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Head-to-head comparison of ^{68}Ga -PSMA-11 and ^{18}F -Fluciclovine PET/CT in a case series of 10 patients with prostate cancer recurrence

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ABSTRACT

Purpose: This is a head-to-head comparison between Gallium-68 Prostate Specific Membrane Antigen (^{68}Ga -PSMA-11) and ^{18}F -Fluciclovine Positron Emission Tomography/Computed Tomography (PET/CT) in a series of 10 patients with prostate cancer (PCa) recurrence. **Methods:** 288 patients with PCa recurrence were enrolled in a prospective study of ^{68}Ga -PSMA-11 PET/CT imaging for recurrent disease localization (NCT02940262). We retrospectively identified 10 patients who underwent clinical indicated ^{18}F -Fluciclovine PET/CT prior enrollment. **Results:** The median time between both scans was 2.3 months (range 0.2-4.2). The median PSA value was 1.0 ng/ml (mean 4.7 ng/ml; range 0.13-18.1) and 1.1 ng/ml (mean 6.2 ng/ml; range 0.24-31.3) at the time of ^{18}F -Fluciclovine and ^{68}Ga -PSMA-11 PET/CT, respectively. 5/10 patients (50%) were negative on ^{18}F -Fluciclovine PET/CT but showed positive results on ^{68}Ga -PSMA-11 PET/CT. 2/10 patients (20%) had both positive ^{18}F -Fluciclovine and ^{68}Ga -PSMA-11 PET/CT but ^{68}Ga -PSMA-11 PET/CT showed additional lymph nodes (LN) metastasis. 3/10 patients (30%) had both negative ^{18}F -Fluciclovine and ^{68}Ga -PSMA-11 PET/CT. **Conclusion:** This case series suggests improved detection rates of ^{68}Ga -PSMA-11 when compared to ^{18}F -Fluciclovine PET/CT in patients with recurrent PCa. Prospective trials designed to directly compare ^{68}Ga -PSMA-11 and ^{18}F -Fluciclovine PET/CT should be initiated.

INTRODUCTION

Localizing recurrent PCa with PET/CT imaging is clinically relevant as these patients can undergo salvage therapies with curative intent (1). Identifying recurrence site(s) with a high accuracy is important to select the best therapeutic approach. Several molecular imaging approaches have been proposed over the last decade. The best results for assessing patients with PCa recurrence were obtained with ^{18}F -Fluciclovine and PSMA-targeted PET radiotracers (2–5).

^{18}F -Fluciclovine or Axumin™ (anti-1-amino-3- ^{18}F -fluorocyclobutane-1-carboxylic acid) is a synthetic amino acid and likely a substrate of L amino acid (LAT1 in particular) and the alanine-serine-cysteine (ASC) transporters (specifically ASCT2) (6). The results obtained of the first prospective studies led to Food and Drug Administration (FDA) approval in 2016 and to the Center for Medicare and Medicaid Service (CMS) reimbursement in 2017 for patients with PCa recurrence (7). Thus it serves as a reference standard for evaluating other PET prostate cancer approaches.

Prostate specific membrane antigen (PSMA) is a membrane bound metallo-peptidase over expressed at high levels in 90-100% of PCa lesions (8). ^{68}Ga -PSMA-11 is a highly specific urea-based inhibitor (Glu-NH-CO-NH-Lys-(Ahx)-[^{68}Ga (HBED-CC)]) that internalizes upon ligand binding (8). ^{68}Ga -PSMA-11 PET/CT demonstrates high efficacy in restaging PCa and is thus widely used in clinical trials and routine practice worldwide (2,4,9). These investigations reported also a favorable tumor to background ratio for ^{68}Ga -PSMA-11 to detect PCa lesion(s) and a high sensitivity for lesion detection even at low serum PSA values (PSA < 2ng/mL) (2).

To date there is only one single case report of a patient imaged with both ^{18}F -fluciclovine and ^{18}F -radiolabeled PSMA-ligand (^{18}F -DCFPyL) PET/CT (10) and no head-to-head comparison between ^{68}Ga -PSMA-11 and ^{18}F -Fluciclovine PET/CT has been published. Here we report the first case series of 10 patients with recurrent PCa who underwent both ^{68}Ga -PSMA-11 and ^{18}F -Fluciclovine PET/CT. While we are aware that the present case series can at best provide the impetus for a large prospective trial we nevertheless felt that these observations are worthwhile reporting.

MATERIALS AND METHODS

Patient Population

From October 2016 to November 2017, 288 patients with PCa recurrence were enrolled in a prospective study of ^{68}Ga -PSMA-11 PET/CT imaging for recurrent disease localization (NCT02940262). The institutional review board approved this study (IRB#16-001095) and all subjects signed a written informed consent. We retrospectively identified 10 patients who underwent clinical indicated ^{18}F -Fluciclovine PET/CT at other institutions within 4 months prior to ^{68}Ga -PSMA-11 PET/CT. We obtained all DICOM files and clinical reports of ^{18}F -Fluciclovine PET/CT scans to perform a head-to-head image analysis. Patient characteristics are listed in Table 1. Four patients had a history of primary surgery and salvage radiation therapy (SRT) (Patient #2, #4, #5, #10), two had primary surgery and adjuvant radiation therapy (Patient #6, #9), two had primary surgery only (Patient #7, #8) and two had undergone a primary combination therapy of external beam radiation, brachytherapy and androgen deprivation (Patients #1 and #3). All patients had prior

inconclusive or negative imaging tests within 3 months before the ^{18}F -Fluciclovine PET/CT study: CT in 6/10 patients (Patients #1, #2, #3, #8, #9, #10), mpMRI (multi-parametric magnetic resonance imaging) in 5/10 patients (Patients #2, #4, #5, #7, #8), ^{18}F -Fluoride PET/CT in 5/10 (Patients #1, #3, #5, #9, #10) and ^{11}C -Choline PET/CT in 2/10 patients (Patients #2, #6).

PET/CT Imaging Acquisition

^{68}Ga -PSMA-11 PET/CT imaging was performed according to recent guidelines (11) with a 64-detector PET/CT device (Biograph True Point 64 or Biograph mCT; Siemens). ^{68}Ga -PSMA-11 was used as the PSMA ligand (8). The median injected dose was 196 MBq (range 137-322 MBq). To reduce bladder activity patients received 20 mg of intravenous furosemide at the time of tracer injection. The median uptake period was 62 min (range 53-68 min). A diagnostic CT scan (200-240 mAs, 120 kV) was performed after intravenous injection of contrast agent (if no contraindication) followed by the whole body PET image acquisition (2-4 min/bed position).

^{18}F -Fluciclovine PET/CT was performed at each site according to manufacturer dosing and administration guidelines (6). ^{18}F -Fluciclovine was manufactured by automated radio synthesis (12). Patients were scanned after avoiding significant exercise for at least 24 h to minimize the muscular background, after fasting for at least 4 h to normalize amino acid levels and immediately after voiding. The median injected dose was 371 MBq (range 337-396). The median uptake period was 4 min (range 2-15 min). A non-diagnostic CT scan PET was performed for attenuation correction followed by PET image acquisition (5 min/bed position in the pelvis, 3 min/bed position in the remainder of the body).

PET/CT Imaging Analysis

^{18}F -Fluciclovine and ^{68}Ga -PSMA-11 PET/CT images were co-registered and analyzed by an experienced nuclear medicine physician according to recent recommendations (6,11,13) using OsiriX: any focal uptake above surrounding background and not associated with physiological uptake or known pitfalls (14) was considered suspicious for malignancy. Based on TNM staging the following regions were systematically analyzed: prostate bed/ seminal vesicle remnants (T), pelvic LN (N) (internal Iliac, obturator, external Iliac, perirectal, pre-sacral, common Iliac), extra-pelvic LN (M1a) (retro-peritoneal, inguinal, chest, other), bone (M1b) and other visceral organs (M1c).

RESULTS

PET/CT results and detailed findings are listed in Tables 1 and 2. The median time between both scans was 2.6 months (range 0.2-4.2). The median PSA value was 1.0 ng/ml (mean 4.7 ng/ml; range 0.13-18.1) and 1.1 ng/ml (mean 6.2 ng/ml; range 0.24-31.3) at the time of ^{18}F -Fluciclovine and ^{68}Ga -PSMA-11 PET/CT, respectively. Recurrence sites were localized by ^{18}F -Fluciclovine PET/CT in only 2/10 patients (20%) while ^{68}Ga -PSMA-11 PET/CT detected recurrence sites in 7/10 patients (70%). Five of 8 patients (63%) with negative ^{18}F -Fluciclovine PET/CT studies had positive ^{68}Ga -PSMA-11 PET/CT findings (Patients #1, #2, #5, #9, #10). One patient had positive findings for local recurrence on both scans but the ^{68}Ga -PSMA-11 PET/CT study revealed additional extra-pelvic LN involvement (Patient #3). One patient had positive findings for single external iliac LN

recurrence on both scans but the ^{68}Ga -PSMA-11 PET/CT study revealed additional obturator LN involvement (Patient #7). Three patients had concordantly negative scans (Patient #4, #6, #8). No difference was observed between our ^{18}F -Fluciclovine PET/CT analysis and the original ^{18}F -Fluciclovine PET/CT clinical reports.

Specifically, the 5 patients with negative ^{18}F -Fluciclovine but positive ^{68}Ga -PSMA-11 PET/CT study had the following findings. Patient #1 had multiple PSMA-positive lesions involving a small right external iliac LN (5 mm, SUVmax 7.7), multiple small retroperitoneal LN (4 to 5 mm, SUVmax 17), a right hilar LN (SUVmax 4) and a focal T8 vertebrae bone lesion (Fig. 1). He then received androgen deprivation therapy (ADT). In patient #2 intense PSMA-11 uptake in a solitary osteoblastic T11 lesion (SUVmax 6) and faint PSMA-11 uptake in multiple bilateral common iliac and presacral LN (6 to 8 mm, SUVmax 2.0), as well as multiple bilateral lung nodules (6-10 mm, SUVmax 2.6) were evident (Fig. 2). He received proton therapy focused on T11 metastasis and refused any systemic treatment. In patient #5, four small perirectal LN showed mild PSMA-11 uptake (3 to 4 mm, SUVmax 2.9) (Fig. 3). His referring physician opted for active surveillance. In Patient #8 intense PSMA-11 uptake in multiple left pelvic LN (4 to 8 mm, SUVmax 12.6), retroperitoneal LN (4 to 6 mm, SUVmax 10.3) and supra-diaphragmatic LN (4 to 8 mm, SUVmax 16.1) were seen (Fig. 4). The patient received ADT. Finally, Patient #10 had a single tiny right upper common iliac LN with intense PSMA-11 uptake (3 mm, SUVmax 5.3) (Supplemental Fig. 1). He received focused ablative RT and ADT initiation was put on hold.

The two patients with a positive ^{18}F -Fluciclovine PET/CT study had the following findings. Patient #3 had a small Fluciclovine-positive local recurrence (SUVmax 3.5)

whereas ^{68}Ga -PSMA-11 PET/CT showed a much larger local recurrence with intense uptake (SUVmax 8.9). Moreover, ^{68}Ga -PSMA-11 PET/CT demonstrated additional abnormal retroperitoneal LNs (8 to 10 mm, SUVmax 4.7) (Fig. 5; Supplemental Fig. 2). The patient received ADT. Patient #7 had a Fluciclovine-positive right external iliac LN recurrence (7 mm, SUVmax 4.9). ^{68}Ga -PSMA-11 uptake was much more intense (SUVmax 8.9). In addition, ^{68}Ga -PSMA-11 PET/CT demonstrated an additional abnormal tiny right obturator LN (4 mm, SUVmax 3.0) (Supplemental Fig. 3). The patient underwent unilateral right pelvic LN dissection. Three out of eight resected LN were positive for metastatic adenocarcinoma.

Patients #4, #6 and #8 had concordantly negative ^{68}Ga -PSMA-11 PET/CT and ^{18}F -Fluciclovine PET/CT. Patient #4 and #6 were monitored for PSA changes whereas Patient #8 underwent SRT to both prostate bed and pelvic LN.

DISCUSSION

We are aware that the results obtained in this current small case series do not indicate superiority of ^{68}Ga -PSMA-11 over ^{18}F -Fluciclovine PET/CT imaging. However, findings of the two tests were so strikingly different that we felt a brief report would be prudent. This also seemed justified, as no direct comparisons between these two tests have been published.

While 7/10 studies (70%) were positive with ^{68}Ga -PSMA-11, 8/10 ^{18}F -Fluciclovine scans were negative (80%), and disease extent was underestimated in both patients with

a positive ^{18}F -Fluciclovine studies. Surprisingly, four ^{18}F -Fluciclovine PET/CT scans were negative despite fairly extensive disease on ^{68}Ga -PSMA-11 PET/CT scans.

While extensive evidence has been established to support the use of ^{68}Ga -PSMA-11 PET/CT imaging even in patients with PCa biochemical recurrence at very low serum PSA levels (2,9) much less is known about the ^{18}F -Fluciclovine performance.

The main study which led the FDA approval for ^{18}F -Fluciclovine was a retrospective analysis of 596 patients (3). The detection rate in the whole population (mean PSA 5.43 ng/mL) was 67.7% and it was 41.4% in the lowest quartile of serum PSA levels (< 0.79 ng/ml). Several studies reported a better diagnostic performance for ^{68}Ga -PSMA-11 PET/CT (9). The high accuracy in the detection of PCa metastases at very low serum PSA levels and the high sensitivity for detecting small lesions were considered the strength of PSMA based imaging (2,4,9).

The high false negative rate of ^{18}F -Fluciclovine scans in the current patients with relatively high serum PSA levels is concerning. Bone marrow and mostly muscle background activity (Fig. 5A) may have interfered with detection of extra-prostatic lesions.

There is of course a significant selection bias in the current case series. Patients likely had negative ^{18}F -Fluciclovine PET/CT studies and were therefore referred for ^{68}Ga -PSMA-11 PET/CT. Moreover, the median time interval between both scans was 2.6 months which likely favored lesion detection with ^{68}Ga -PSMA-11 PET/CT. But the median PSA levels increase between the two scans was only 0.1 ng/ml (range 0.03-13.2).

Another important limitation is that histological confirmation of PSMA-positive lesions was available in only one patient (Patient#7) who underwent surgery. This is

because histological verification of lesions in patients with PCa recurrence is not routinely done. PSMA-positive lesions were not biopsied. Two patients received focal ablative radiation therapy after the scans (Patients #2, #10) whereas the others had non-focal treatment (ADT or SRT to both prostate bed and pelvic LN) or active surveillance. Therefore we cannot exclude that these PSMA-positive lesions were in fact false positive.

CONCLUSION

This case series suggests improved detection rates of ^{68}Ga -PSMA-11 when compared to ^{18}F -Fluciclovine PET/CT in patients with recurrent PCa. While far from definitive evidence for superiority, the observation strongly supports the initiation of prospective trials to directly compare the performance of ^{68}Ga -PSMA-11 and ^{18}F -Fluciclovine PET/CT.

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TABLES AND TABLES LEGENDS

Table 1: Patients characteristics and PET/CT scans results

PSA levels is ng/ml.

Abbreviations: XRT: External Beam Radiation therapy, Brachy. : Brachytherapy, ADT: Androgen Deprivation therapy, RP: radical prostatectomy, SRT: Salvage radiation Therapy, mpMRI: multiparametric magnetic resonance imaging, Choline: ¹¹C-Choline PET/CT, Na-F: ¹⁸F-Fluoride PET/CT; Met.: metastasis.

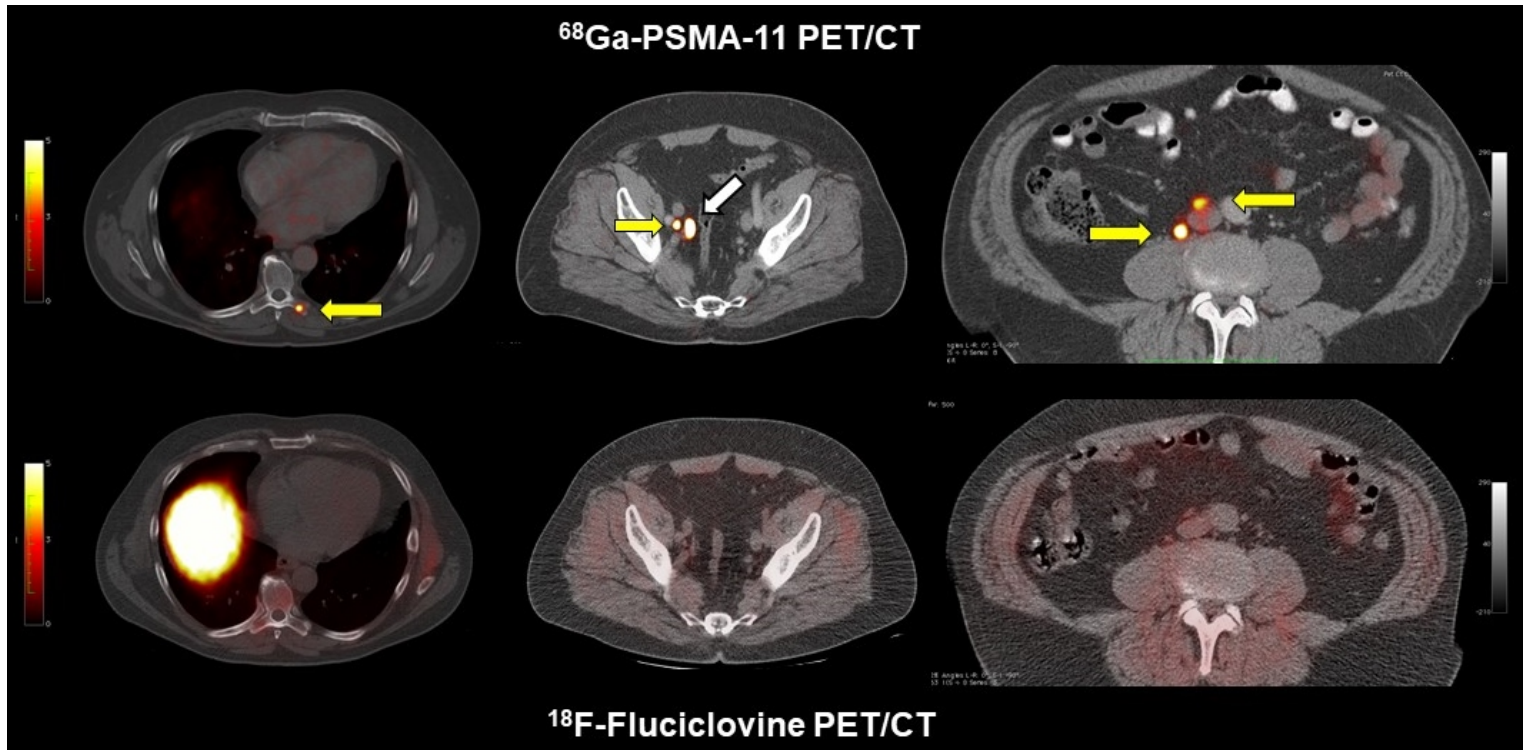
Patient Number #	Age	Initial PSA	Gleason Score	pTNM	Primary therapy	Date of primary therapy	Salvage Therapy	Date of salvage therapy	Prior Imaging within past 3 months	¹⁸ F-Fluciclovine	⁶⁸ Ga-PSMA-11	Management strategy After ⁶⁸ Ga-PSMA-11
#1	65	7.8	4+3=7	cT2c	XRT + Brachy. + ADT	2014			CT + Na-F	0	N1 M1aM1b	ADT
#2	76	7.17	4+3=7	pT3b N0 Mx	RP	2009	SRT + ADT	2012	CT + mpMRI + Choline	0	N1 M1bM1c	Proton therapy on bone met.
#3	63	20.6	4+4=8	NA	XRT + Brachy. + ADT	2015			CT+ Na-F	T+	T+ M1a	ADT
#4	72	NA	3+4=7	pT2c N0 Mx	RP	2002	SRT + ADT	2016	mpMRI	0	0	Active surveillance
#5	78	5.1	4+5=9	pT2b	RP	2009	SRT	2012	mpMRI+ Na-F	0	N1	Active surveillance
#6	67	4.5	4+5=9	pT3b, N0	RP + Adj. XRT + ADT	2015			Choline	0	0	Active surveillance
#7	72	NA	4+3=7	pT3b	RP	2017			mpMRI	N1	N1	LN dissection
#8	71	7.9	3+4=7	pT2c N0 Mx	RP	2014			CT + mpMRI	0	0	SRT
#9	74	5	NA	NA	RP + Adj. XRT	2008	ADT	2013-2017	CT+ Na-F	0	N1 M1a	ADT
#10	70	6	5+4=9	pT2 N0 Mx	RP	2011	SRT	2015	CT+ Na-F	0	N1	Ablative RT on single LN met.

Table 2 : PET/CT detailed finding.
 Abbreviations: LN: Lymph Node; Met: metastasis.

Patient Number #	PET/CT Probe	Date PET/CT	PSA at PET/CT ng/ml	Positive Scan	T	Prostate fossa (T) Analysis Detailed findings	SUV max	N	Pelvic Lymph Nodes (N) Analysis Detailed findings	SUV max	M	Extra-Pelvic (M) Analysis Detailed findings	SUV max
#1	¹⁸ F-Fluciclovine	4/12/2017	10.6	0	0			0			0		
	⁶⁸ Ga-PSMA-11	5/19/2017	10.9	1	0			1	1 External iliac LN (5 mm)	7.7	1	3 Retroperitoneal LN (4-5 mm) 1 Thoracic LN 1 Bone Met (T8)	17.1 4.4 5.1
#2	¹⁸ F-Fluciclovine	3/16/2017	12.27	0	0			0			0		
	⁶⁸ Ga-PSMA-11	6/7/2017	12.66	1	0			1	Multiple common iliac and presacral LN (6-8 mm)	2	1	Multiple Lung nodules (6-10 mm) 1 Bone Met (T11)	2.6 6
#3	¹⁸ F-Fluciclovine	3/15/2017	18.10	1	1	Faint localized uptake in left lobe	3.5	0			0		
	⁶⁸ Ga-PSMA-11	7/10/2017	31.30	1	1	Intense Diffuse Bilateral uptake	8.9	0			1	Multiple retroperitoneal LN (8-10mm)	4.7
#4	¹⁸ F-Fluciclovine	5/25/2017	1.50	0	0			0			0		
	⁶⁸ Ga-PSMA-11	7/24/2017	1.60	0	0			0			0		
#5	¹⁸ F-Fluciclovine	3/23/2017	0.22	0	0			0			0		
	⁶⁸ Ga-PSMA-11	7/31/2017	0.30	1	0			1	4 perirectal LNs (3-4 mm)	2.9	0		
#6	¹⁸ F-Fluciclovine	5/9/2017	0.13	0	0			0			0		
	⁶⁸ Ga-PSMA-11	9/15/2017	0.24	0	0			0			0		
#7	¹⁸ F-Fluciclovine	10/5/2017	0.50	1	0			1	1 External iliac LN (7 mm)	4.9	0		
	⁶⁸ Ga-PSMA-11	10/11/2017	0.65	1	0			1	1 External iliac LN (7mm) 1 Obturator LN (4 mm)	14.1 3.0	0		
#8	¹⁸ F-Fluciclovine	9/19/2017	0.30	0	0			0			0		
	⁶⁸ Ga-PSMA-11	10/25/2017	0.33	0	0			0			0		
#9	¹⁸ F-Fluciclovine	8/8/2017	3.04	0	0			0			0		
	⁶⁸ Ga-PSMA-11	10/26/2017	3.90	1	0			1	Multiple common and external iliac LN (4-8 mm)	12.6	1	Multiple retroperitoneal LN (4-6mm) Multiple thoracic LN (4-8mm)	10.3 16.1
#10	¹⁸ F-Fluciclovine	10/11/2017	0.20	0	0			0			0		
	⁶⁸ Ga-PSMA-11	11/13/2017	0.30	1	0			1	1 common iliac LN (3 mm)	5.3	0		

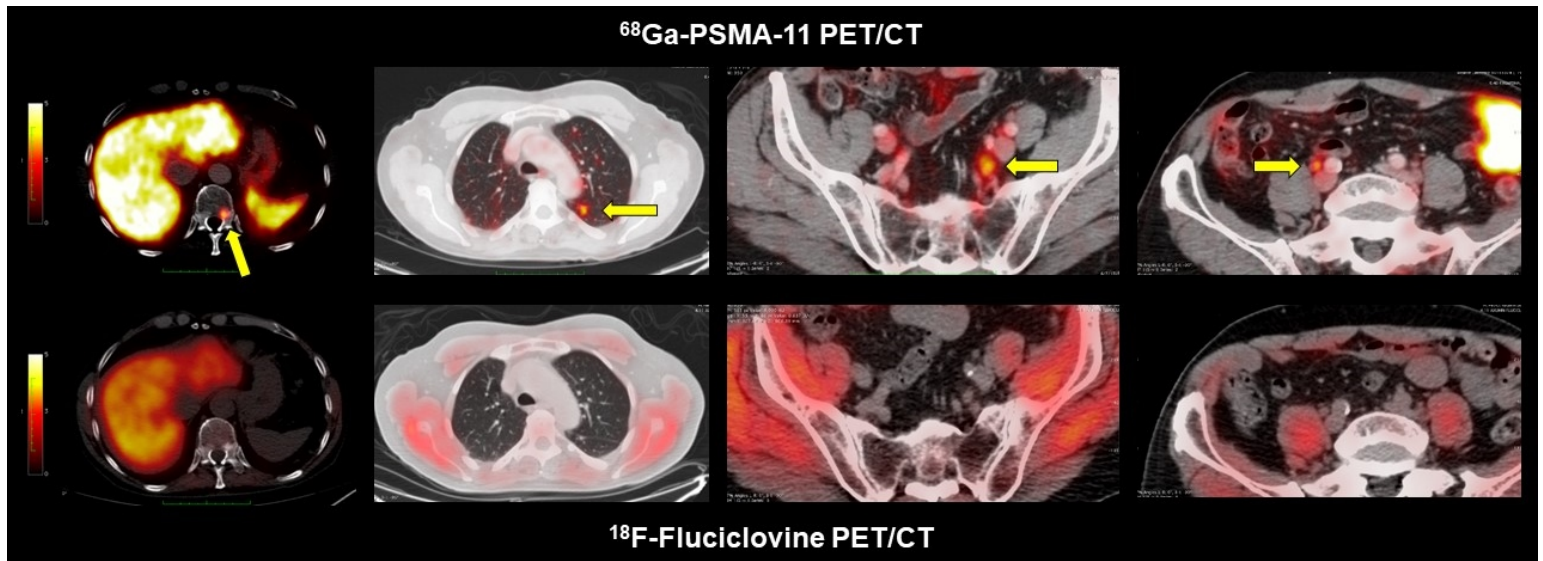
FIGURES LEGENDS

Figure 1:



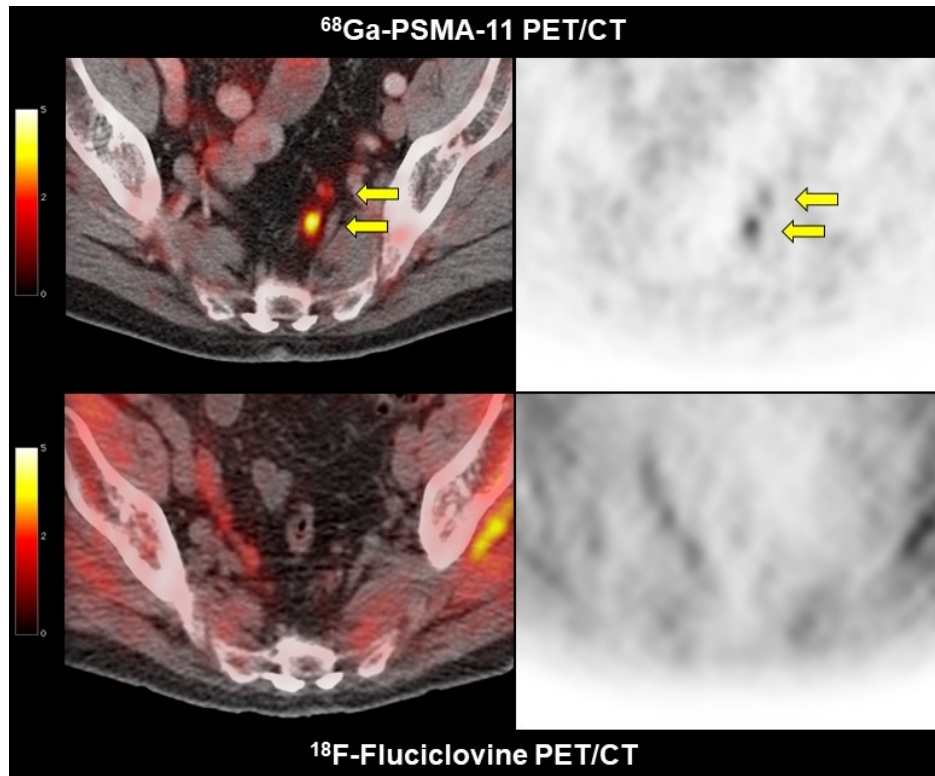
Patient #1 had a negative ¹⁸F-Fluciclovine PET/CT (bottom row) while he had a positive PSMA-11 PET/CT (top row). Yellow arrows show intense PSMA-11 uptake in a focal T8 vertebrae bone lesion, right external iliac LN (5 mm), and tiny retroperitoneal LN (4 to 5 mm). There was no ¹⁸F-Fluciclovine uptake in the corresponding structures on the ¹⁸F-Fluciclovine PET/CT. The white arrow indicates urinary excretion of PSMA-11 in a ureteral dilation.

Figure 2:



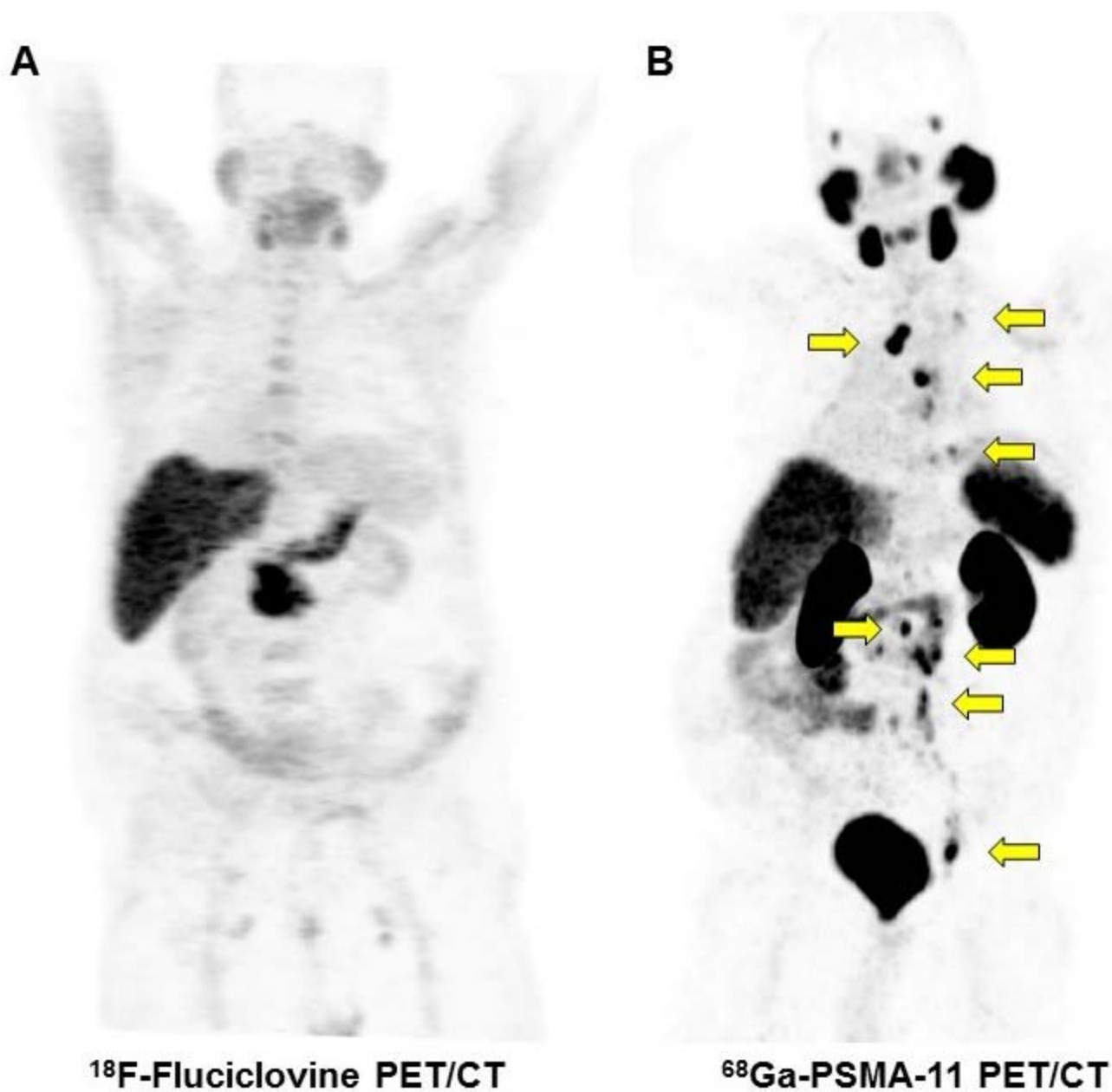
Patient #2 had a negative ¹⁸F-Fluciclovine PET/CT (bottom row) and a positive ⁶⁸Ga-PSMA-11 PET/CT (top row). Yellow arrows show PSMA-11 uptake in a T11 vertebrae bone lesion, lung micronodules, presacral LN and common iliac LN. There was no ¹⁸F-Fluciclovine uptake in the corresponding structures on the ¹⁸F-Fluciclovine PET/CT.

Figure 3:



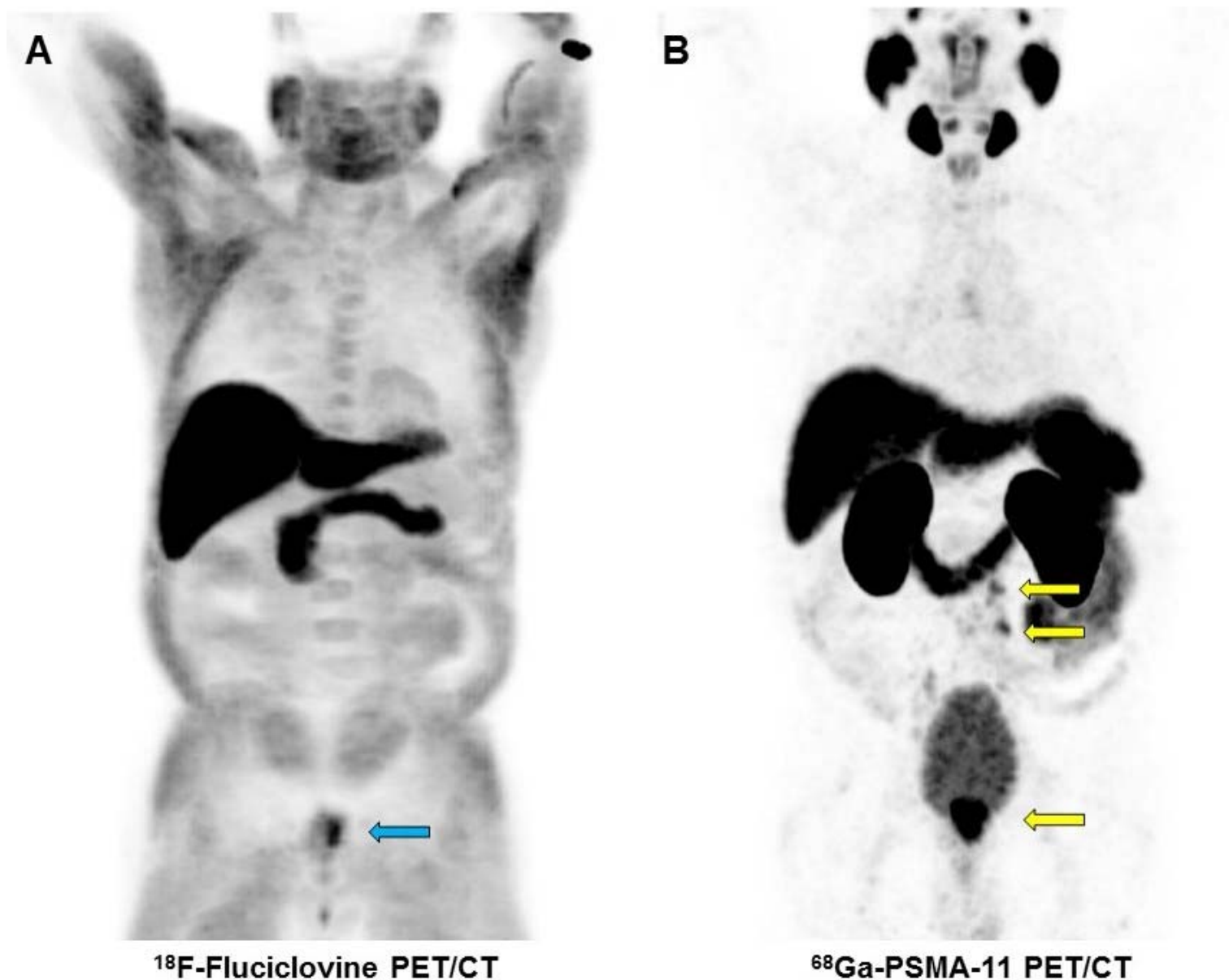
Patient #5 had a negative ¹⁸F-Fluciclovine PET/CT (bottom row) and a positive ⁶⁸Ga-PSMA-11 PET/CT (top row). Yellow arrows show PSMA-11 uptake in tiny peri-rectal LN (3 to 4 mm). The corresponding LN showed no ¹⁸F-Fluciclovine uptake.

Figure 4:



Patient #8. Maximum Intensity Projections (MIP) of ^{18}F -Fluciclovine PET (A, left panel) and ^{68}Ga -PSMA-11 PET (B, right panel). The yellow arrows (B) indicate intense PSMA-11 uptake in multiple pelvic LN, abdominal LN, thoracic LN and supra-clavicular LN. The corresponding LN showed no ^{18}F -Fluciclovine uptake (A).

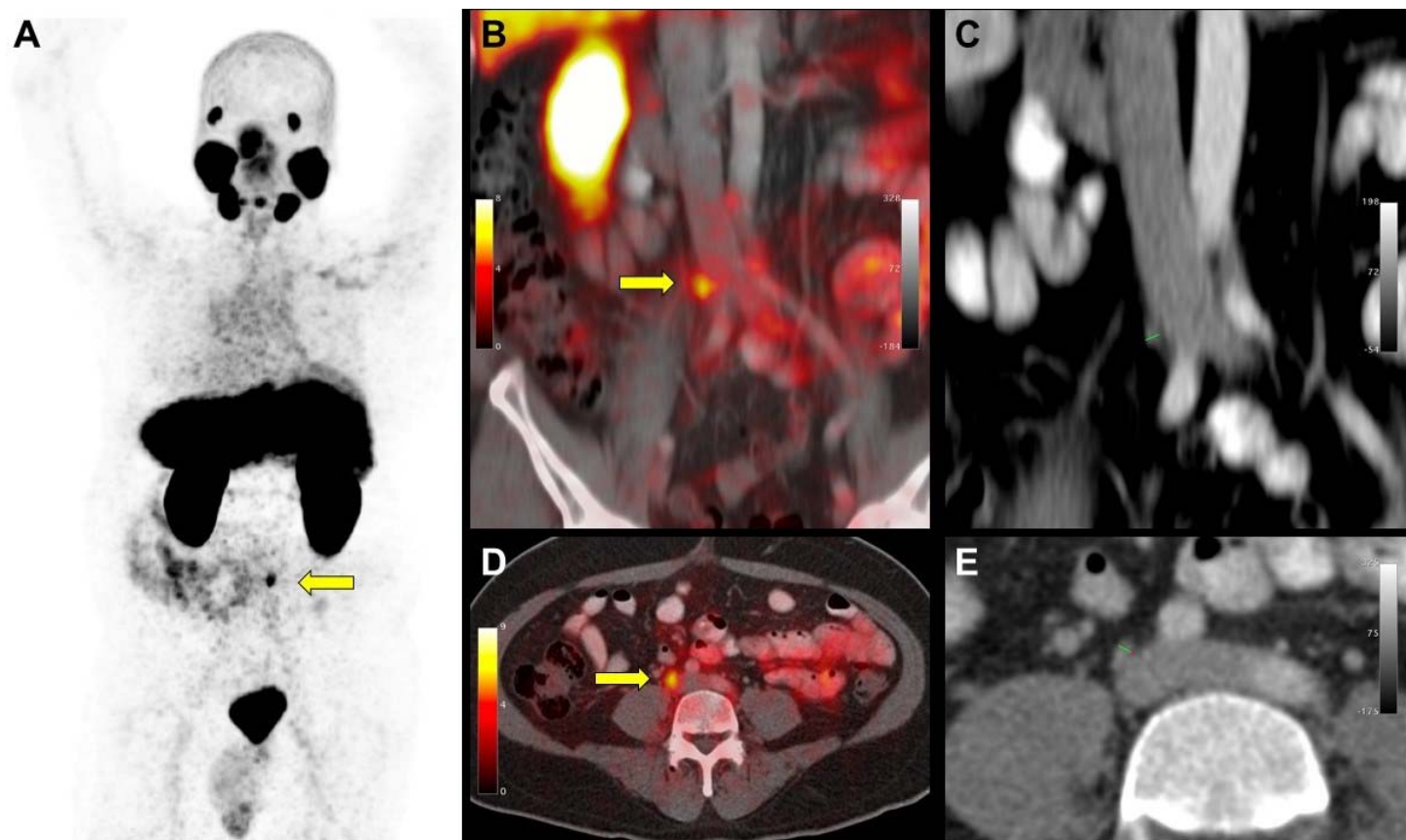
Figure 5:



Patient #3. Maximum Intensity Projections (MIP) of ^{18}F -Fluciclovine PET (A, left panel) and ^{68}Ga -PSMA-11 PET (B, right panel). The blue arrow (A) indicates a faint and limited uptake of ^{18}F -Fluciclovine in the left prostate gland. The yellow arrows (B) indicate diffuse and intense ^{68}Ga -PSMA-11 uptake in the prostate gland and in extra-pelvic LN.

SUPPLEMENTAL FIGURES LEGENDS

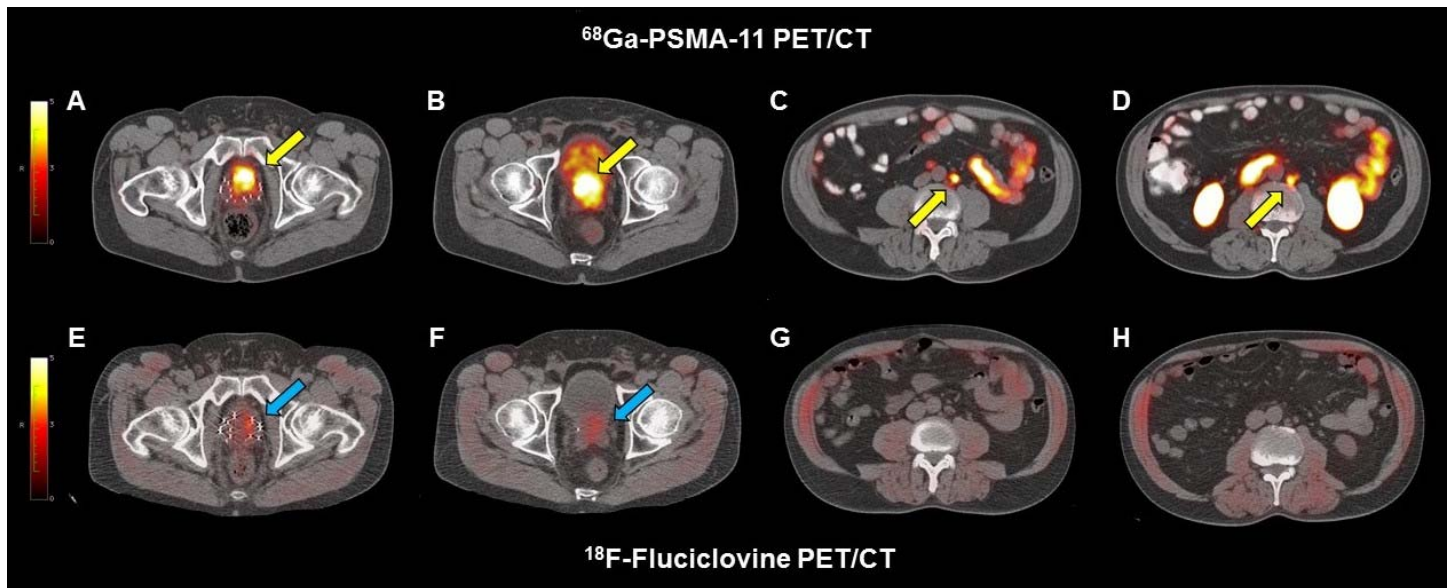
Supplemental Figure 1:



Patient #10. Patient #10 had a negative ^{18}F -Fluciclovine PET/CT scan a positive ^{68}Ga -PSMA-11 PET/CT. Yellow arrows show PSMA-11 uptake in a single tiny right upper common iliac LN (3 mm).

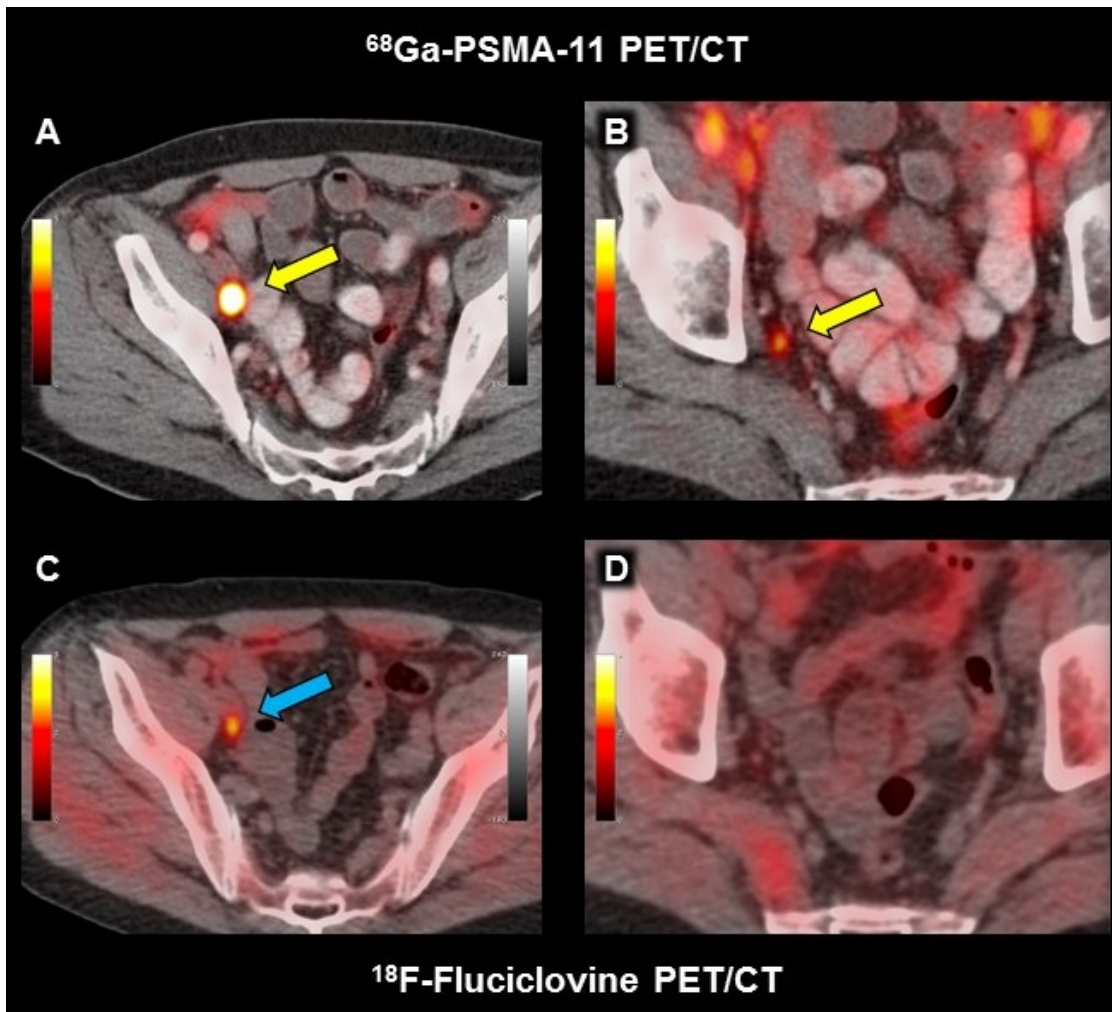
A: Maximum Intensity Projections (MIP) of ^{68}Ga -PSMA-11 PET; B: fused ^{68}Ga -PSMA-11 PET/CT coronal view; C: CT coronal view; D: fused ^{68}Ga -PSMA-11 PET/CT axial view; E: CT axial view.

Supplemental Figure 2:



Patient #3 had a positive ^{18}F -Fluciclovine PET/CT (bottom row) for a local recurrence only with a faint and limited uptake in the left prostate gland (E,F; blue arrows). The ^{68}Ga -PSMA-11 PET/CT (top row) showed a diffuse and intense uptake in the whole prostate gland (A,B; yellow arrows) and PSMA-11 uptake in multiple extra-pelvic LN (C,D, yellow arrows). The corresponding LN showed no ^{18}F -Fluciclovine uptake (G,H).

Supplemental Figure 3:



Patient #7 had a positive ¹⁸F-Fluciclovine PET/CT (bottom row) for a right external iliac LN (C; blue arrows). The ⁶⁸Ga-PSMA-11 PET/CT (top row) showed a much intense uptake in the corresponding LN (A; yellow arrow) and PSMA-11 uptake in a tiny 4 mm right obturator LN (B, yellow arrow). The corresponding LN showed no ¹⁸F-Fluciclovine uptake (D).



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Head-to-head comparison of ^{68}Ga -PSMA-11 PET/CT and ^{18}F -Fluciclovine PET/CT in a case series of 10 patients with prostate cancer recurrence

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