Diuresis during ^{18}F-flotufolastat (rhPSMA-7.3) PET/CT Improves Recurrence Detection Post-Prostatectomy: A Prospective Phase II Trial

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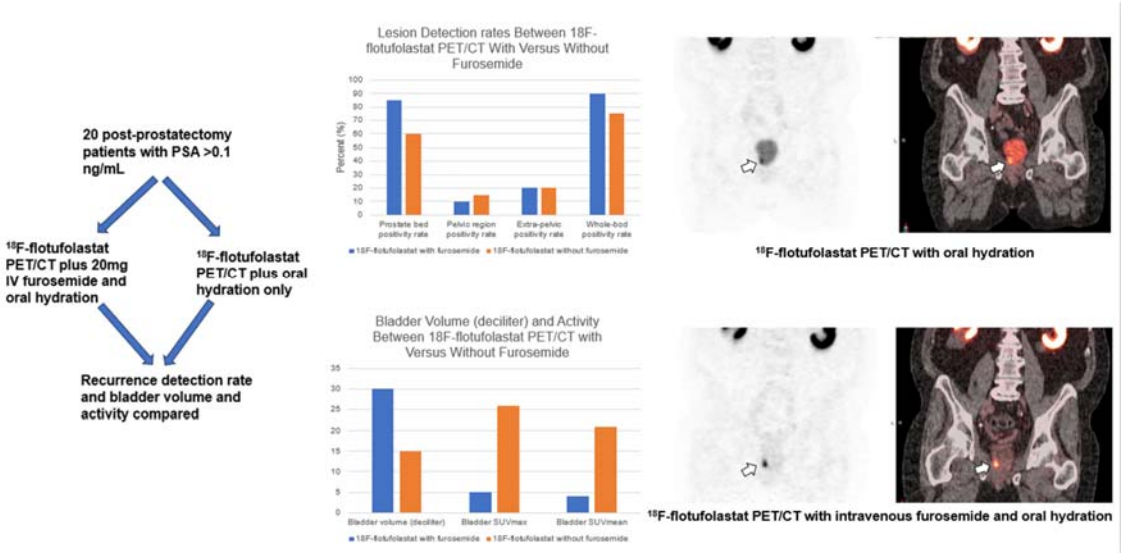
GRAPHICAL ABSTRACT



ABSTRACT

Background: Radiopharmaceuticals targeting prostate-specific membrane antigen (PSMA) have emerged as a sensitive tool for positron emission tomography (PET) imaging of prostate cancer (PCa) recurrence. Yet urinary bladder activity may obscure the visualization of prostate bed recurrence. Among the Food and Drug Administration (FDA)-approved PSMA radiopharmaceuticals, ^{18}F-flotufolastat (rhPSMA-7.3) has the lowest urinary excreted activity. We investigated the impact of diuresis with intravenous furosemide and oral hydration on bladder activity and PCa recurrence detection in patients with PCa post-prostatectomy with biochemical recurrence (BCR).

Methods: This phase II study (NCT05779943) prospectively recruited men with PCa post-prostatectomy with rising PSA ≥ 0.1 ng/ml. All patients had two ^{18}F-flotufolastat PET/CT scans, one with

20 mg furosemide administered intravenously with the radiotracer and the other without. SUVmean, SUVmax, and bladder volume were compared between the with- and without-furosemide PET/CT studies. PCa lesion detection was compared between the two sets of scans.

Results: Twenty men with a median PSA of 0.61 ng/mL (IQR = 0.18 – 1.15) completed both sets of scans. Bladder activity was significantly lower for the with- compared to without-furosemide; median SUVmax = 4.20 (range=1.70 – 19.80) versus 13.35 (range=3.90 – 165.4), respectively, p=0.014, and median SUVmean = 2.95 (range=0.80 – 17.60) versus 10.00 (range=1.90 – 140.00), respectively, p=0.017. Multivariable analysis demonstrated both furosemide administration and bladder distention were independent covariates for reduced bladder activity. the prostate bed region level, the recurrence detection rates were 17/20 (85%) and 12/20 (60%) for the with- and without-furosemide studies, respectively, p=0.025. No difference in detection rates was present at the per-patient, pelvic, and extra-pelvic regions between the two sets of studies. 3/20 without-furosemide studies had mild non-interfering peri-bladder halo artifact, but none had artifact with-furosemide.

Conclusion: In men with BCR and PSA ≥ 0.1 ng/ml after prostatectomy for PCa, a strategy with ^{18}F-flotufolastat PET/CT and concordant low dose furosemide further reduces urinary bladder intensity and increases local recurrence detection. Even without the use of a diuretic, relative bladder distension alone also reduces bladder activity, though not to the same degree as with a diuretic.

Keywords: Prostate cancer; Biochemical recurrence; Prostate bed region; ^{18}F-flotufolastat; rhPSMA-7.3; Furosemide

INTRODUCTION

Biochemical recurrence of prostate cancer (PCa) after prostatectomy is detected during serial measurement of serum prostate-specific antigen (PSA) [1]. Salvage radiotherapy (sRT) is a recommended treatment with curative potential [2]. Patients who receive sRT at lower PSA levels are at a lesser risk for secondary biochemical failure and have improved metastatic progression-free survival, prostate cancer-specific mortality, and all-cause mortality [3-5]. Currently, sRT is recommended at serum PSA of ≤0.5 ng/mL post-prostatectomy with rising PSA [2].

Advanced molecular imaging with positron emission tomography (PET) is the most sensitive imaging modality for localizing the site of PCa recurrence and guiding sRT management decisions and planning [6,7]. Prostate-specific membrane antigen (PSMA), a cell surface receptor overexpressed by the majority of PCa, is a sensitive molecular target for PET imaging of PCa recurrence. Three PSMA radioligands; ^{68}Ga-PSMA-11, ^{18}F-DCFPyL (^{18}F-piflufolastat), and 18F-rhPSMA-7.3 (^{18}F-flotufolastat), are currently approved by the Food and Drug Administration (FDA) for PET imaging of PCa recurrence [8-10].

The prostate bed region (PBR) is the most common site of early PCa recurrence [11]. Reducing bladder activity is a reasonable strategy to improve PSMA PET diagnostic performance to lessen the potential of false negative interpretation because of intense excreted radiotracer activity obscuring sites of recurrence that are adjacent to the urinary bladder (12). ^{18}F-flotufolastat has significantly lower urinary excreted activity than reported for other approved PSMA radioligands [13-15]. The detection rates for ^{68}Ga-PSMA-11, ^{18}F-piflufolastat, and ^{18}F-flotufolastat at PSA < 0.5 ng/mL are 38%, 36%, and 64%, respectively [8-10]. As demonstrated by Rauscher and coworkers a relatively high rate of local detection contributes to overall detection at low PSA [16].

Despite this higher local detection with ^{18}F-flotufolastat, further reduction in bladder activity of ^{18}F-flotufolastat may be helpful for improved prostate bed detection. Furosemide, a high ceiling loop diuretic, increases urinary clearance, causing rapid bladder filling. Therefore, the aim of this study was to prospectively investigate the impact of diuresis with intravenous furosemide combined with oral hydration on the excreted urinary bladder activity and PCa recurrence detection with ^{18}F-flotufolastat PET/CT in men who experienced rising PSA after radical prostatectomy for prostate adenocarcinoma. We hypothesized that a simple strategy utilizing low-dose furosemide at the time of radiotracer administration would further reduce bladder activity, improving recurrent lesion detection. To test our hypothesis, we conducted a prospective phase II trial (NCT05779943) in which each patient served as his own control, undergoing two ^{18}F-flotufolastat PET/CT scans, one with and one without furosemide.

MATERIALS AND METHODS

This phase II trial (NCT05779943) was performed under the approval of the institutional review board and all patients provided written informed consent. Target accrual was 20 men with the following inclusion criteria: 18 years and older, post radical prostatectomy with PSA of ≥0.1 ng/mL, ability to provide written informed consent, and serum creatinine of ≤1.3 mg/dL within 90 days prior to enrolment. Exclusion criteria included contraindication to furosemide administration and urinary incontinence.

Imaging protocol

No special patient preparation was observed. All 20 patients were scheduled for two sets of ^{18}F-flotufolastat PET/CT at least two days apart. The first 10 patients underwent ^{18}F-flotufolastat PET/CT with furosemide first, followed by ^{18}F-flotufolastat PET/CT without furosemide. The second set of 10 patients had their ^{18}F-flotufolastat PET/CT without furosemide first, followed by ^{18}F-flotufolastat PET/CT with furosemide.

For each diuretic scan, 296 MBq (8 mCi) of ^{18}F-flotufolastat was administered intravenously followed immediately by intravenous 20 mg furosemide. Patients were encouraged to drink up to 500 mL of oral fluid during the uptake period of 60 minutes. The patients were encouraged to void during the uptake period but asked to refrain from voiding 15 minutes prior to the commencement of PET/CT imaging to allow for adequate bladder distention. The ^{18}F-flotufolastat PET/CT without diuresis was completed in a similar manner except that furosemide was not administered.

Imaging was performed on a GE Discovery 690 TOF PET/CT scanner (GE Healthcare, Milwaukee, WI). Following CT imaging, thigh-to-skull base PET imaging was acquired in 3D mode at 3 minutes per bed position. The PET data was corrected for randoms, scatter, dead time, and attenuation. Image reconstruction was done with the OSEM iterative reconstruction algorithm.

Image interpretation

Two board-certified nuclear medicine physicians (DMS and CM with more than 20 years and 10 years of experience, respectively) performed independent blind interpretation of the with- and without-furosemide ^{18}F-flotufolastat PET/CT on a dedicated workstation equipped with MIM software version 7.3. The mean and maximum standardized uptake values (SUVmean and SUVmax) of bladder activity and the bladder volume for the with- and without-furosemide PET/CT scans were determined. Using SUVmean and SUVmax, the physiologic radiotracer activity in the right parotid, liver, spleen, right kidney, and the lumen of the abdominal aorta (blood pool) were determined.

Each study was assessed for PCa recurrence, defined as a focal area of increased radiotracer uptake corresponding to the typical pattern of PCa recurrence and not conforming to known physiological radiotracer biodistribution or artifact. When identified, the site of PCa recurrence was classified as either prostate bed, pelvic, or extra-pelvic. Prostate bed recurrence was defined as recurrent lesions localized to the prostatectomy surgical bed and contiguous areas, including the vesico-urethral anastomosis, the resection margins/ remnant seminal vesicle, retrovesicular region, and the anterior rectal wall. Pelvic recurrence was defined as recurrent lesions localized to the pelvic nodes. Extra-pelvic recurrence was defined as recurrence in extra-pelvic nodes, any skeletal or soft tissue visceral sites. Each PET/CT was assessed for the presence of a photopenic halo around the urinary bladder. The scan interpretation of the two blinded readers was then compared. Disagreements were resolved by a consensus read. If consensus was required on the bladder halo artifact, the readers then applied the criteria of mild (narrow photopenic rind with no interference to pelvic structures); moderate (interference with structures adjacent to the bladder such as prostate bed); and severe (interference with structures more remote from bladder such as acetabulum or iliac regions).

Statistical analysis

Descriptive statistics were generated for all patient characteristics, including age, serum PSA, the injected activity of ^{18}F-flotufolastat for the with- and without-furosemide PET/CT scans, and the interval (days) between with- and without-furosemide PET/CT scans. Frequency and percentage were reported for categorical variables. Mean ± standard deviation and median with interquartile range (IQR)/range were reported for numeric variables. Using the paired t-test, the with- and without-furosemide PET/CT scans were compared with respect to the injected radiotracer activity, bladder volume, and SUVmean and SUVmax of radiotracer activity in the bladder, parotid gland, liver, spleen, kidney, and blood pool.

We compared the with- and without-furosemide PET/CT scan with respect to whole-body, prostate bed, pelvic, and extra-pelvic scan positivity using McNemar's test for 2-level categorical covariates. The association between PET positivity (with- and without-furosemide studies) and the SUVmean, SUVmax, and bladder volume was determined using an ANOVA test.

The association of bladder activity (SUVmax and SUVmean) with bladder volume was estimated using Spearman’s correlation coefficient, and a p-value was reported separately for the with-furosemide and the without-furosemide studies.

Univariate and multivariable generalized estimating equations analysis for bladder SUVmax/SUVmean outcomes separately was performed assuming a normal distribution for the outcome and ‘cs’ correlation structure, accounting for the repeated measures between the subjects (with furosemide and without furosemide PET/CT studies). Bladder volume, age, PSA, and injected activity were included in the multivariable model. A separate modeling approach with backward elimination and including only those covariates that met an alpha of 0.2 in the univariate models, was performed to see if using with-furosemide PET/CT scan correlates with SUVmax or SUVmean outcomes separately after adjusting for other covariates.

Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC), and statistical significance was assessed at the 0.05 level.

RESULTS

Between July 2023 and March 2024, a total of 20 men who met inclusion criteria were recruited. The mean age of the patients was 67.95 ± 8.17 years, and the median PSA was 0.61 ng/mL (IQR = 0.18 – 1.15). All patients tolerated the study interventions (20 mg intravenous furosemide and oral hydration) and successfully completed the two sets of PET/CT scans with a mean interval between with- and without-furosemide ^{18}F-flotufolastat PET/CT scans of 7 days (table 1).

Table 1: Baseline characteristics of the patients

Variable	Level	N (%) = 20
Age (years)	Mean ± SD	67.95 ± 8.17
Serum PSA (ng/mL)	Median (IQR)	0.61 (0.18 – 1.15)
Interval between PET scans (days)	Median (Range)	7.00 (6.00 – 10.00)

PSA: Prostate-Specific Antigen

Comparison of ^{18}F-flotufolastat biodistribution on the with- and without-furosemide studies

As demonstrated in Table 2, the mean administered activity of ^{18}F-flotufolastat was not significantly different between the with- and without-furosemide studies, 308.21 ± 23.31 MBq (8.33 ± 0.63 mCi) versus 304.51 ± 9.99 MBq (8.23 ± 0.27 mCi), respectively, p=0.558. The median SUVmax of bladder activity was significantly lower on the with-furosemide PET/CT compared with the without-furosemide study, 4.20 (range=1.70 – 19.80) versus 13.35 (range=3.90 – 165.4), p=0.014. Similarly, the median SUVmean of bladder activity was significantly lower on the with-furosemide PET/CT compared with the without-furosemide study, 2.95 (range=0.80 – 17.60) versus 10.00 (range=1.90 – 140.00), p=0.017. Bladder volume was significantly higher on the with-furosemide PET/CT compared with the without-furosemide study, 296.50 (range=59.90 – 630.00) versus 94.75 (range=18.10 – 717.00), p=0.003.

The median kidney SUVmax was significantly lower on the with-furosemide study compared with the without-furosemide study (p=0.039). While the kidney SUVmean was also lower on the with-furosemide study compared with the without-furosemide study, the difference did not reach statistical significance (p=0.223). The physiologic radiotracer activity of ^{18}F-flotufolastat in the parotoid gland, liver, spleen, and abdominal aorta was not significantly different between the with- and without furosemide PET/CT studies. Mild peri-bladder halo artifact was detected in 3/20 without-furosemide and 0/20 with-furosemide PET/CTs.

Table 2: Comparison of injected activity and normal organ radiotracer uptake between the with-furosemide and without-furosemide ^{18}F-flotufolastat PET/CT

Lasix (yes/no)				
Covariate	**Statistics**	**no N=20**	**yes N=20**	**Parametric P-value**
Injected activity (mCi)	N	20	20	0.558
	Mean ± SD	8.23 ± 0.27	8.33 ± 0.63	
	Median (range)	8.19 (7.70 – 8.80)	8.13 (8.00 – 10.90)	
Bladder SUVmax	N	20	20	**0.014**
	Mean ± SD	26.43 ± 38.06	5.21 ± 4.04	
	Median (range)	13.35 (3.90 – 165.40)	4.2 (1.70 – 19.80)	
Bladder SUVmean	N	20	20	**0.017**
	Mean ± SD	20.64 ± 31.50	3.9± 3.71	
	Median (range)	10 (1.90 – 140.00)	2.95 (0.80 – 17.60)	
Bladder Volume (mLs)	N	20	20	**0.003**
	Mean ± SD	147.69 ± 172.31	300.22 ± 151.30	
	Median (range)	94.75 (18.10 – 717.00)	296.5 (59.90 – 630.00)	
Kidney SUVmax	N	20	20	**0.039**
	Mean ± SD	42.98 ± 11.59	38.64 ± 11.13	
	Median (range)	43.10 (20.90 – 62.90)	38.35 (16.60 – 55.90)	
Kidney SUVmean	N	20	20	0.223
	Mean ± SD	27.12 ± 8.46	24.87 ± 7.95	
	Median (range)	26.85 (11.2 – 41.2)	24.65 (9.90 – 44.90)	
Abdominal Aorta SUVmax	N	20	20	0.590
	Mean ± Sd	3.30 ± 0.93	3.41 ± 0.90	
	Median (range)	3.20 (2.10 – 6.40)	3.35 (1.60 – 5.10)	
Abdominal Aorta SUVmean	N	20	20	0.813
	Mean	2.40 ± 0.58	2.44 ± 0.53	
	Median (range)	2.35 (1.40 – 4.10)	2.45 (1.00 – 3.30)	
Liver SUVmax	N	20	20	0.204

		Lasix (yes/no)		
Covariate	**Statistics**	**no N=20**	**yes N=20**	**Parametric P-value**
	Mean ± SD	11.11 ± 3.21	12.4 ± 6.31	
	Median (range)	10.9 (6.90 – 19.90)	10.6 (5.40 – 32.90)	
Liver SUVmean	N	20	20	0.582
	Mean ± SD	7.67 ± 1.95	7.48 ± 2.20	
	Median (range)	7.45 (4.80 – 11.70)	7.25 (3.50 – 11.10)	
Spleen SUVmax	N	20	20	0.342
	Mean ± SD	12.74 ± 4.25	13.49 ± 5.64	
	Median (range)	12.35 (6.30 – 20.40)	12.75 (6.50 – 25.60)	
Spleen SUVmean	N	20	20	0.883
	Mean ± SD	10.14 ± 3.83	10.23 ± 4.18	
	Median (range)	9.80 (5.10 – 17.70)	9.60 (5.00 – 17.40)	
Parotid SUVmax	N	20	20	0.129
	Mean ± SD	20.81 ± 5.03	19.15 ± 4.78	
	Median (range)	19.75 (14.50 – 32.20)	19.30 (11.50 – 29.30)	
Parotid SUVmean	N	20	20	0.560
	Mean ± SD	13.06 ± 2.28	12.42 ± 4.26	
	Median (range)	13.20 (9.20 – 19.50)	12.05 (4.50 – 24.60)	

Comparison of recurrent lesion detection on the with- and without-furosemide studies

On a per-patient basis, 18/20 (90%) with-furosemide studies were positive for the site of PCa recurrence, while 15/20 (75%) without-furosemide studies positively localized the site of PCa recurrence, but the difference in detection rate did not reach statistical significance (p=0.212).

PCa recurrence was localized in the prostate bed on 17/20 (85%) with-furosemide PET/CT studies compared with 12/20 (60%) without-furosemide PET/CT studies, p=0.025 (Figures 1 and 2). The detection rate of PCa recurrent lesions in the pelvic and extra-pelvic regions was similar between the with- and without-furosemide studies (Table 3). Reader agreement was not significantly different between the with- and without-furosemide studies (Table 3).

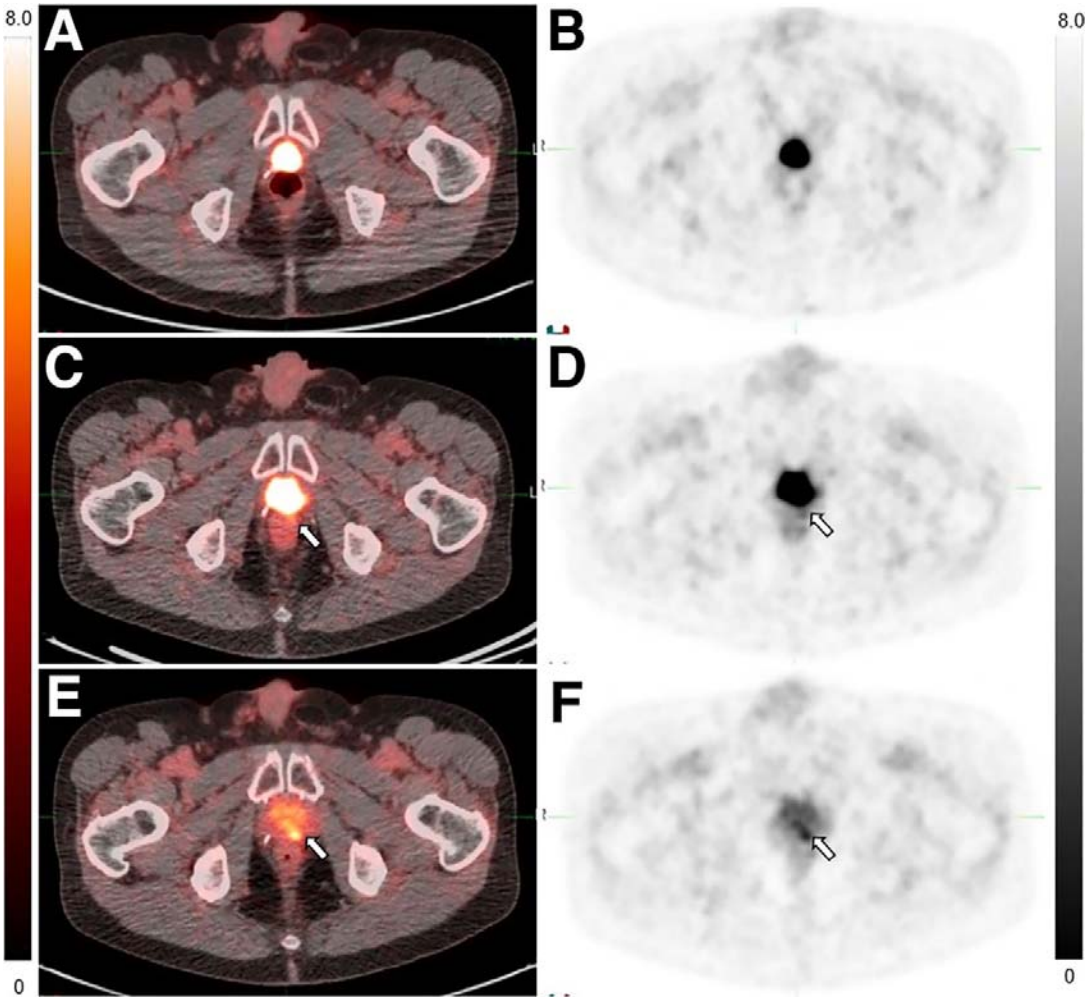


Figure 1. An 83-y-old man with PSA of 0.60 ng/mL after radical prostatectomy received clinical ^{18}F-piflufolastat (^{18}F-DCFPyL) PET/CT imaging (A and B), which failed to localize site of recurrence. He was subsequently enrolled in this phase II study. Initial ^{18}F-flotufolastat PET/CT without furosemide (C and D) was interpreted as negative. ^{18}F-flotufolastat PET/CT with furosemide demonstrates left retrovesicular focus of increased radiotracer uptake with SUV_{max} of 6.3 consistent with prostate bed recurrence (arrows in E and F). In retrospect, lesion was visible in left retrovesicular region on without-furosemide study (arrows in C and D) though obscured by bladder activity.

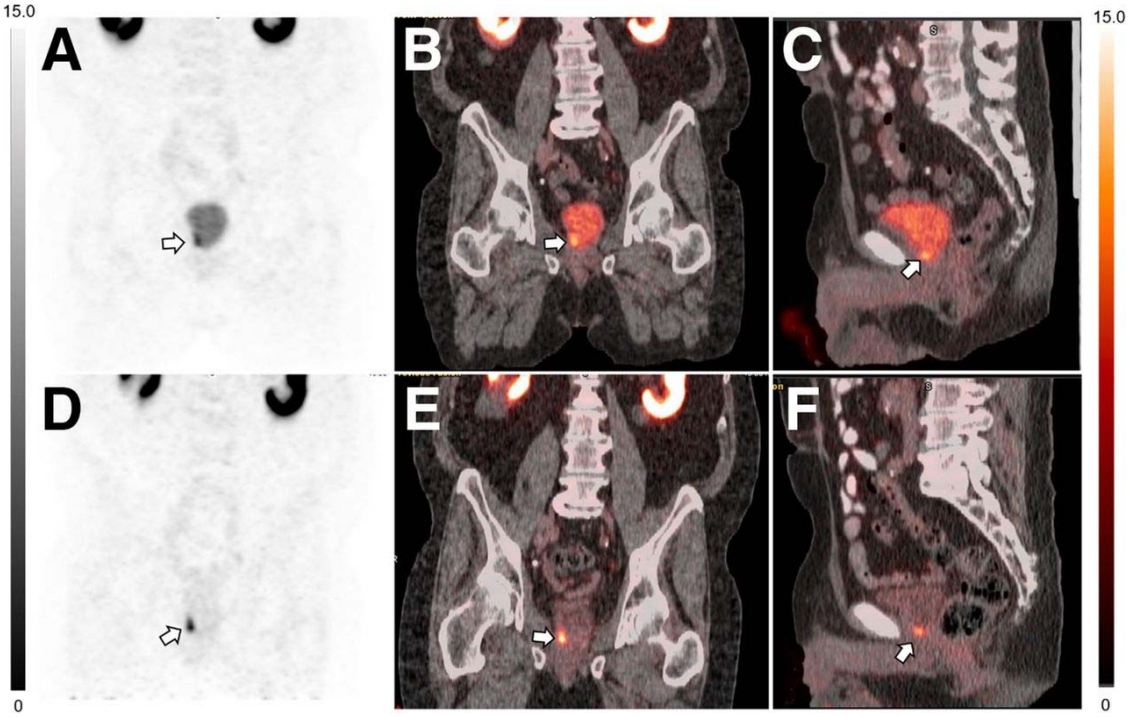


Figure 2. ^{18}F-flotufolastat PET/CT obtained without (A–C) and with (D–F) furosemide in 78-y-old man with PSA of 2.98 ng/mL after radical prostatectomy. Both sets of images demonstrate focus of increased radiotracer uptake in right lateral resection margin consistent with prostate bed recurrence. Although lesion is seen on both sets of studies, it is more conspicuous on with-furosemide study. He received sRT, and PSA became undetectable.

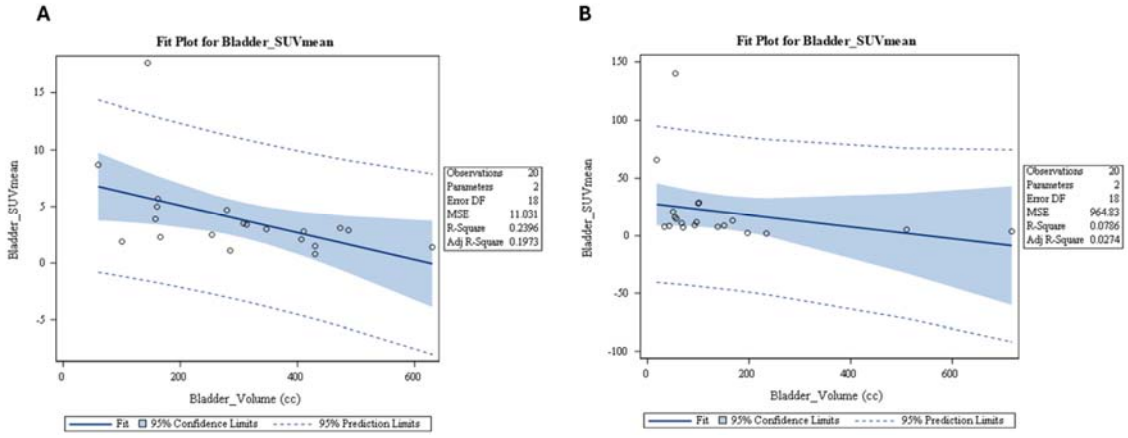


Fig 3: Scatter plots showing the inverse relationship between bladder activity level measured by SUVmean and bladder volume on the ^{18}F-flotufolastat PET/CT with furosemide (A) and ^{18}F-flotufolastat PET/CT without furosemide (B).

Table 3: Comparison of lesion detection rates and reader agreement between the with-furosemide and without-furosemide 18F-flotufolastat PET/CT

Covariate	Level	Furosemide (Yes/No) No N=20	Furosemide (Yes/No) Yes N=20	Parametric P-value
PET imaging findings				
Prostate bed finding	Negative	8 (40)	3 (15)	**0.025**
	Positive	12 (60)	17 (85)	
Pelvic finding	Negative	17 (85)	18 (90)	0.317
	Positive	3 (15)	2 (10)	
Extra-pelvic finding	Negative	16 (80)	16 (80)	NA
	Positive	4 (20)	4 (20)	
Patient Level finding	Negative	5 (25)	2 (10)	0.212
	Positive	15 (75)	18 (90)	
Reader agreement				
Prostate bed finding	Agree	10 (50)	9 (45)	0.705
	Disagree	10 (50)	11 (55)	
Pelvic finding	Agree	19 (95)	19 (95)	NA
	Disagree	1 (5)	1 (1)	
Extra-pelvic finding	Agree	15 (75)	15 (75)	1.00
	Disagree	5 (25)	5 (25)	

Association between bladder activity and bladder volume

Bladder activity demonstrated a moderate and inverse association with bladder volume on the with-furosemide study with a Spearman correlation coefficient of -0.536 (p=0.015) for SUVmax and -0.550 (p=0.012) for SUVmean. On the without-furosemide PET/CT studies, there was a strong inverse level of association between the bladder volume and SUVmax of the bladder activity (Spearman correlation coefficient of -0.603, p=0.005), while a moderate and inverse association was demonstrated between bladder volume and SUVmean of bladder activity (Spearman correlation coefficient of 0.561, p=0.010), Figure 3.

Using the age of the patients, administered activity of ^{18}F-flotufolastat, serum PSA at the time of PET/CT imaging, bladder volume, and furosemide administration (yes or no) as covariates, we performed univariate analysis to determine factors with significant association with bladder activity. Among the covariates, bladder volume and furosemide demonstrated an independent significant association with

bladder activity; an inverse relationship between bladder volume and bladder activity and furosemide administration positively associated with reduced bladder activity. The other covariates were not significantly associated with bladder activity (supplementary tables 1 and 2). On multivariable analysis, furosemide administration and a larger bladder volume remained significantly associated with lower bladder activity (supplementary tables 3 and 4).

DISCUSSION

We set out to investigate if the use of a low-dose diuretic strategy with ^{18}F-flotufolastat PET-CT results in lower bladder activity, resulting in increased detection of local recurrence in the prostate bed post-prostatectomy. We found that the use of 20 mg of furosemide IV at the time of radiotracer injection significantly lowers bladder SUVmax and SUVmean and significantly increases the detection of prostate bed recurrence. We also found that furosemide significantly decreases renal SUVmax, and that no other organ systems are affected. In our multivariable analysis, both furosemide administration and bladder distention were independent covariates for reduced bladder activity. This finding suggests that, even without medication-induced diuresis, bladder distention, such as with increased oral hydration and ceasing urination 15 minutes before imaging, is effective on its own in reducing bladder activity. All patients tolerated the protocol well.

These findings are important because offering sRT to patients early following the biochemical recurrence of PCa improves survival [3-5]. Therefore, positive and correct localization of the site of recurrence may be important to achieve desired outcomes by providing the radiation oncologist with a definitive target, as demonstrated in a randomized trial [6]. Clinical target volume delineation guided by PSMA PET findings has been reported to improve lesion coverage in sRT planning for PBR recurrence [17-19]. In addition, it has been our experience that a positive study offers the patient a degree of comfort in distinction to being informed that recurrence is present but cannot be localized.

The bladder activity in the without-furosemide ^{18}F-flotufolastat PET/CT in our study was slightly lower compared with the levels from the LIGHTHOUSE and SPOTLIGHT trials with median SUVmax (range) of without-furosemide study in our study of 13.35 (3.90-165.40) compared with 17.1 (1.3-130.6) in the LIGHTHOUSE and SPOTLIGHT trials. The median SUVmean (range) of the without-furosemide PET/CT in our study was 10.00 (1.90-140.00) versus 12.5 (0.7-887) in the LIGHTHOUSE and SPOTLIGHT trial cohorts [20]. Consistent oral hydration of patients may play a part in the slightly reduced average bladder activity reported in our study. Differences in camera sensitivity between studies (the LIGHTHOUSE and SPOTLIGHT trials were multicenter international phase III trials) may be another reason for the slight differences in the reported bladder activity level. We also observed 3/20 mild peri-bladder halo artifact not interfering with interpretation in the without-furosemide ^{18}F-flotufolastat PET/CTs, but 0/20 in the with-furosemide studies. This is in agreement with the post-hoc analysis of the LIGHTHOUSE and SPOTLIGHT trial cohorts, reporting peri-bladder halo artifact in 2/710 patients (0.3%), since our “minor” criteria (narrow photopenic rind with no interference to pelvic structures) would be considered as no artifact in that study’s binary methodology which only considered artifact present if there was interference with adjacent or distant structures [20.

The whole-body detection rate of ^{18}F-flotufolastat PET/CT reported in the phase III SPOTLIGHT trial was 83%, which compares with the whole-body detection rates of 75% and 59%-66% for ^{68}Ga-PSMA-11 and ^{18}F-piflufolastat in phase III UCSF/UCLA and CONDOR trials, respectively, [8-10]. In the subset of patients with PSA <0.5 ng/mL, ^{18}F-flotufolastat has a higher detection rate of 64% compared with 38% and 36% for ^{68}Ga-PSMA-11 and ^{18}F-piflufolastat, respectively [8-10]. At low PSA levels below 0.5

ng/mL, most recurrences occur in the PBR, at sites adjacent to the urinary bladder [11,12]. While ^{18}F-flotufolastat has a lower urinary excretion (6% of the administered activity) compared with ^{68}Ga-PSMA-11 and ^{18}F-piflufolastat (11% of the administered activity) [13-15], which may make it more sensitive for prostate bed recurrence detection, the relative performance of these three FDA-approved radiopharmaceuticals can only be objectively determined in a prospective head-to-head comparison.

The presence of relatively intense bladder activity with most PSMA radiotracers may obscure the detection of recurrence in the pelvis, especially in locations such as the prostate bed. Freitag and coworkers, in a study of ^{68}Ga-PSMA PET versus mpMR, noted that 18/119 patients had local recurrence on mpMR, yet the detection rate was only half that (9/119) with PET/CT, and that detection on PET was adversely influenced by proximity to the bladder [21]. Thus, strategies employing intravenous furosemide, oral or intravenous hydration, and early and delayed imaging, in different combinations, have been investigated for their utility in reducing bladder activity [22-30]. Yet, the higher the baseline bladder activity, the more difficult it may be to reduce the activity to less interfering levels with any of these techniques. For example, Donswijk and coworkers reported on a retrospective study with approximately 500ml oral pre-hydration in which 10 mg of furosemide was or was not administered at the time of ^{18}F-piflufolastat injection with imaging 60 minutes later in which bladder median SUVmax without furosemide was 61.7 and reduced to 22.8 with furosemide [25]. Wondergem and coworkers utilized in a retrospective study, a more stringent workflow of 40 mg furosemide at the time of ^{18}F-piflufolastat injection with 1500 ml oral hydration and imaging at 60 minutes reported a mean SUVmax of 9.9, yet with a halo artifact occurring in 89.2% of subjects [24].

Though there have been reports of similar strategies for ^{68}GaPSMA-11, the efforts by Uprimny and coworkers are most representative. In a retrospective study, baseline median SUVmax 60 minutes after ^{68}GaPSMA-11 injection without diuresis was 63.0 with a local detection rate after prostatectomy of 17.3%, while utilizing a protocol of 20 mg furosemide at the time of radiotracer injection with 500 ml IV saline demonstrated a median SUVmax of 8.9 with a higher local detection rate of 20.5.% [28]. In a different manuscript, the authors report that this latter strategy results in a 40% rate of urinary urgency [27]. Our findings in the current study of ^{18}F-flotufolastat in which median SUVmax at baseline without diuresis of 13.35, reducing to median SUVmax of 4.2, and mean SUVmax of 5.21, with no interfering halo artifact, and a detection rate in the prostate bed of 60% at baseline increasing to 85% with a well-tolerated diuretic protocol compare quite favorably. Though immediate and delayed imaging involving various combinations of forced diuresis strategies have also been reported (22,26,29,30), these seem disruptive to usual clinical workflow and less tolerable to patients. Encouraged by the effectiveness and tolerability of the technique in this study, we have modified our clinical protocol accordingly.

^{18}F-PSMA-1007, though not currently FDA-approved, has an inherent low rate of urinary excretion among common PSMA radioligands [31]. In a retrospective study, Rahbar and coworkers reported a bladder median SUVmean at 60 minutes post-injection of 3.08 without diuresis [30]. With the diuretic strategy we have tested with the FDA-approved ^{18}F-flotufolastat, the bladder median SUVmean is 2.95, similar to that of ^{18}F-PSMA-1007.

One interesting observation is that a full bladder is a requirement during CT simulation for radiotherapy planning. Fusion of PSMA PET image with CT simulation image is increasingly being applied for targeted delivery of radiotherapy to recurrent lesions. Difficulty often results from attempting to fuse PET images acquired with an empty or near-empty bladder with CT simulation images acquired with a full bladder during radiotherapy planning. The combination of a higher bladder volume in addition to lower bladder activity and improved lesion conspicuity, theoretically, has the potential to improve image fusion for radiotherapy planning. But this would need to be proven in larger trials.

The strengths of our study include a rigorous prospective design where each patient serves as their own control. Limitations include a relatively small sample size though our baseline results align with larger phase 3 trials. We also recruited patients with normal renal function without incontinence. Thus, results cannot be generalized to those populations, and in fact, we believe this strategy should not be employed in patients with severe incontinence. Finally, histologic proof was not obtained in most cases; yet, PSMA targeting radiopharmaceuticals, including ^{18}F-piflufolastat are known to have high specificity. We have several cases in which the bed activity was targeted by radiotherapy, resulting in undetectable PSA, but this investigation was not included in our aims. We also note that one patient was an outlier with a very high baseline SUVmean of 140.0, which was significantly higher than the highest SUVmean of 88.7 in the Phase 3 analysis [20]. Despite investigation, we have discovered no cause for this phenomenon, though activity reduced to SUVmean of 17.6 with furosemide. We have included this patient in data analysis for scientific veracity, but if eliminated, median SUVmax would be 3.90 (mean ± SD = 4.44 ± 2.18) with furosemide and 13.30 (mean ± SD = 19.12 ± 19.99) without furosemide. The corresponding median SUVmean would be 2.9 (mean ± SD = 3.17 ± 1.88) with furosemide and 9.10 (mean ± SD = 14.36 ± 14.63) without furosemide.

CONCLUSION

In men with rising serum PSA after radical prostatectomy for prostate adenocarcinoma, an intravenous furosemide strategy with ^{18}F-flotufolastat PET/CT imaging further reduces urinary bladder activity from a low baseline and increases local prostate bed recurrence detection. In a multivariable analysis, both furosemide administration and bladder distention were independent covariates for reduced bladder activity, suggesting that even without the use of a diuretic, relative bladder distension alone from withholding urination for a short time before imaging also reduces bladder activity, though not to the same degree as with diuretic use.

DISCLOSURE

Research funding was provided by Blue Earth Diagnostics Ltd. David Schuster has acted as a consultant for Global Medical Solutions Taiwan, Progenics Pharmaceuticals, Inc., Heidelberg University, and DuChemBio Co. Ltd.; participates through the Emory Office of Sponsored Projects in full compliance with Emory University sponsored research and conflict-of-interest regulations in sponsored grants including those funded or partially funded by Blue Earth Diagnostics, Nihon MediPhysics Co, Ltd., Telix Pharmaceuticals (US) Inc., Advanced Accelerator Applications, FUJIFILM Pharmaceuticals USA, Inc., Amgen Inc.; participates in educational initiatives with School of Breast Oncology and PrecisCa. Charles Marcus has received funding from Blue Erath Diagnostics Ltd and Nuclear Medicine Clinical Trial Group, LLC. No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We are grateful to all patients who consented to participate in this study. We also thank our research team in the Division of Nuclear Medicine and Molecular Imaging at Emory University's Department of Radiology and Imaging Sciences. Specifically, we thank Bridget Fielder, our research nurse, and Dene Voisin, our clinical research coordinator, for their contributions to this project.

KEY POINTS

QUESTION: Does diuresis with intravenous furosemide with oral hydration improve prostate cancer recurrence detection on ^{18}F-flotufolastat PET/CT imaging?

PERTINENT FINDINGS: In this phase II trial investigating prostate cancer recurrence detection after prostatectomy, diuresis with 20mg furosemide reduces bladder activity while increasing bladder volume, which leads to an improvement in prostate bed recurrence detection of prostate cancer on ^{18}F-flotufolatstat PET/CT. Diuresis with 20 mg intravenous furosemide is safe and well-tolerated by all patients.

IMPLICATIONS FOR PATIENT CARE: Improved prostate bed recurrence detection is achieved with reduced bladder activity and bladder distention induced by intravenous furosemide administration during ^{18}F-flotufolatst PET/CT imaging.

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