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Original Article

Clinical utility of ^{18}F-Fluciclovine PET/CT in recurrent prostate cancer with very low (≤0.3 ng/mL) prostate-specific antigen levels

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Abstract: The purpose of this study was to evaluate ^{18}F-fluciclovine PET/CT detection rates in the evaluation of biochemical recurrence in prostate cancer patients with very low (≤0.3 ng/mL) serum prostate-specific antigen (PSA) levels following definitive treatment. Prostate cancer patients with biochemical recurrence and very low serum PSA (≤0.3 ng/mL) who underwent clinical ^{18}F-fluciclovine PET/CT were included in this single-institution retrospective study. PET/CT clinical reports at the time of interpretation were reviewed and categorized as positive or negative. In patients who had further evaluation with imaging and/or biopsy, the results were recorded to determine the true detection rate. Of the 64 eligible patients with very low serum PSA (median serum PSA of 0.17 ng/mL), 57.8% (37/64) scans were categorized as positive. Stratified by PSA levels, positivity rates were 43.8% (7/16), 60.0% (15/25) and 65.2% (15/23) for PSA<0.1 ng/mL, 0.1-<0.2 ng/mL and 0.2-≤0.3 ng/mL, respectively. The most common location of disease was the prostate bed (73%), followed by pelvic lymph nodes (22%) and distant disease (14%). In the small subset of patients who had further evaluation after a positive study (n=7), all had confirmed disease with a positive predictive value of 100%. In conclusion, among prostate cancer patients with biochemical recurrence, ^{18}F-fluciclovine PET/CT is useful in patients with very low serum PSA of ≤0.3 ng/mL, with a 57.8% positivity rate, higher than previously reported. Though standard of truth could only be ascertained in 19% (7/37) of patients with a positive study, the positive predictive value was 100%.

Keywords: Prostate cancer, PSA, PET/CT, ^{18}F-Fluciclovine, biochemical recurrence

Introduction

Prostate cancer remains one of the most common cancers in men with an estimated 248,530 new cases and 34,130 disease specific deaths in the United States in 2021 [1]. Following primary treatment, prostate cancer recurrence is diagnosed in approximately 20-50% of these patients [2]. The American Urological Association and European Association of Urology guidelines define biochemical recurrence of prostate cancer post-prostatectomy as an initial prostate-specific antigen (PSA) of ≥0.2 ng/mL, obtained 6 weeks after surgery to allow for appropriate washout of any residual PSA. This is confirmed by a subsequent confirmatory PSA value of ≥0.2 ng/mL [3, 4].

Following primary radiation therapy, disease recurrence is diagnosed when there is an increase in the PSA level by ≥2 ng/mL above the nadir (the lowest value of serum PSA after treatment) [5, 6]. Early detection of recurrent disease and appropriate management can improve patient outcomes [7]. ^{18}F-Fluciclovine positron emission tomography (PET)/computed tomography (CT) has shown promise in the detection of recurrent prostate cancer with significant impact on treatment planning [8]. ^{18}F-Fluciclovine or ^{18}F-FACBC is an amino acid analogue that localizes to prostate cancer cells via transport through amino acid transporters, especially alanine-cysteine and larger neutral amino acid transporters [8]. ^{18}F-Fluciclovine PET/CT guided salvage therapy has shown to

result in a better PSA response in comparison to patients in whom the modality was not used (FALCON trial) [9].

Although it has been shown that ^{18}F-fluciclovine PET/CT is useful in the detection of recurrent disease in patients with serum PSA≤1 ng/mL [10], varying results have been reported in patients with very low serum PSA (≤0.3 ng/mL) [9-12].

The other alternative molecular imaging modality that is emerging for the evaluation of prostate cancer is PET/CT imaging using prostate specific membrane antigen (PSMA) radiotracers. A meta-analysis (^{18}F-Fluciclovine vs ^{18}F or ^{68}Ga-PSMA PET/CT) comparing the two modalities reported pooled detection rates of 37% vs 45% in patients with serum PSA<0.5 ng/mL [13]. Most PSMA radiotracers demonstrate fairly intense bladder activity and thus ^{18}F-fluciclovine may have superior detection rate in the prostate bed, while PSMA radiotracers may have improved detection for more distant disease with the detection rates for local disease at least similar between the two modalities [14, 15]. Eiber et al. reported detection rate of 71% in patients with biochemical recurrence of prostate cancer after radical prostatectomy who underwent ^{18}F-rhPSMA-7 PET/CT, which does not have high urinary bladder activity, with serum PSA levels 0.2-0.5 ng/mL with relatively higher detection of local recurrence [16]. Further studies may be useful in this regard to arrive at an imaging algorithm based on the strength and weakness of each radiotracer.

In this paper, we report our single academic center experience of ^{18}F-fluciclovine PET/CT in the clinical evaluation of biochemically recurrent prostate cancer in patients with serum PSA≤0.3 ng/mL following primary local treatment.

Material and methods

Patient eligibility and follow-up

This was a retrospective study performed under a waiver of informed consent as approved by the Institutional Review Board. The guidelines of the Health Insurance and Portability and Accountability Act were followed. Patients with biopsy-proven prostate adenocarcinoma with rising serum PSA≤0.3 ng/mL after completion of primary treatment and underwent ^{18}F-fluciclovine PET/CT between September 2016 and July 2019 were included in the study. Five hundred and fifteen prostate cancer patients who had undergone a clinical ^{18}F-fluciclovine PET/CT were identified from our PET/CT database. Of these, 64 patients met our inclusion criteria, due to a PSA≤0.3 ng/mL as a trigger for the study. The indication of all the PET/CT studies was rising serum PSA following definitive treatment.

^{18}F-fluciclovine PET/CT protocol

Patients were scanned following the institutional ^{18}F-fluciclovine PET/CT imaging protocol. Patients were instructed not to undertake any significant physical exercise 24 hours and fasted for at least 4 hours prior to the scan, following which oral contrast (16oz) was given. The scans were acquired on a GE Discovery 690 Elite TOF, GE Discovery MV600 or Siemens Biograph mCT TOF scanner. Following intravenous bolus infusion of approximately 370 MBq (10 mCi) of ^{18}F-fluciclovine, a CT scan was acquired for attenuation correction (120 kV, auto-mA, 0.5-7 s tube rotation, 1.2-1.375 pitch, reconstructed slice thickness of 3-3.75 mm) from the skull base to the mid-thighs. PET emission scan (3.5 min/bed position for 6-7 bed positions) was then acquired 3-5 minutes after radiotracer administration from the mid-thighs to the skull base in a caudocranial direction. Images were reconstructed with iterative technique.

Image analysis

Board-certified nuclear medicine physicians interpreted the ^{18}F-fluciclovine PET/CT images at the time of imaging as per the routine clinical imaging review protocol at our institution. Readers at the institution had dedicated reader training prior to interpretation of the studies per institution protocol with standard interpretation guidelines [17]. Original reports were used to categorize the results to reflect actual clinical interpretation in daily practice. The scan reports were retrospectively reviewed and categorized as positive, indeterminate, or negative for recurrent malignancy by a dual nuclear medicine and radiology trained molecular imaging clinical fellow. Positive reports clearly identified disease recurrence or metastases related to the primary prostate cancer. If reports were identified as positive, the site of disease recurrence or metastases was noted. Locations of positive lesions were categorized into prostate/

Table 1. Patient characteristics (n=64)

Age, mean ± SD/median (range)	65±8/66 (48-79)
Gleason grade group at diagnosis, no. (%)	
1 (3+3)	7 (11.0%)
2 (3+4)	12 (18.7%)
3 (4+3)	15 (23.4%)
4 (4+4, 5+3)	10 (15.6%)
5 (5+4, 4+5)	13 (20.3%)
Unknown	7 (11.0%)
Primary treatment, no. (%)	
Radical Prostatectomy*	55 (85.9%)
Radiation therapy**	7 (10.9%)
Hormone therapy	2 (3.1%)
PSA (ng/mL), mean ± SD/median (range)	0.16±0.08/0.17 (0.01-0.3)

*1 patient had prostatectomy + hormone therapy + radiation. **2 patients had radiation and hormone therapy.

Table 2. Patient characteristics based on ^{18}F-Fluciclovine PET/CT positivity

Patient characteristics	^{18}F-Fluciclovine PET/CT		*P*-value
	Positive (n=37)	Negative (n=27)	
Age, mean ± SD (y)	66±8	64±8	0.22
Serum PSA, mean ± SD	0.18±0.08	0.14±0.08	0.08
Gleason score			
6	3 (8.1%)	4 (14.8%)	0.57
7	18 (48.6%)	9 (33.3%)	
8	4 (10.8%)	6 (22.2%)	
9	8 (21.6%)	5 (18.5%)	
Unknown	4 (10.8%)	3 (11.1%)	
Primary treatment			
Radical Prostatectomy	31 (83.8%)*	24 (88.9%)	0.81
Radiation Therapy	5 (13.5%)**	3 (11.1%)**	
Hormone Therapy	4 (10.8%)	1 (3.7%)	

*1 patient had prostatectomy + hormone therapy + radiation. **2 patients (1 in each category) had radiation and hormone therapy.

bed, pelvic nodes, and distant metastases. Indeterminate reports did not clearly identify or exclude disease; the scan report impression included terminology such as indeterminate or cannot exclude disease recurrence. Negative scan reports clearly excluded the possibility of disease. For clinical utility and analysis purposes, the indeterminate scans were conservatively categorized as negative to align with clinical classification. Indication for the PET/CT study was determined from the latest clinical note.

Standard of truth

When available, primary standard of truth for calculating positive predictive value (PPV) was histopathology. Secondary standard of truth was characteristic appearance and/or evolution over time on confirmatory imaging, such as magnetic resonance imaging (MRI) for bone lesions.

Statistical analysis

Descriptive features of variables were presented using median and range. ^{18}F-Fluciclovine PET results were categorized as positive or negative and positivity rate was calculated. Mann-Whitney U, chi square and Fisher's exact tests were used to analyze the differences between groups. *P*-values less than 0.05 were considered statistically significant. Statistical analysis was performed with SAS Version 9.4 (SAS Institute Inc. Cary, NC, USA).

Results

Patient characteristics

The demographics of the 64 men included in the study are presented in **Table 1**. All patients had a serum PSA≤0.3 ng/mL. At the time of ^{18}F-fluciclovine PET, the median age was 66 years (range, 48-79 years) and median PSA was 0.17 ng/mL (range, 0.01-0.30 ng/mL). Thirty-eight (59.4%) patients had Gleason score ≥4+3. The most common primary treatment was radical prostatectomy with or without pelvic lymph node dissection in 55 patients (85.9%).

^{18}F-fluciclovine positivity rate

Of the 64 scans, 37 (57.8%) were categorized as positive, 24 (37.5%) as negative and 3 (4.7%) as indeterminate. For analysis, the indeterminate results were categorized as negative. There was no significant difference in PSA (P=0.08), GS (P=0.57) and primary definitive treatment (P=0.81) between patients with positive and negative scans (**Table 2**). When stratified by PSA levels, positivity rates were 43.8% (7/16), 60.0% (15/25) and 65.2% (15/23) for PSA <0.1 ng/mL, 0.1-<0.2 ng/mL and 0.2-≤0.3

Table 3. Disease location stratified by serum PSA levels

Disease Location	Serum PSA (ng/mL)			
	<0.1 (n=16)	0.1-<0.2 (n=25)	0.2-≤0.3 (n=23)	≤0.3 (n=64)
Overall	7 (43.8%)	15 (60.0%)	15 (65.2%)	37 (57.8%)
Prostate bed	6 (37.5%)*	10 (40.0%)**	11 (47.8%)	27 (42.2%)
Pelvic nodes	0 (0.0%)	5 (20.0%)**	3 (13.0%)	8 (12.5%)
Distant metastasis	2 (12.5%)*	2 (8.0%)**	1 (4.3%)	5 (7.8%)

*1 patient had uptake in the prostate bed and in a distant metastasis. **1 patient had uptake in the prostate bed and pelvic nodes and 1 patient had uptake in the prostate bed and in a distant metastasis.

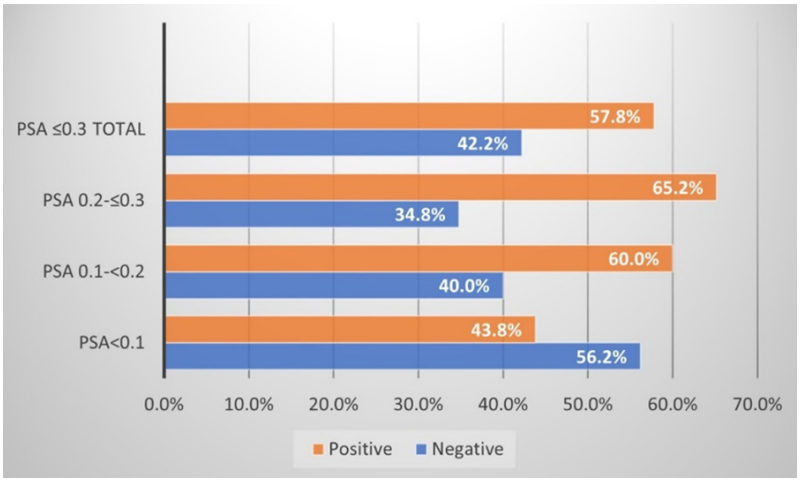

Figure 1. ^{18}F-fluciclovine PET/CT positivity rates stratified by PSA levels in prostate cancer patients with biochemical recurrence after definitive treatment.

ng/mL, respectively (**Table 3** and **Figure 1**). There was no statistical difference in ^{18}F-fluciclovine positivity rates across PSA levels (P=0.39).

Lesion detection

Among the patients who had a positive PET/CT, radiotracer avid foci were identified in the prostate/bed in 27/37 (73.0%) patients (**Figure 2**), nodal disease was identified in 8/37 (21.6%) patients (**Figure 3**) and distant disease in 5/37 (13.5%) patients. In patients with radiotracer avid distant metastatic disease (n=5), 3 were localized to the bones (**Figure 4**), 1 to the lung and 1 to a subcutaneous implant. There was no statistical difference in region of uptake between patients with PSA<0.2 ng/mL versus 0.2-≤0.3 ng/mL (P=0.71). The lesion detection stratified by serum PSA levels is presented in **Table 3**.

Positive predictive value

Among the clinical patients with a positive study, only 7 (19%) of the patients had further evaluation of the findings with biopsy (4/7) or MRI (3/7). Of these patients, 6 had confirmed disease either on histopathology (1 in prostate bed, 1 abdominal wall nodule, 1 pulmonary nodule) or MRI (3 in prostate bed). The seventh patient had a negative biopsy of a sclerotic iliac lesion. However, retrospective review of the lesion showed enlarging sclerosis in comparison to prior CT imaging consistent with progression of a skeletal metastasis and was therefore considered a true positive lesion with a false negative biopsy. The overall positive predictive value in this small subset of patients was 100%.

Discussion

^{18}F-Fluciclovine PET/CT has become a valuable tool in the clinical evaluation of prostate cancer patients with biochemical recurrence [8]. In comparison to conventional imaging modalities such as CT and MRI, ^{18}F-fluciclovine PET/CT has shown superior performance in diagnosing recurrent disease, especially in patients with extra-prostatic disease recurrence [18, 19]. It is well established that the recurrent disease detection efficacy improves with increasing serum PSA values, especially values greater than 1 ng/mL [10, 20]. Few studies have reported the detection rate of recurrent disease on ^{18}F-fluciclovine PET/CT in patients with lower serum PSA values, especially in the very low range of ≤0.3 ng/mL. Although patients with a serum PSA of ≤0.2 ng/mL would not technically meet criteria for biochemical recurrence following primary surgery, some patients were referred from outside centers for evaluation of rising serum PSA from previous undetectable levels. Most of the patients in the study popula-

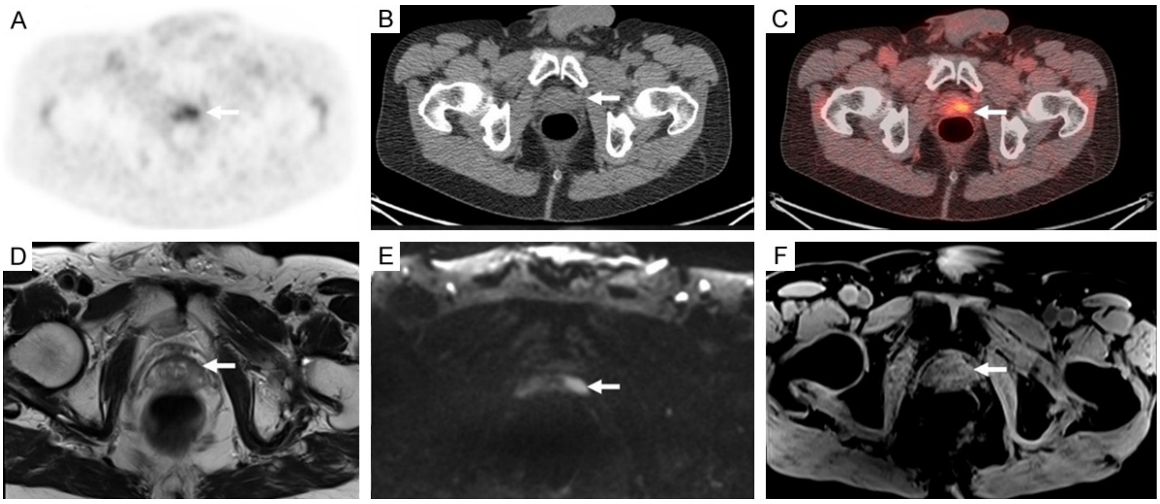

Figure 2. Axial ^{18}F-fluciclovine PET (A), axial CT (B) and axial fused ^{18}F-fluciclovine PET/CT (C) images of a 73-year-old male with Gleason 3+4 prostate adenocarcinoma, status post primary radiation therapy who was referred for a ^{18}F-fluciclovine PET/CT examination due to rising serum PSA which was previously undetectable. His serum PSA at the time of the study was 0.18 ng/mL. ^{18}F-fluciclovine PET/CT images demonstrate heterogeneous radiotracer activity within the prostate gland with asymmetric focal uptake (white arrows) in the left mid prostate gland (SUVmax 4.9). Axial T2-weighted MR (D), axial DWI-MR (E) and axial dynamic contrast enhanced (DCE) MR (F) of a pelvis MRI examination performed for further evaluation demonstrates a corresponding focal lesion which is hypointense on the T2-weighted images with restricted diffusion and heterogeneous contrast enhancement in the peripheral zone of the left mid prostate gland. Subsequent biopsy of the lesion demonstrated prostate adenocarcinoma (Gleason 3+4) with features of perineural invasion.

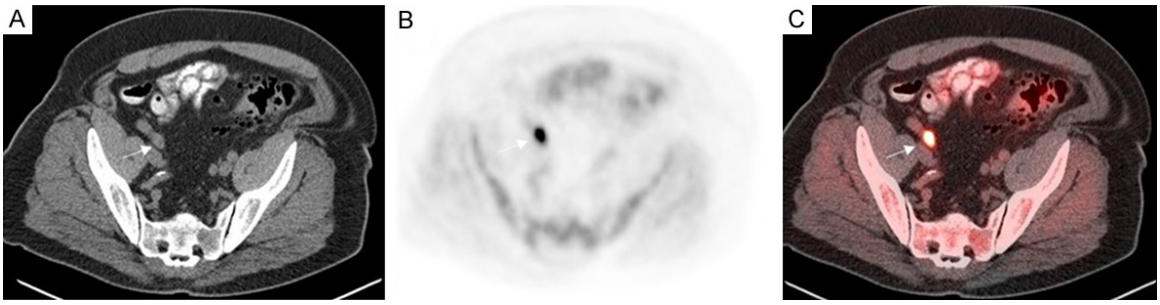

Figure 3. 68-year-old male with Gleason 9 prostate cancer, status post primary radical prostatectomy, who presented with rising serum PSA. The serum PSA at the time of presentation was 0.29 ng/mL. Axial CT (A), axial ^{18}F-Fluciclovine (B) and axial fused ^{18}F-Fluciclovine PET/CT (C) images demonstrate radiotracer avid right pelvic lymph node, suggestive of nodal metastasis.

tion were treated with primary surgical management.

The reported detection rates in patients with very low serum PSA ranges from 0% to 33%. Results from the FALCON trial in prostate cancer patients with biochemical recurrence, reported a detection rate of 33% (6/18) in patients with serum PSA 0-0.2 ng/mL [9]. Teyateeti et al. reported a detection rate of 11% (6/56) in patients with serum PSA≤0.3 ng/mL [12]. Wang et al. reported no positive findings in patients with very low serum PSA values (0/17) (**Table 4**) [21]. However, in our patient population with serum PSA of ≤0.3 ng/mL, the overall detection rate was 58%. This was also supported by the positivity rates seen in a subset of patients with serum PSA≤0.3 ng/mL among our research patient population (EMPIRE I and II), with an overall detection rate of 65% (**Table 5**). ^{18}F-Fluciclovine is even successful in detecting recurrent disease below the standard definition of biochemical recurrence. Thus, our results seem to be similar to those of Armstrong, Garza and coworkers [11, 22], yet higher than the other reports. The differences may be due

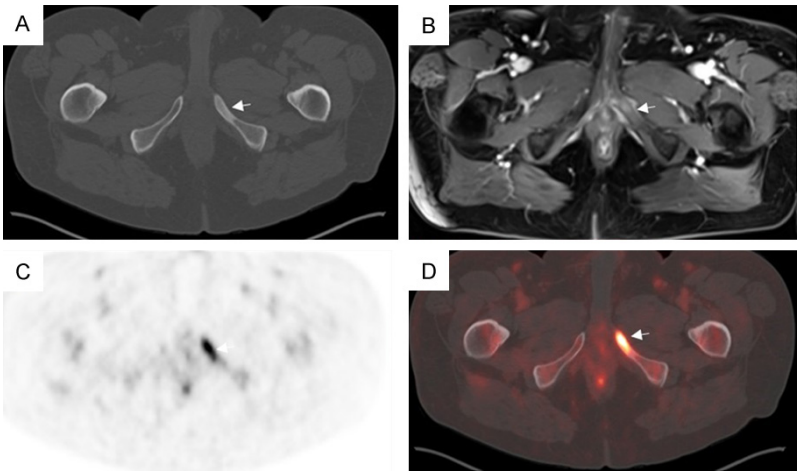

Figure 4. 59-year-old man with Gleason 4+5 prostate adenocarcinoma, status post radical prostatectomy, with rising serum PSA from previous undetectable level. Serum PSA at the time of presentation was 0.09 ng/mL. Axial CT (A), axial post-contrast T1-weighted MR (B), axial ^{18}F-Fluciclovine PET (C) and axial fused ^{18}F-Fluciclovine PET/CT (D) demonstrates a sclerotic, enhancing lesion in the left inferior pubic ramus (white arrows) which demonstrates focal increased radiotracer uptake, consistent with osseous metastasis.

Table 4. Summary of reported patient-level prostate cancer recurrence detection rates in patients with serum PSA≤0.5 ng/mL

Studies	Serum PSA range (ng/mL)	Detection rate
LOCATE trial [10]	0.0-0.5 (n=81)	31%
FALCON trial [9]	0.0-0.2 (n=18)	33%
	0.2-0.5 (n=27)	26%
Teyateeti et al. [12]	0.0-0.3 (n=30)	20%
Wang et al. [21]	0.0-0.3 (n=17)	0%
Nakamoto et al. [28]	0.0-0.5 (n=26)	15%
Armstrong et al. [11]	0.0-0.5 (n=22)	55%
Garza et al. [22]	0.0-0.5 (n=n/a)	50%

to a combination of factors such as specific patient population as well as reader experience.

The foci of disease identified in our scans were most localized to the post-surgical bed/prostate (73%). Yet, recurrent disease was also identified in pelvic lymph nodes (22%) and distant metastases (14%) in these patients with very low serum PSA, including bone, lung and subcutaneous implants. Similar detection rates for pelvic nodal distant metastatic disease have been reported by other studies evaluating prostate cancer recurrence with ^{18}F-fluciclovine PET/CT [23]. In the small subset of patients with further evaluation of the PET/CT findings, all had confirmation of disease by primary or secondary standard of truth. These findings can have an impact on treatment planning and patient outcome. As reported by our group, in a prospective randomized trial, the use of ^{18}F-fluciclovine PET/CT in planning salvage radiotherapy results in statistically significant failure free survival over radiotherapy planned with conventional imaging alone [24].

The other alternative molecular imaging modality that is emerging for the evaluation of prostate cancer is PET/CT imaging using prostate specific membrane antigen (PSMA) radiotracers. A meta-analysis (^{18}F-Fluciclovine vs ^{18}F or ^{68}Ga-PSMA PET/CT) comparing the two modalities reported pooled detection rates of 37% vs 45% in patients with serum PSA<0.5 ng/mL [13]. In prostate cancer patients with biochemical recurrence Hoffman et al. found detection rates of 41% with serum PSA<0.2 ng/mL and 45% with serum PSA 0.2-0.5 ng/mL with ^{68}Ga-PSMA-11 PET/CT [25]. Similarly, Kranzbuhler et al. reported a detection rate of 65% in patients with serum PSA 0.2-0.5 ng/mL and 39% in serum PSA<0.2 ng/mL. More disease was diagnosed in lymph nodes than local recurrence or distant metastasis (34% lymph nodes, 12% local recurrence and 8% distant metastasis), evaluated with ^{68}Ga-PSMA-11 PET/MR [26]. A prospective trial comparing ^{18}F-fluciclovine PET/CT and ^{68}Ga-PSMA-11 PET/CT reported detection rates of 27% and 46% in patients (n=26) with serum PSA 0.2-0.5 ng/mL [14]. In patients evaluated with ^{18}F-DCFPyL PET/CT, the reported detection rate was 64% with serum PSA≤0.2 ng/mL, yet detection of local recurrence (9%) was lower than that of nodal (18%) or skeletal disease (18%) [27]. Most PSMA radiotracers demonstrate fairly intense bladder activity and thus ^{18}F-fluciclovine may have superior detection rate in the prostate bed, while PSMA radiotracers may have improved detection for more distant disease

Table 5. ^{18}F-fluciclovine PET/CT positivity rates in a subset of research patients with serum PSA≤0.3 ng/mL from two relevant clinical trials (NCT01666808 and NCT03762759)

Trial	Whole body	Prostate bed	Pelvic nodes
EMPIRE I Trial (n=36) [29]	21/36 (58.3%)	20/36 (55.6%)	3/36 (8.3%)
EMPIRE II Trial (n=16)	13/16 (81.3%)	13/16 (81.3%)	3/16 (18.8%)
Total (n=52)	34/52 (65.4%)	33/52 (63.5%)	6/52 (11.5%)

with the detection rates for local disease at least similar between the two modalities [14, 15]. Eiber et al. reported detection rate of 71% in patients with biochemical recurrence of prostate cancer after radical prostatectomy who underwent ^{18}F-rhPSMA-7 PET/CT, which does not have high urinary bladder activity, with serum PSA levels 0.2-0.5 ng/mL with relatively higher detection of local recurrence [16]. Further study may be useful in this regard to arrive at an imaging algorithm based on the strength and weakness of each radiotracer.

This study has several limitations. This is a single center study, and all the ^{18}F-fluciclovine PET/CT examinations were read by physicians with extensive training in its interpretation, given the high clinical and research volume of this modality in our institution, and may not be representative of all nuclear medicine practices. The scan positivity was retrospectively extracted from non-blinded routine clinical image interpretation and does not account for biases from clinical information and other prior imaging findings. Being a tertiary referral center, some of these patients were referred from outside hospitals. This may explain the inclusion of patients with very low serum PSA who had undergone non-surgical management, before meeting diagnostic criteria for biochemical recurrence. As is common with clinical studies, disease confirmation was available only in a subset of patients to confirm positive predictive value; but in this small cohort, the PPV was 100%.

Conclusion

In prostate cancer patients with biochemical recurrence, ^{18}F-fluciclovine PET/CT is useful in patients with very low serum PSA of ≤0.3 ng/mL with a 57.8% positivity rate. Though standard of truth could only be ascertained in 19% of patients with a positive study, the positive predictive value was 100%.

Disclosure of conflict of interest

Olayinka Abiodun-Ojo received funding from Blue Earth Diagnostics Ltd. through the Emory University Office of Sponsored Projects for clinical trials using ^{18}F-Fluciclovine. Ashesh Jani received Personal fees from Blue Earth Diagnostics for advisory board services outside the submitted work. David Schuster is consultants of Syncona, AIM Specialty Health, Global Medical Solutions Taiwan and Progenics Pharmaceuticals, Inc. He 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, Ltd; Nihon MediPhysics Co, Ltd.; Telix Pharmaceuticals (US) Inc.; Advanced Accelerator Applications; FUJIFILM Pharmaceuticals U.S.A., Inc; Amgen Inc. The educational is School of Breast Oncology and PrecisCa.

Abbreviations

^{18}F, fluorine-18; PSMA, prostate specific membrane antigen; PET/CT, positron emission tomography/computed tomography; SUV, standardized uptake value; PSA, Prostate Specific Membrane Antigen.

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