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Characterizing and Mitigating Bladder Radioactivity on ^{18}F-fluciclovine PET/CT

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Short title: Bladder Activity in Fluciclovine PET/CT.

Characterizing and Mitigating Bladder Radioactivity on ^{18}F-fluciclovine PET/CT

Purpose: F-18-fluciclovine PET is approved for prostate cancer recurrence imaging. According to the radiopharmaceutical package insert only 3% of the tracer is expected to be excreted in the urine over the first four hours. Yet, in clinical practice we noticed a higher percentage of bladder excretion. We sought to evaluate and quantify early fluciclovine bladder radioactivity and determine if refraining from voiding before fluciclovine injection would mitigate it.

Materials and Methods: 159 patients underwent fluciclovine PET/CT imaging as part of their clinical workup. The first 36 patients were instructed to void just before fluciclovine injection, the subsequent 123 patients were not requested to void. The SUV_{max} and SUV_{mean} of the bladder, aorta, marrow, liver, and bladder volumes were collected. Comparing SUV_{mean} of bladder to background, we characterized bladder radioactivity as: "Insignificant" (bladder<aorta), "Mild" (bladder>aorta, <marrow), "Moderate" (bladder >marrow, <liver) and "Intense" (bladder>liver). Differences between the protocols were investigated.

Results: Overall, 22% (35/159) of patients had moderate, and 8.8% (14/159) had intense bladder activity. A negative association was found between bladder volumes and SUV_{mean}. A significant difference was found between voiding and non-voiding protocol groups, with 38.9% (14/36) vs. 17.1% (21/123) of patients having moderate, and 22.2% (8/36) vs. 4.9% (6/123) of patients having intense bladder activity, respectively.

Conclusion: Refraining from voiding prior to F-18-fluciclovine injection results in significantly lower urinary bladder radioactivity compared to purposeful voiding pre-injection. We have modified our

practice accordingly, particularly as moderate and intense bladder activity may mask/mimic local prostate cancer recurrence. Mechanisms underlying this phenomenon should be further investigated.

Key words: Fluciclovine, PET/CT, Bladder, Quantification, Pharmacokinetics

Introduction

Prostate cancer imaging using the synthetic amino acid analog F-18-fluciclovine (fluciclovine, FACBC, Axumin) was recently approved by the Food and Drug Administration (FDA). The synthetic amino acid fluciclovine enters the cells via amino acid transporters and is not metabolized by the cell or incorporated into protein synthesis (1). Normal biodistribution of fluciclovine includes the liver, bone marrow, pancreas, and skeletal muscles (2-5). The amino acid transporters also mediate fluciclovine reabsorption by the kidneys at the proximal tubules, which results in slow urinary excretion over time (1). Slow fluciclovine urinary excretion makes it a favorable radiotracer for pelvic tumor imaging due to reduced potential for interference from intense bladder activity, especially in the evaluation of locally recurrent prostate cancer (4, 6-10). High bladder fluciclovine activity may interfere with the evaluation of local prostate cancer recurrence, as it may mimic or mask areas of local prostate cancer recurrence. Fluciclovine prescribing information states that only 3% of administered radioactivity is excreted in the urine in the first 4 hours post-injection (11). Schuster et al. reported intense fluciclovine bladder activity (≥ liver) in 15.2% of the delayed images (approximately 30 min after radiotracer injection) performed in 128 patients who underwent fluciclovine PET/CT, yet no intense uptake was reported in early time point images (approximately 5 min after radiotracer injection) (5).

In our clinical practice, however, we have noticed a higher than expected degree of fluciclovine urinary excretion using the standard PET/CT protocol which included instructing the patient to void before radiotracer injection and commencing PET acquisition at approximately 4 min after radiotracer injection. As part of our quality control process, we decided to examine a new protocol in which the patients are not being asked to purposefully empty their bladder prior to the start of the study, in the expectation that a distended urinary bladder may mitigate the quantity and intensity of early fluciclovine excretion.

In this analysis, we retrospectively evaluated and quantified early fluciclovine bladder excretion in our clinical practice. We also examined if the proposed non-voiding imaging protocol affected bladder activity and compared these results to a subset of patients studied before we made the proposed protocol change.

Methods

Patient population

We retrospectively assessed scans of 159 patients who underwent fluciclovine PET/CT imaging at our institution as part of their clinical evaluation, from August 2016 to November 2017. This retrospective cohort analysis was approved by the Institutional Review Board and is in compliance with the Health Insurance Portability and Accountability Act and requirement to obtain the documentation of informed consent was waived.

Imaging Protocol

PET/CT images were acquired on an Ingenuity Time of Flight PET/CT scanner (Philips, Andover, Massachusetts). All patients were instructed to fast for 4 to 6 hours prior to the injection of fluciclovine. Patients were allowed to have water with medications. Fluciclovine (PETNET Solutions, Des Plaines, IL; Louisville, KY) was injected into patients while in the PET/CT scanner as an intravenous bolus injection with arms down, followed by a flush of sterile 0.9% sodium chloride injection. The mean dose ± SD was 370 ± 44.4 MBq, range 173.9 – 425.5 MBq. The patients subsequently underwent a CT scan from the mid-thigh to the skull base in a supine position, with arms up, without oral or intravenous contrast. Using a stopwatch, PET image acquisition began at exactly 4 min after injection, from the mid-thigh to the skull base, in a supine position, with arms up. The first 36 patients were instructed to empty their bladder prior to the injection of fluciclovine as part of the standard protocol. As we noticed a high

number of patients have unexpectedly high urinary fluciclovine excretion, we changed the protocol prospectively to eliminate purposeful voiding prior to the scan, as part of our clinical quality control. Thus, the subsequent 123 patients were no longer requested to void immediately prior to the scanning.

Image Analysis

Images were reviewed on Hermes Gold workstations (Hermes Medical Solutions, Stockholm, Sweden). Based on visualization, bladder radioactivity was defined positive if the bladder could be visualized on the maximum intensity projection (MIP) images. Subsequently, quantitative data were collected: The maximum standardized uptake value (SUV_{max}) and mean standardized uptake value (SUV_{mean}) of the bladder cavity, aorta, marrow (at the level of L3) and liver were recorded. Bladder cavity SUV_{mean} was compared to the SUV_{mean} of the aorta, marrow, and liver. Bladder excretion "activity" was characterized as "Insignificant activity" (bladder < aorta), "Mild activity" (bladder ≥ aorta, < marrow), "Moderate activity" (bladder ≥ marrow, < liver) and "Intense activity" (bladder ≥ liver) (Figure 1). Subsequently, the patients were divided into two groups according to the different imaging protocol: "Voiding protocol" (patients voided just before fluciclovine injection), "Non-voiding protocol" (patients were not requested to void prior to fluciclovine injection). The bladder activities were calculated for all the patients. Bladder 3D volumes were measured using Volume of Interest Interpolation tool of Hermes 3D software.

Statistics

Data analysis was conducted on STATA 15 (StataCorp LLP) statistics software. All continuous variables were expressed as median, with related interquartile range (IQR). A Wilcoxon rank-sum test was used to compare the differences between the demographic characteristics of the patients in two different protocol groups, including age, fluciclovine dose, and the medians of bladder activity, volume and background SUV_{max} and SUV_{mean}. Pearson Chi-square test was used to compare the statistical significance between bladder activity levels in each protocol group. Spearman correlation between

bladder volume and bladder SUV_{mean} was performed. A p-value of less than 0.05 was considered to be statistically significant.

Results

Demographics

159 patients were included in this analysis. The median (IQR) patients' age was 69 (64, 73) years. The median SUV_{mean} (IQR) of the bladder was 1.6 (1.6, 3.6). Median (IQR) bladder to aorta, bladder to marrow, and bladder to liver ratios were 1.1 (0.4, 2.3), 0.52 (0.2, 1.1) and 0.5 (0.2, 1.1), respectively. All demographic characteristics and measured activities are summarized in Table 1.

Overall bladder activity

Based on subjective visualization, the bladder radioactivity was noticed on the MIP images in 53.5% (85/159) of patients. Based on quantitation, insignificant radioactivity in the bladder was found in 48.4% (77/159) of patients, mild activity in 20.8% (33/159) of patients, moderate in 22.0% (35/159) of patients, and 8.8% (14/159) of patients had intense bladder activity (Table 1). A significant negative association was found between bladder volumes and bladder SUV_{mean} (r_s=-0.64, p<0.001) (Figure 2). Significantly larger volumes were noted in the insignificant bladder activity group and smaller volumes in the intense bladder activity group (p<0.001).

Effect of voiding protocol on bladder activity

Among 159 patients, 36 patients were imaged with the voiding protocol and 123 patients were imaged with the non-voiding protocol. Among the voiding protocol patients, the bladder $SUV_{max,}$ SUV_{mean}, and bladder to background ratios were significantly higher than in the non-voiding protocol patients (Table 2). The median SUV_{max} (IQR) and SUV_{mean} (IQR) of the bladder between the voiding and the non-voiding

protocols were 4.9 (3.4, 8.1) and 2.8 (2.1,6.0) vs. 2.1 (1.1, 5.6) and 1.3 (0.5, 2.8), respectively ($p \leq 0.001$) (Figure 3a). Medians (IQR) of bladder to aorta, bladder to marrow, and bladder to liver ratios between the voiding protocol and the non-voiding protocol were 2.2 (1.5, 4.49) vs. 0.8 (0.4, 1.8), 1.1 (0.6, 2.2) vs. 0.4 (0.2, 0.9) and 0.4 (0.2, 0.7) vs. 0.2 (0.1, 0.3), respectively ($p<0.001$).

Among the patients in the voiding protocol, the bladder was visualized on the MIP images in a significantly higher number of scans: 77.8% (28/36) of scans in the voiding protocol and only 46.3% (57/123) in the non-voiding protocol ($p<0.001$).

A significantly higher number of patients with intense bladder activity and a significantly lower number of patients with insignificant bladder activity were found among patients in the voiding protocol, and the reverse was found among patients in the non-voiding protocol (Figure 3b). For patients in the voiding protocol, insignificant bladder activity was found in only 19.4% (7/36) of patients and 22.2% (8/36) of patients had intense bladder activity. For patients in the non-voiding protocol, insignificant bladder activity was found in 56.9% (70/123) of patients and only 4.6% (6/123) of patients had intense bladder activity ($p<0.001$). No significant differences were found for the frequencies of the mild bladder activities between the two protocols (Table 2).

Overall, lower bladder volumes were associated with the voiding protocol group compared with the non-voiding protocol group, with median volume (IQR) of 18.0 (12.6, 30.6) ml vs. 51.9 (25.4, 87.1) ml, respectively ($p<0.001$). For the insignificant and mild bladder activities, the volumes were also significantly lower in the voiding protocol group ($p<0.05$). However, for the moderate and intense bladder activities, no significant differences in volume were observed between the voiding and non-voiding protocol groups ($p>0.05$).

Discussion

This retrospective comparative study was prompted by our observation that in our clinical practice, there was relatively higher-than-expected fluciclovine urinary excretion into the bladder compared to what was reported in the published literature. Moreover, we observed that this effect seemed to be minimized by a simple change in protocol in which patients were not instructed to void before fluciclovine injection and imaging. In this analysis, we sought to quantify the incidence and degree of early fluciclovine urinary excretion into the bladder and to determine if the changes we applied to our patient preparation protocol (as part of our quality control effort) mitigated bladder activity. Our analysis confirmed that when we stopped asking the patients to void prior to the injection of fluciclovine, we observed a significantly lower number of patients with increased bladder activity ($p<0.05$).

Our findings are important since intense fluciclovine activity in the bladder, though usually visually less bothersome than that seen with FDG, for example, may still interfere with the evaluation of local prostate cancer recurrence. For example, fluciclovine activity in the bladder or urethra may mimic or obscure suspicious activity in the prostate or prostate bed. Our findings related to the degree and extent of early fluciclovine urinary bladder activity differ from available literature (2, 4). Schuster et al. investigated bladder activity among 128 patients that underwent fluciclovine PET/CT and reported moderate fluciclovine bladder activity (≥ marrow) in only 3.1% of the scans at 5 min post-injection and no intense activity (≥ liver). Schuster also reported moderate and intense bladder activity in 59.1% and 14.2% of patients, respectively, but only at a delayed time point of 17 min post-injection (5). We documented moderate and intense bladder activity in 38.9% and 22.2% patients, respectively, in a clinical protocol commencing scanning at 4 min post radiotracer injection in which patients are instructed to void before injection, as they had been instructed in the referenced research studies. Yet,

when patients were not instructed to void before radiotracer injection, moderate and intense bladder activity was present in only 17.1% and 4.9% of patients, respectively.

Fluciclovine is advantageous for prostate cancer recurrence imaging, particularly due to its low urinary excretion compared with other radiotracers (1, 4, 12). Fluciclovine biodistribution in clinical studies demonstrated only minimal and slow urine exertion (2). This phenomenon of sporadic increased early bladder excretion of fluciclovine in research patients, though not to the degree we have seen clinically, had been investigated by Amzat et al., including its correlation with radiotracer dose, body mass index, body weight, blood urea nitrogen, creatinine, glucose, and routine urinalysis, as well as radiotracer activity in liver, marrow, muscle, and blood pool (13). A subset of patients underwent thin layer chromatography of their urine. The investigators concluded that the bladder activity reflected a lack of reabsorption of the parent compound in the kidney. Of the investigated parameters, only proteinuria was associated with higher bladder activity in the entire cohort, yet it was not present in the majority of patients with abnormal bladder activity (defined as greater than marrow for this analysis). Recent work by Ono et al. investigated the mechanism of fluciclovine reabsorption by the kidneys and found that its slow urinary excretion is mediated in part by reuptake via amino acid transporters, but not by drug transporters such as P-glycoprotein. The group reported that alanine-serine-cysteine amino acid transporters, including alanine-serine-cysteine transporter type 2 (ASCT2), are likely the primary transporters responsible for fluciclovine reuptake by renal proximal tubules (1).

Based on earlier work and our current analysis, as best as we can determine, the observation of increased bladder activity likely represents relatively earlier urinary excretion of the parent radioligand similar to what had been reported at delayed imaging in research patients (5, 13). This phenomenon is likely secondary to differences in renal reuptake kinetics mediated by amino acid transporters, yet the

exact reason for these differences is not fully understood. Validation studies demonstrated that the fluciclovine molecular structure of the commercial and research preparation, as well as radiochemical purity and identity, is the same, and the complex demonstrated excellent stability over a wide range of radioactivity concentrations (personal communication, Blue Earth Diagnostics Ltd). As demonstrated in the bladder uptake and volume scatterplot graph (figure 2), there is a negative association between bladder volume and bladder SUV_{mean}. Thus, the high bladder excretion phenomenon seen in the manufactured radiotracer may be mitigated by a distended bladder. It may be that under less carefully controlled conditions and patient population than what was present in the research studies, this phenomenon is now seen to a greater degree in clinical patients, but this would require further study.

Though the mechanism of early fluciclovine bladder activity is not fully understood, there is a need to investigate different methods to minimize bladder visualization, since higher bladder activity may interfere with interpretation in some instances. Therefore, we examined a tailored protocol to address these findings. Our proposed protocol of not asking patients to void prior to fluciclovine injection significantly decreased bladder activity and helped to maintain acceptable target to background ratio within the pelvis allowing better evaluation of local prostate cancer recurrence as a result. For the non-voiding protocol scans, we demonstrated a lower bladder activity and a negative correlation with the bladder volume. As a result, we have adopted the new protocol in our routine clinical practice (14,15). While we do not suggest that refraining from voiding changes the mechanism of fluciclovine urinary excretion, we hypothesize that bladder distension might mitigate the effect of urinary radiotracer excretion into the bladder by a combination of two proposed mechanisms. The first hypothesis is that in men who did not void prior to fluciclovine administration, the resultant higher volume of urine in the bladder results in a lower concentration of radioactivity in the bladder. This is consistent with a reported lower concentration of FDG in the urine of rats and humans when the bladder was distended by the use

of a hydrochlorothiazide and furosemide diuretics, retrospectively (16, 17). The second hypothesis is that elevated pressure in the urinary collecting system secondary to a full bladder may result in slower fluciclovine urinary excretion. This theory could be derived from the known effects of mechanical obstruction on renal function such as, reduced glomerular filtration rate, decreased renal plasma flow and profound changes in renal tubular cell function (18).

Two major limitations of this study are the lack of prospective controls randomized to voiding or not voiding, and the lack of urinalysis data. This protocol was devised as part of our clinical practice quality control to limit the visualized bladder activity, and not as a prospective study. Therefore, we did not collect the urine to evaluate the percentage of urinary excreted fluciclovine or its urine concentration in each patient. The use of diuretics in each patient was also not known. Unlike the research studies, we do not obtain dual or triple time point imaging which would help in the analysis of the bladder activity over time. Also, in our department, a restroom is available in the patient waiting area, so we cannot fully account for patients on the non-voiding protocol voiding just before the scan without our knowledge.

For the intense bladder activity group, overall, we found statistically lower bladder volumes compared to other bladder activity groups. However, no significant volume differences were found in the intense activity classification between the voiding and non-voiding protocol groups. In fact, all 6 patients with intense bladder activity in the non-voiding protocol had a contracted bladder, with only minimal urine volume (average volume (SD) measured was 23 ml ± (7.6) and Median (IQR) of 24.4 (17.7, 27.2)). This finding suggests these patients may have voided before the scan without our knowledge, thus affecting our final analysis.

Conclusion

Fluciclovine urinary excretion was found to be higher than expected in our clinical practice compared to that reported in research studies. Voiding just prior to the injection of fluciclovine may increase the potential for visualized bladder activity. Refraining from voiding prior to the fluciclovine injection and scan has resulted in a significant decrease in bladder radiotracer activity. The resulting decrease in the number of scans with intense bladder activity makes the image interpretation more convenient and improves the evaluation of the prostate/prostate bed. Hence, we have adopted the new protocol in our routine clinical practice. Mechanisms underlying this phenomenon should be further investigated.

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Figures

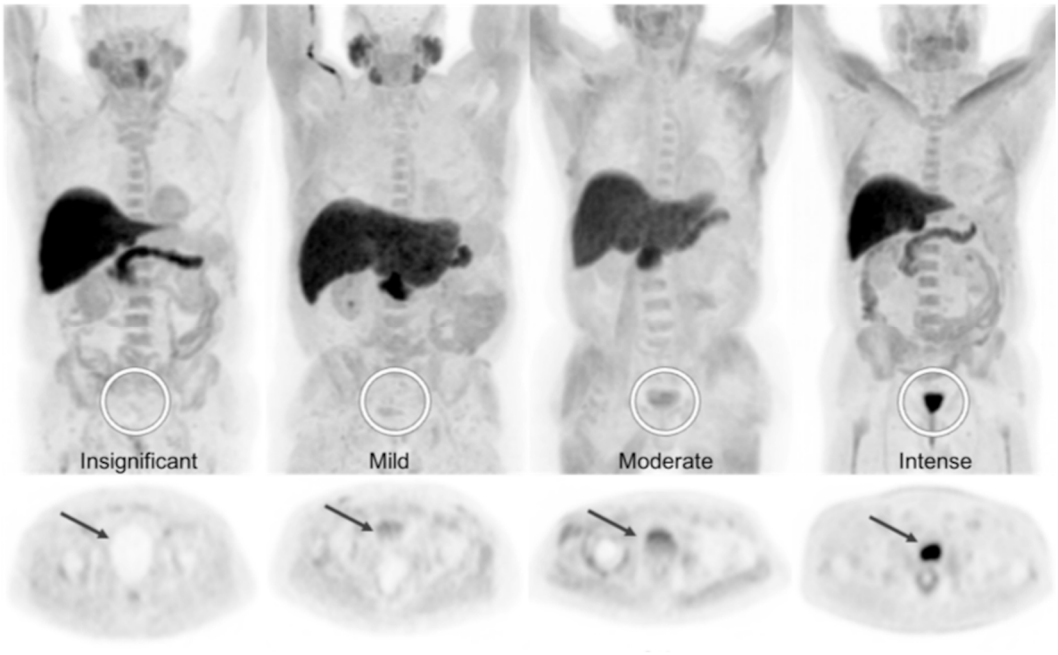

FIGURE 1. Groups of Bladder Activity – SUV_{max} threshold in all images is 7.0

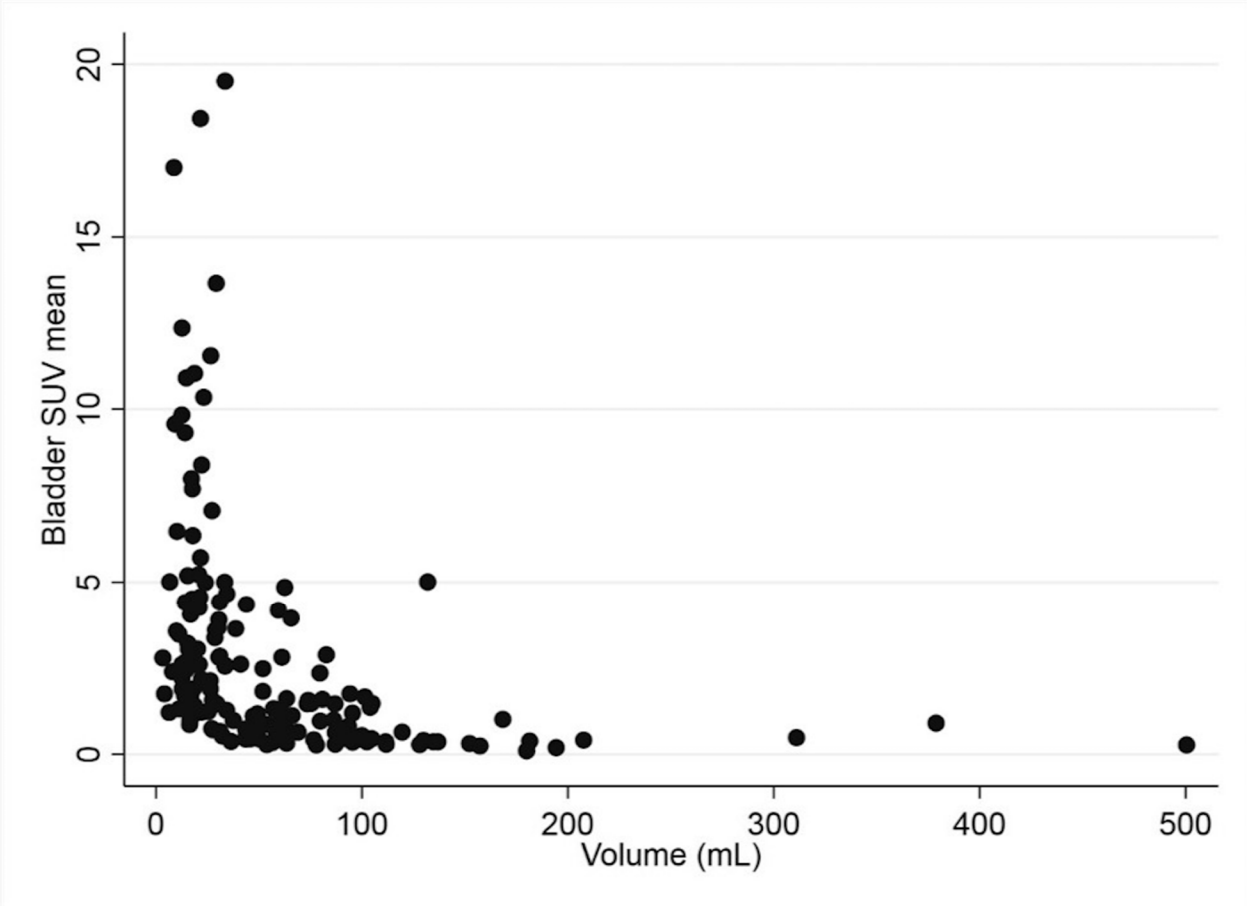

FIGURE 2. Bladder radioactivity and volume scatterplot. Spearman (r^s=-0.64, p<0.001)

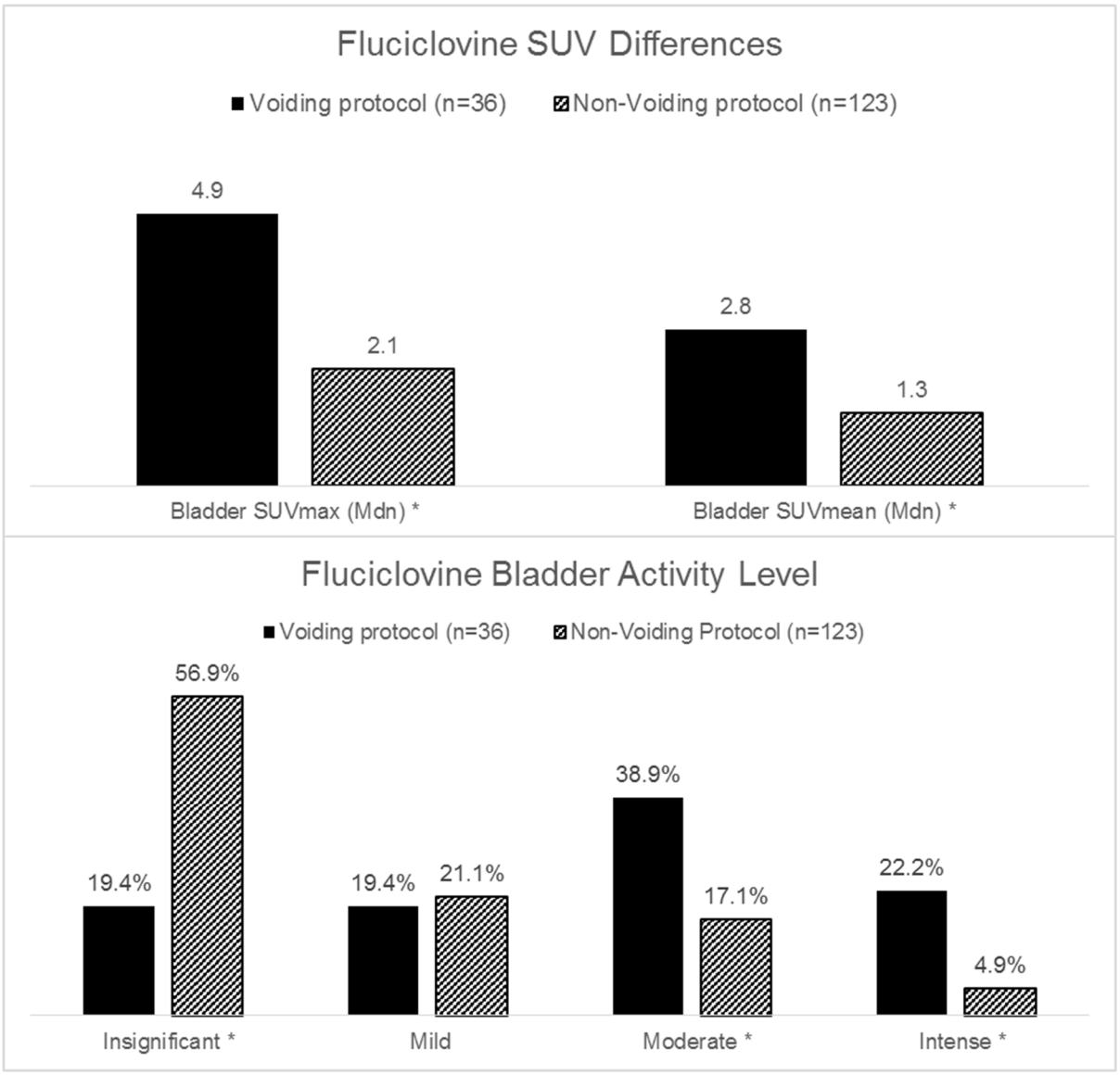

*FIGURE 3a. Bladder SUV_{max} and SUV_{mean} difference between protocols; 3b. Distribution of different bladder activity groups between protocols; * indicates a statistically significant difference ($p<0.05$)*

Tables

DEMOGRAPHICS (N=159)	**Median (IQR)**
Age (years)	69 (64, 73)
Fluciclovine dose (MBq)	381.1 (362.6, 392.2)
Aorta SUV_{mean}	1.6 (1.4, 1.8)
Marrow SUV_{mean}	3.3 (2.7, 3.9)
Liver SUV_{mean}	8.6 (7.5, 10.3)
Bladder SUV_{max}	3.1 (1.1, 6.0)
Bladder SUV_{mean}	1.6 (1.6, 3.6)
Bladder SUV_{mean} / Aorta SUV_{mean} Ratio	1.1 (0.4, 2.3)
Bladder SUV_{mean}/ Marrow SUV_{mean} Ratio	0.5 (0.2, 1.1)
Bladder SUV_{mean} / Liver SUV_{mean} Ratio	0.2 (0.1, 0.5)
BLADDER RADIOACTIVITY	**Percent**
Bladder visualized on MIP	53.5% (85/159)
Quantitation	
Insignificant (Bladder SUV_{mean} < Aorta SUV_{mean})	48.4% (77/159)
Mild (Bladder SUV_{mean} ≥ Aorta SUV_{mean}, < Marrow SUV_{mean})	20.8% (33/159)
Moderate (Bladder SUV_{mean} ≥ Marrow SUV_{mean}, < Liver SUV_{mean})	22.0% (35/159)
Intense (Bladder SUV_{mean} ≥ Liver SUV_{mean})	8.8% (14/159)
BLADDER Volume (ml)	**Median (IQR), p-value**
Bladder Volume (n=159)	34.4 (18.6, 77.9)
Insignificant (n=77)	64.9 (43.7, 102.4), p<0.001
Mild (n=33)	26.4 (16.9, 62.5), p=0.004
Moderate (n=35)	20.7 (14.2, 30.9), p<0.001
Intense (n=14)	20.2 (14.1, 26.3), p<0.001

TABLE 1. Demographics and overall bladder activity and volume; IQR = Interquartile range (25^{th}-75^{th} percentile)

	Voiding Protocol (N=36)	Non-Voiding Protocol (N=123)	P-value
DEMOGRAPHICS	**Mdn (IQR)**	**Mdn (IQR)**	
Age (years)	67 (67, 63)	69 (64, 74)	0.21
Fluciclovine dose (MBq)	381.1 (362.6, 399.6)	381.1 (362.6, 392.2)	0.49
Aorta SUV_{mean}	1.5 (1.3,1.6)	1.6 (1.4, 1.8)	0.003
Marrow SUV_{mean}	3.2 (2.7,3.8)	3.4 (2.7, 4.0)	0.12
Liver SUV_{mean}	8.4 (7.5, 9.5)	8.7 (7.5, 10.3)	0.31
Bladder SUV_{max}	4.9 (3.4, 8.1)	2.1 (1.1, 5.6)	0.001
Bladder SUV_{mean}	2.8 (2.1, 6.0)	1.3 (0.5, 2.8)	<0.001
Bladder SUV_{mean} /Aorta SUV_{mean} Ratio	2.2 (1.5, 4.4)	0.8 (0.4, 1.8)	<0.001
Bladder SUV_{mean} /Marrow SUV_{mean} Ratio	1.1 (0.6, 2.2)	0.4 (0.2, 0.9)	<0.001
Bladder SUV_{mean} /Liver SUV_{mean} Ratio	0.4 (0.2, 0.7)	0.2 (0.1, 0.3)	<0.001
Volume (ml)	18.0 (12.6, 30.6)	51.9 (25.4, 87.1)	<0.001
BLADDER RADIOACTIVITY (%)	**Percent**	**Percent**	
Bladder visualized on MIP	77.8% (28/36)	46.3% (57/123)	<0.001
Quantitation			
Insignificant (Bladder SUV_{max} < Aorta SUV_{mean})	19.4% (7/36)	56.9% (70/123)	<0.001
Mild (Bladder SUV_{mean} ≥ Aorta SUV_{mean}, < Marrow SUV_{mean})	19.4% (7/36)	21.1% (26/123)	0.826
Moderate (Bladder SUV_{mean} ≥ Marrow SUV_{mean}, < Liver SUV_{mean})	38.9% (14/36)	17.1% (21/123)	0.005
Intense (Bladder SUV_{mean} ≥ Liver SUV_{mean})	22.2% (8/36)	4.9% (6/123)	<0.001
BLADDER Volume (ml)	**Mdn (IQR)**	**Mdn (IQR)**	**P-value**
Insignificant	36.5 (16.5, 66.0)	71.2 (49.2, 104.8)	0.039
Mild	15.4 (8.0, 18.1)	31.1 (21.0, 73.9)	0.015
Moderate	19.0 (12.60, 30.11)	20.9 (15.5, 30.9)	0.381
Intense	18.2 (12.6, 22.4)	24.4 (17.7, 27.2)	0.196

TABLE 2. Quantification differences and fluciclovine bladder activity comparison between two different protocol groups. Mdn = Median. IQR = Interquartile range (25th-75th percentile)