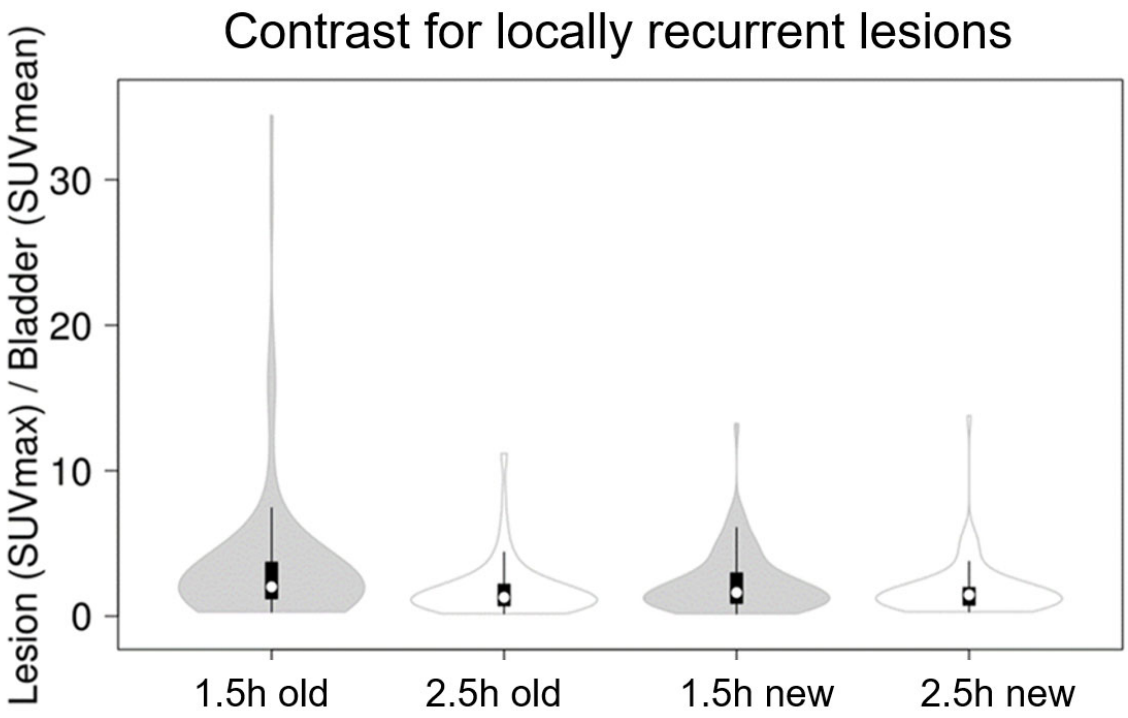

Fig. 3. Violin plots showing change in the locally recurrent lesion (prostatic fossa/seminal vesicle) tumor uptake in SUVmax versus the bladder, i.e. the lesion to bladder contrast. Whereas a decrease in tumor to bladder ratio (i.e. lesion visibility) is seen at 2.5h in the old protocol, this was not the case in the new protocol

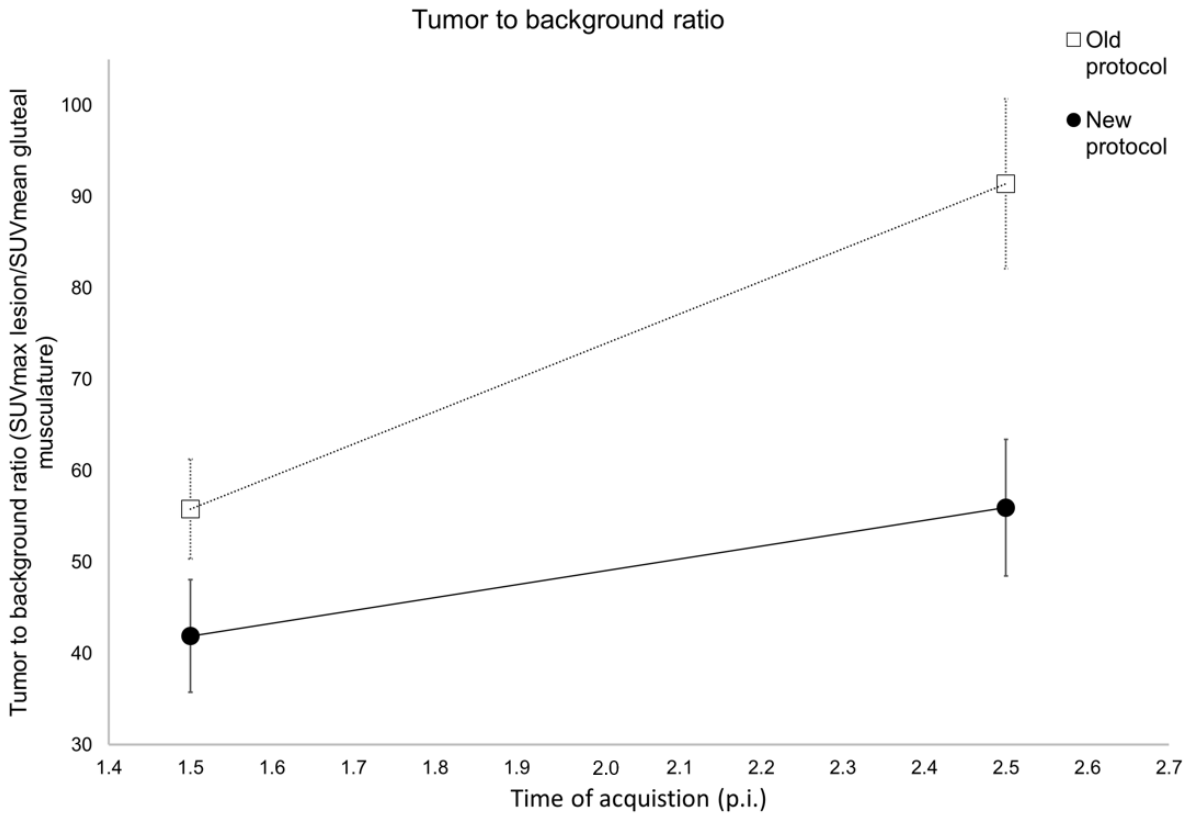

Fig. 4. Tumor to background ratio (TBR) change at 1.5h and 2.5h. The points the show the mean TBR ± standard error. The increase in TBR was lower for the new protocol than for the old protocol.

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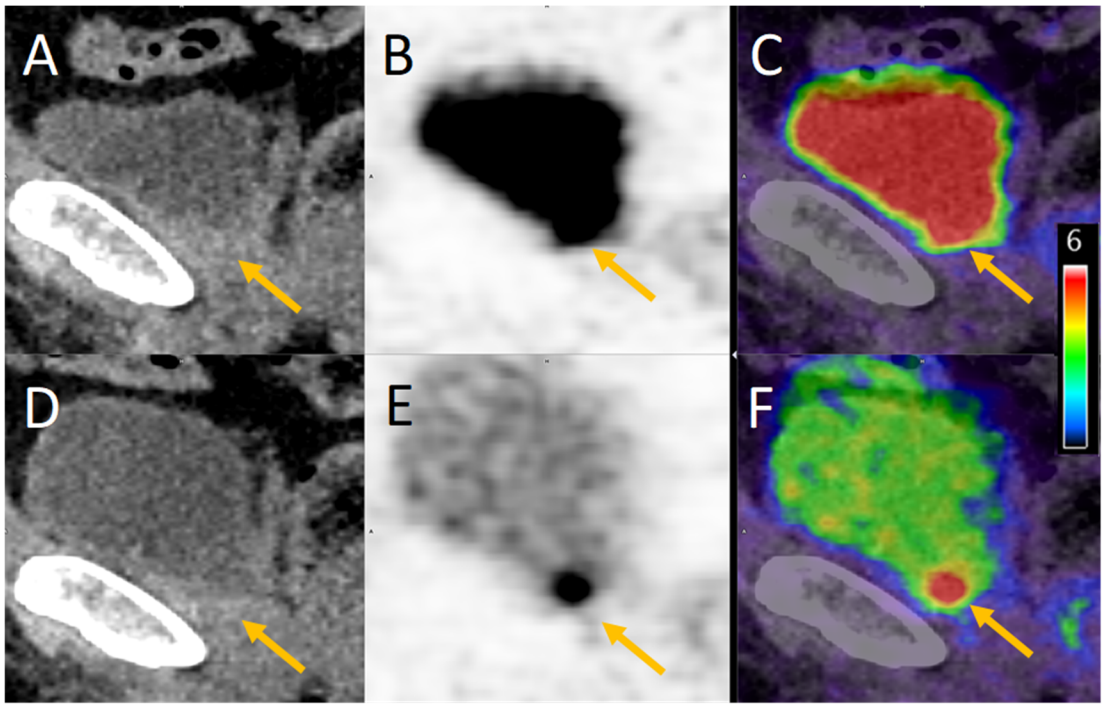
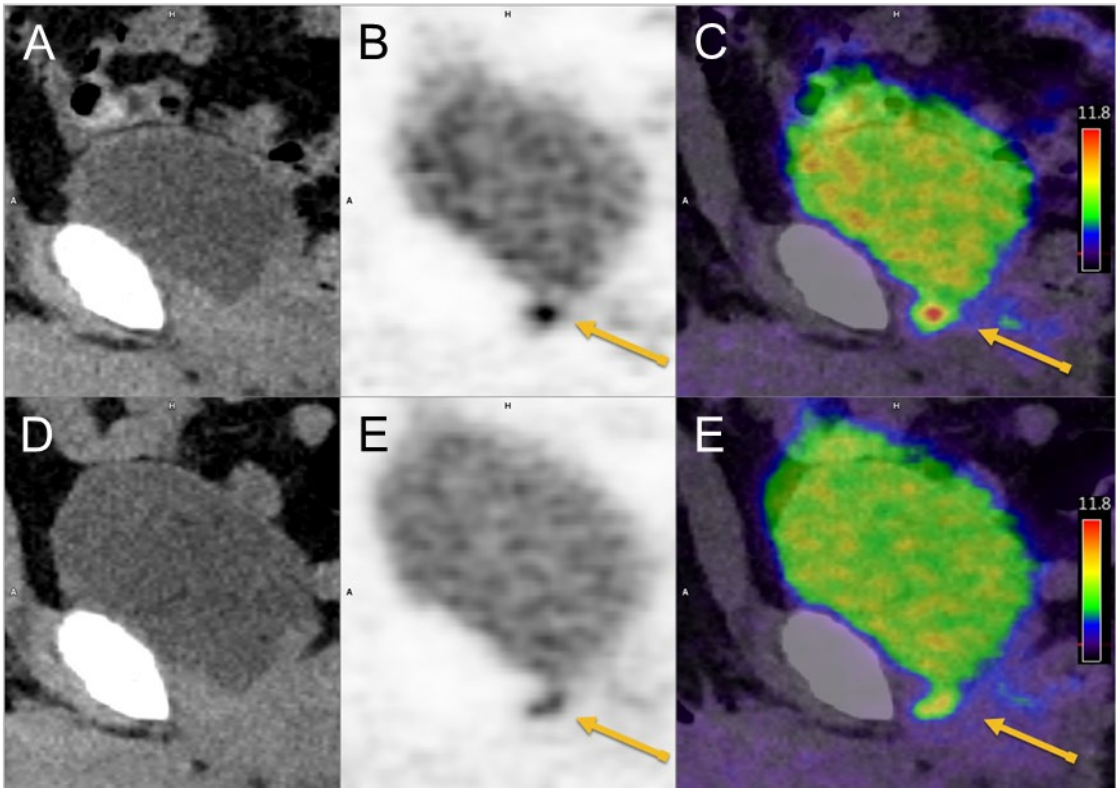


Fig. 5. Example patient scan showing locally recurrent lesions obscured by high bladder activity in the "old" protocol at late imaging. A/D $CT_{low\text{-}dose}$, B/E PET, C/F Fusion of PET and $CT_{low\text{-}dose}$, top row (A:C) 2.5h p.i., bottom row (D:F) 1.5h p.i. The lesions are each highlighted by a yellow arrow.

Supplementary Figure 1



Supplementary Fig. 1. Locally recurrent lesion examined in the new protocol, which is faintly visible in the early images (bottom row, SUVmax lesion 8.8, SUVmean bladder 9.4) and more clearly discernible in the late images (top row, SUVmax lesion 13.9, SUVmean bladder 10.9). Compared to the old protocol the bladder activity in the late scans is visually less intense. Tiles are as in figure 5.