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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This was a head-to-head comparison between ^{68}Ga-labeled prostate-specific membrane antigen (PSMA)-11 and ^{18}F-fluciclovine PET/CT in a series of 10 patients with prostate cancer (PCa) recurrence. **Methods:** In total, 288 patients with PCa recurrence were enrolled in a prospective study of ^{68}Ga-PSMA-11 PET/CT imaging for recurrent disease localization (ClinicalTrials.gov identifier NCT02940262). We retrospectively identified 10 patients who underwent clinically indicated ^{18}F-fluciclovine PET/CT prior to enrollment. **Results:** The median time between the 2 scans was 2.2 mo (range, 0.2–4.2 mo). The median prostate-specific antigen (PSA) value was 1.0 ng/mL (mean, 4.7 ng/mL; range, 0.13–18.1 ng/mL) and 1.1 ng/mL (mean, 6.2 ng/mL; range, 0.24–31.3 ng/mL) at the time of ^{18}F-fluciclovine and ^{68}Ga-PSMA-11 PET/CT, respectively. Five of 10 patients (50%) were negative with ^{18}F-fluciclovine but positive with ^{68}Ga-PSMA-11 PET/CT. Two of 10 patients (20%) were positive with both ^{18}F-fluciclovine and ^{68}Ga-PSMA-11 PET/CT, but ^{68}Ga-PSMA-11 PET/CT showed additional lymph nodes metastasis. Three of 10 patients (30%) were negative with both ^{18}F-fluciclovine and ^{68}Ga-PSMA-11 PET/CT. **Conclusion:** This case series suggests improved detection rates for ^{68}Ga-PSMA-11 PET/CT when compared with ^{18}F-fluciclovine PET/CT in patients with recurrent PCa. Prospective trials designed to directly compare the two should be initiated.

Key Words: prostate cancer; PSMA; PET/CT; fluciclovine; biochemical recurrence

J Nucl Med 2018; 59:789–794
DOI: 10.2967/jnumed.117.203257

Localizing recurrent prostate cancer (PCa) with PET/CT imaging is clinically relevant because these patients can undergo salvage therapies with curative intent (*1*). Identifying sites of recurrence 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*).

Received Oct. 6, 2017; revision accepted Nov. 26, 2017.
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Guest Editor: Michael Graham, University of Iowa
Published online Dec. 14, 2017.

Anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (^{18}F-fluciclovine [Axumin; Blue Earth Diagnostics]) is a synthetic amino acid and likely a substrate of L-amino acid (L-type amino acid transporter 1 in particular) and the alanine-serine-cysteine transporters (specifically alanine-serine-cysteine transporter 2) (*6*). The results of the first prospective studies led to Food and Drug Administration approval in 2016 and to reimbursement by the Center for Medicare and Medicaid Service in 2017 for patients with PCa recurrence (*7*). Thus, ^{18}F-fluciclovine serves as a reference standard for evaluating other PET PCa approaches.

Prostate-specific membrane antigen (PSMA) is a membrane-bound metallopeptidase overexpressed 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 on 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 also reported a favorable tumor-to-background ratio for ^{68}Ga-PSMA-11 to detect PCa lesions and a high sensitivity for lesion detection even at low serum levels of prostate-specific antigen (PSA) (<2 ng/mL) (*2*).

To date, there has been only a 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 to our knowledge, no head-to-head comparison between ^{68}Ga-PSMA-11 and ^{18}F-fluciclovine PET/CT has been published. Here, we report a case series of 10 patients with recurrent PCa who underwent both ^{68}Ga-PSMA-11 PET/CT and ^{18}F-fluciclovine PET/CT. Although 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 were 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 (ClinicalTrials.gov identifier, NCT02940262). The institutional review board approved this study (approval 16-001095), and all subjects gave written informed consent. We retrospectively identified 10 patients who had undergone clinically indicated ^{18}F-fluciclovine PET/CT at other institutions within 4 mo before ^{68}Ga-PSMA-11 PET/CT. We obtained all DICOM files and clinical reports on the ^{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 (patients 2, 4, 5, and 10), 2 had primary

TABLE 1
Patient Characteristics and PET/CT Results

Patient no.	Age (y)	Initial PSA (ng/mL)	Gleason score	pTNM	Primary therapy	Date of primary therapy	Salvage therapy	Date of salvage therapy	Prior imaging within past 3 mo	^{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

XRT = external-beam radiation therapy; brachy = brachytherapy; Na-F = ^{18}F-fluoride PET/CT; RP = radical prostatectomy; SRT = salvage radiation therapy; mpMRI = multiparametric MRI; choline = ^{11}C-choline PET/CT; met = metastasis; NA = not applicable; adj = adjunctive; RT = radiotherapy.

TABLE 2
Detailed PET/CT Results

Patient no.	PET/CT			PSA at PET/CT (ng/mL)	Prostatic fossa			Pelvic			Extrapelvic		
	Probe	Date	Positive result		T	Detailed findings	SUV_{max}	N	Detailed findings	SUV_{max}	M	Detailed findings	SUV_{max}
1	^{18}F-fluciclovine	4/12/2017	0	10.6	0			0			0		
	^{68}Ga-PSMA-11	5/19/2017	1	10.9	0			1	1 external iliac LN (5 mm)	7.7	1	3 retroperitoneal LNs (4–5 mm)	17.1
												1 thoracic LN	4.4
												1 bone met (T8)	5.1
2	^{18}F-fluciclovine	3/16/2017	0	12.27	0			0			0		
	^{68}Ga-PSMA-11	6/7/2017	1	12.66	0			1	Multiple common iliac and presacral LNs (6–8 mm)	2	1	Multiple lung nodules (6–10 mm)	2.6
												1 bone met (T11)	6
3	^{18}F-fluciclovine	3/15/2017	1	18.10	1	Faint localized uptake in left lobe	3.5	0			0		
	^{68}Ga-PSMA-11	7/10/2017	1	31.30	1	Intense diffuse bilateral uptake	8.9	0			1	Multiple retroperitoneal LNs (8–10 mm)	4.7
4	^{18}F-fluciclovine	5/25/2017	0	1.50	0			0			0		
	^{68}Ga-PSMA-11	7/24/2017	0	1.60	0			0			0		
5	^{18}F-fluciclovine	3/23/2017	0	0.22	0			0			0		
	^{68}Ga-PSMA-11	7/31/2017	1	0.30	0			1	4 perirectal LNs (3–4 mm)	2.9	0		
6	^{18}F-fluciclovine	5/9/2017	0	0.13	0			0			0		
	^{68}Ga-PSMA-11	9/15/2017	0	0.24	0			0			0		
7	^{18}F-fluciclovine	10/5/2017	1	0.50	0			1	1 external iliac LN (7 mm)	4.9	0		
	^{68}Ga-PSMA-11	10/11/2017	1	0.65	0			1	1 external iliac LN (7 mm)	14.1	0		
									1 obturator LN (4 mm)	3.0			
8	^{18}F-fluciclovine	9/19/2017	0	0.30	0			0			0		
	^{68}Ga-PSMA-11	10/25/2017	0	0.33	0			0			0		
9	^{18}F-fluciclovine	8/8/2017	0	3.04	0			0			0		
	^{68}Ga-PSMA-11	10/26/2017	1	3.90	0			1	Multiple common and external iliac LNs (4–8 mm)	12.6	1	Multiple retroperitoneal LNs (4–6 mm)	10.3
												Multiple thoracic LNs (4–8 mm)	16.1
10	^{18}F-fluciclovine	10/11/2017	0	0.20	0			0			0		
	^{68}Ga-PSMA-11	11/13/2017	1	0.30	0			1	1 common iliac LN (3 mm)	5.3	0		

Met = metastasis.

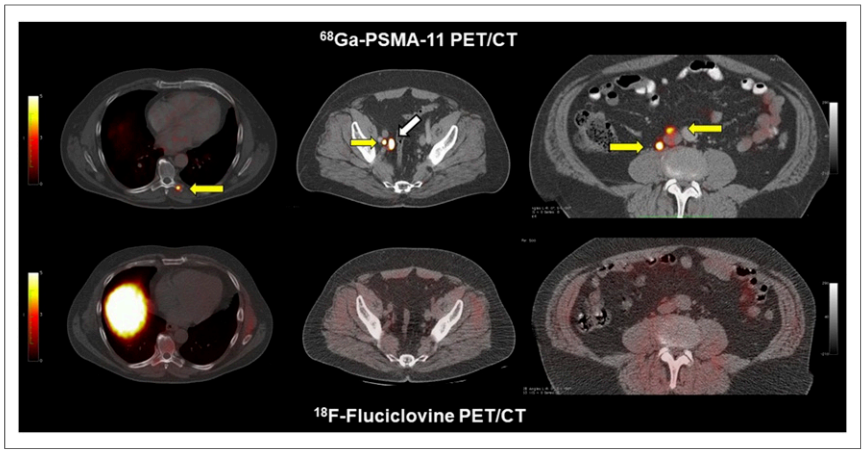

FIGURE 1. Patient 1 had negative ^{18}F-fluciclovine PET/CT results but positive ^{68}Ga-PSMA-11 PET/CT results. Yellow arrows show intense focus of uptake in T8 lesion, right external iliac LN (5 mm), and tiny retroperitoneal LN (4–5 mm). White arrow indicates urinary excretion of tracer in ureteral dilation. There was no uptake in corresponding structures on ^{18}F-fluciclovine PET/CT.

surgery and adjuvant radiation therapy (patients 6 and 9), 2 had primary surgery only (patients 7 and 8), and 2 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 results within 3 mo before the ^{18}F-fluciclovine PET/CT study: CT in 6 of 10 patients (patients 1, 2, 3, 8, 9, and 10), multiparametric MRI in 5 of 10 (patients 2, 4, 5, 7, and 8), ^{18}F-fluoride PET/CT in 5 of 10 (patients 1, 3, 5, 9, and 10), and ^{11}C-choline PET/CT in 2 of 10 (patients 2 and 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 not contraindicated) 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 radiosynthesis (*12*). Patients were scanned after avoiding significant exercise for at least 24 h to minimize uptake in background muscle, 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 MBq). The median uptake period was 4 min (range, 2–15 min). A nondiagnostic CT scan was obtained 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 coregistered and analyzed by an experienced nuclear medicine physician according to recent recommendations (*6,11,13*) using OsiriX: any focal uptake above the level of the surrounding background and not associated with physiologic uptake or known pitfalls (*14*) was considered suggestive of malignancy. On the basis of TNM staging, the following regions were systematically analyzed: prostate bed/seminal vesicle remnants (T), pelvic lymph nodes (LNs) (N) (internal iliac, obturator, external iliac, perirectal, presacral, common iliac), extrapelvic LNs (M1a) (retroperitoneal, 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 the 2 scans was 2.2 mo (range, 0.2–4.2 mo). The median PSA levels were 1.0 ng/mL (mean, 4.7 ng/mL; range, 0.13–18.1 ng/mL) and 1.1 ng/mL (mean, 6.2 ng/mL; range, 0.24–31.3 ng/mL) 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 of 10 patients (20%), whereas ^{68}Ga-PSMA-11 PET/CT detected recurrence sites in 7 of 10 patients (70%). Five of 8 patients (63%) (patients 1, 2, 5,

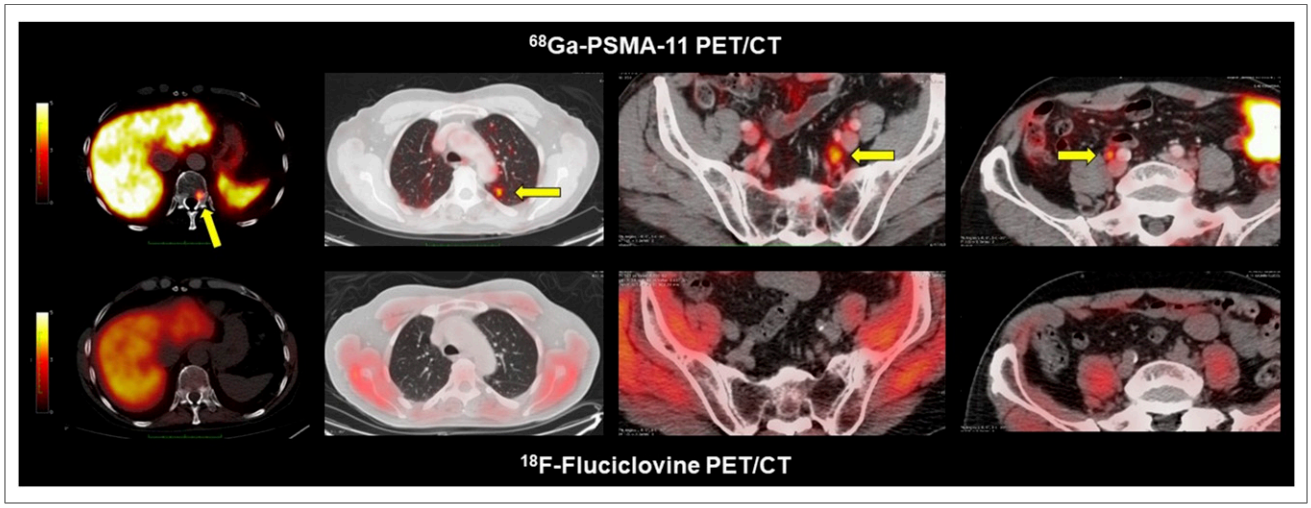

FIGURE 2. Patient 2 had negative ^{18}F-fluciclovine PET/CT results and positive ^{68}Ga-PSMA-11 PET/CT results. Arrows show uptake in T11 lesion, lung micronodules, presacral LN, and common iliac LN. There was no uptake in corresponding structures on ^{18}F-fluciclovine PET/CT.

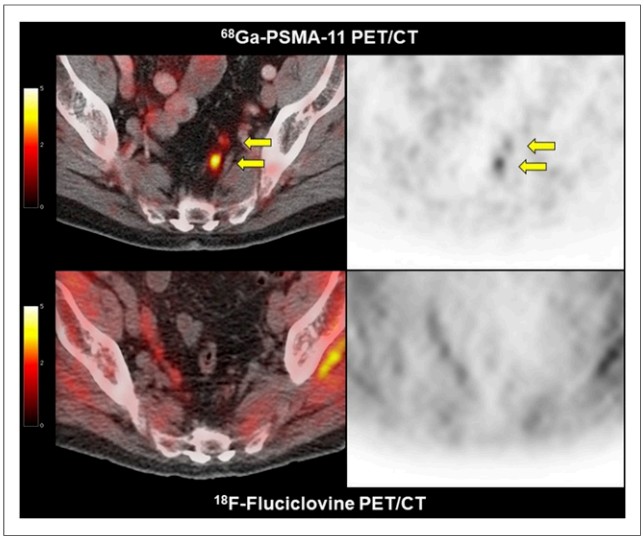

FIGURE 3. Patient 5 had negative ^{18}F-fluciclovine PET/CT results and positive ^{68}Ga-PSMA-11 PET/CT results. Arrows show uptake in tiny perirectal LN (3–4 mm). Corresponding LN on ^{18}F-fluciclovine PET/CT showed no uptake.

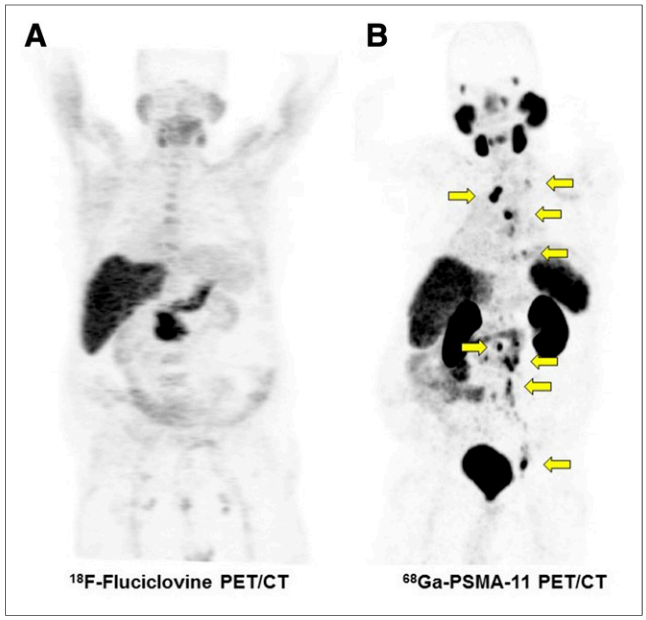

FIGURE 4. Maximum-intensity-projection ^{18}F-fluciclovine PET (A) and ^{68}Ga-PSMA-11 PET (B) in patient 9. Arrows indicate intense uptake in pelvic, abdominal, thoracic, and supraclavicular LNs. Corresponding LNs on ^{18}F-fluciclovine PET showed no uptake.

9, and 10) were negative with ^{18}F-fluciclovine PET/CT but positive with ^{68}Ga-PSMA-11. One patient (patient 3) was positive for local recurrence with both tracers but ^{68}Ga-PSMA-11 revealed additional extrapelvic LN involvement. One patient (patient 7) was positive for a single external iliac LN recurrence with both tracers but ^{68}Ga-PSMA-11 revealed additional obturator LN involvement. Three patients (patients 4, 6, and 8) had concordantly negative scans. 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 who were negative with ^{18}F-fluciclovine but positive with ^{68}Ga-PSMA-11 had the following findings. Patient 1 had multiple ^{68}Ga-PSMA-11–positive lesions involving a small right external iliac LN (5 mm, SUV_{max}, 7.7), multiple small retroperitoneal LNs (4–5 mm, SUV_{max}, 17), a right hilar LN (SUV_{max}, 4), and T8 (Fig. 1). He then received androgen deprivation therapy (ADT). In patient 2, intense ^{68}Ga-PSMA-11 uptake in a solitary osteoblastic T11 lesion (SUV_{max}, 6) and faint ^{68}Ga-PSMA-11 uptake in multiple bilateral common iliac and presacral LNs (6–8 mm; SUV_{max} 2.0), as well as multiple bilateral lung nodules (6–10 mm; SUV_{max}, 2.6), were evident (Fig. 2). He received proton therapy focused on the T11 metastasis and refused any systemic treatment. In patient 5, 4 small perirectal LNs showed mild ^{68}Ga-PSMA-11 uptake (3–4 mm; SUV_{max}, 2.9) (Fig. 3). His referring physician opted for active surveillance. In patient 9, intense ^{68}Ga-PSMA-11 uptake in multiple left pelvic LNs (4–8 mm; SUV_{max}, 12.6), retroperitoneal LNs (4–6 mm; SUV_{max}, 10.3), and supradiaphragmatic LNs (4–8 mm; SUV_{max}, 16.1) were seen (Fig. 4). The patient received ADT. Finally, patient 10 had a single tiny right upper common iliac LN with intense ^{68}Ga-PSMA-11 uptake (3 mm; SUV_{max}, 5.3) (Supplemental Fig. 1; supplemental materials are available at http://jnm.snmjournals.org). He received focused ablative RT and ADT initiation was put on hold.

The 2 patients who were positive with ^{18}F-fluciclovine had the following findings. Patient 3 had a small ^{18}F-fluciclovine–positive local recurrence (SUV_{max}, 3.5) whereas ^{68}Ga-PSMA-11 PET/CT showed a much larger local recurrence with intense uptake (SUV_{max}, 8.9). Moreover, ^{68}Ga-PSMA-11 PET/CT demonstrated additional abnormal retroperitoneal LNs (8–10 mm; SUV_{max}, 4.7) (Fig. 5; Supplemental Fig. 2). The patient received ADT. Patient 7 had a ^{18}F-fluciclovine–positive right external iliac LN recurrence (7 mm; SUV_{max}, 4.9). ^{68}Ga-PSMA-11 uptake was much more intense (SUV_{max}, 8.9). In addition, ^{68}Ga-PSMA-11 PET/CT demonstrated an additional abnormal tiny right obturator LN (4 mm; SUV_{max}, 3.0) (Supplemental Fig. 3). The patient underwent unilateral right pelvic LN dissection. Three of 8 resected LNs were positive for metastatic adenocarcinoma.

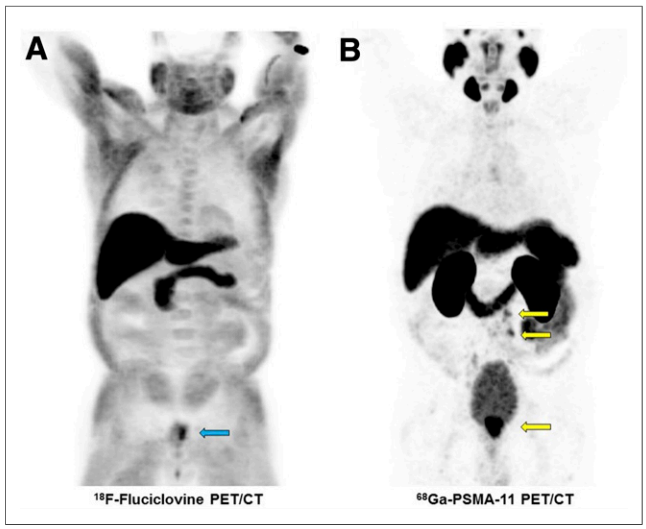

FIGURE 5. Maximum-intensity-projection ^{18}F-fluciclovine PET (A) and ^{68}Ga-PSMA-11 PET (B) in patient 3. Blue arrow indicates faint and limited uptake in left prostate gland. Yellow arrows indicate diffuse and intense uptake in prostate gland and in extrapelvic LN.

Patients 4, 6, and 8 had concordantly negative findings on ^{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 salvage radiation therapy to both prostate bed and pelvic LNs.

DISCUSSION

We are aware that the results of this small case series do not indicate the superiority of ^{68}Ga-PSMA-11 PET/CT over ^{18}F-fluciclovine PET/CT. However, the findings of the 2 tests were so strikingly different that we felt a brief report would be prudent. Issuing a report also seemed justified because no direct comparisons between these 2 tests have been published.

Although 7 of 10 studies (70%) were positive with ^{68}Ga-PSMA-11, 8 of 10 ^{18}F-fluciclovine studies were negative (80%), and disease extent was underestimated in both of the patients with a positive ^{18}F-fluciclovine study. Surprisingly, 4 ^{18}F-fluciclovine PET/CT studies were negative despite fairly extensive disease on the ^{68}Ga-PSMA-11 PET/CT studies.

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

The main study that led to Food and Drug Administration approval for ^{18}F-fluciclovine was a retrospective analysis of 596 patients (*3*). The detection rates were 67.7% in the whole population (mean PSA level, 5.43 ng/mL) and 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 extraprostatic lesions.

There was, of course, a significant selection bias in the current case series. Patients likely had negative ^{18}F-fluciclovine PET/CT results and were therefore referred for ^{68}Ga-PSMA-11 PET/CT. Moreover, the median interval between the 2 scans, 2.2 mo, likely favored lesion detection with ^{68}Ga-PSMA-11 PET/CT. But the median increase in PSA level between the 2 scans was only 0.1 ng/mL (range, 0.03–13.2 ng/mL).

Another important limitation was that histologic confirmation of ^{68}Ga-PSMA-11–positive lesions was available for only one patient (patient 7) who underwent surgery. Histologic verification of lesions in patients with PCa recurrence is not routinely done, and ^{68}Ga-PSMA-11–positive lesions were not biopsied. Two patients (patients 2 and 10) received focal ablative radiation therapy after the scans, whereas the others had nonfocal treatment (ADT or salvage radiation therapy to both prostate bed and pelvic LNs) or active surveillance. Therefore, we cannot exclude that these ^{68}Ga-PSMA-11–positive lesions were in fact false-positive.

CONCLUSION

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

DISCLOSURE

Jeremie Calais is the recipient of a grant from the Foundation ARC pour la recherche sur le cancer (grant SAE20160604150). Wolfgang Fendler received a scholarship from the German Research Foundation (Deutsche Forschungsgemeinschaft [DFG], grant 807122). Matthias Eiber was supported by the SFB 824 (DFG Sonderforschungsbereich 824, project B11) from the Deutsche Forschungsgemeinschaft, Bonn, Germany. No other potential conflict of interest relevant to this article was reported.

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