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Original Article

Diagnostic performance of ^{18}F-fluciclovine PET/CT in prostate cancer patients with rising PSA level ≤ 0.5 ng/ml after multiple treatment failures

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Abstract: This retrospective study is to assess the performance of ^{18}F-Fluciclovine PET/CT in prostate cancer (PC) patients with multiple treatment failures and prostate-specific antigen (PSA) ≤ 0.5 ng/mL. PC patients with multiple treatment failures who had PSA level within 2-week interval of ^{18}F-Fluciclovine PET/CT (PSA_{PET}) ≤ 0.5 ng/mL were identified in retrospective review of our institution's database (n=28). Patient, tumor, treatment, PSA and castration characteristics as well as findings on ^{18}F-Fluciclovine PET/CT were collected and compared between positive and negative ^{18}F-Fluciclovine PET/CT subgroups by using Fisher's exact test. The overall detection rate of ^{18}F-Fluciclovine PET/CT was 7 of 28 studies (25%). PSA_{PET} > 0.2 ng/mL was associated with higher detection rates in all (33.3 vs 10%, *P*=0.172), castration-resistant (CR) (50 vs 20%, *P*=0.343) and castration-sensitive (CS) (28.6 vs 0%, *P*=0.179) patients. Sites of recurrence were local 42.9% (3/7), nodal 42.9% (3/7) and bone metastases 14.3% (1/7). Higher Gleason score (GS 8-10) (33.3 vs 14.5%, *P*=0.396), advanced tumor stage (T3-T4) (35.7 vs 20%, *P*=0.653), second-line androgen deprivation therapy (ADT) uses (66.7 vs 20%, *P*=0.145), chemotherapy uses (50 vs 23.1%, *P*=0.444) and CRPC (33.3 vs 21.1%, *P*=0.483) related to positivity of ^{18}F-Fluciclovine PET/CT but none reached statistical significance. Performance of ^{18}F-Fluciclovine PET/CT in prostate cancer patients with multiple treatment failures and PSA_{PET} ≤ 0.5 ng/mL was acceptable particularly in patients with PSA_{PET} ≥ 0.3 ng/mL, CRPC, initial GS ≥ 8 or T3-T4.

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

Introduction

Positron emission tomography (PET)/computerized tomography (CT) using prostate-specific radiolabeled molecules, e.g., ^{11}C-choline, ^{68}Ga-prostate specific membrane antigen (^{68}Ga-PSMA) and ^{18}F-anti-1-amino-3-F-18-fluorocyclobutane-1-carboxylic acid (^{18}F-FACBC or ^{18}F-Fluciclovine) have been increasingly integrated into routine work-ups for recurrent prostate cancer after they have been proven to provide superior diagnostic performance over the conventional imaging such as CT or multi-parametric magnetic resonance imaging (MRI) in detecting recurrent disease in prostate cancer patients, particularly in those with low disease volume [1, 2].

^{18}F-Fluciclovine is a food and drug administration (FDA)-approved radiolabeled artificial amino acid transported into prostate cells predominately by alanine, serine, cysteine transporter (ASCT) and L-type amino acid transporter (LAT) system. Expression of some prominent amino acid transporters (AAT) in these two systems such as ASCT2, LAT 1 and LAT 3 with various degree of intensity and affinity during both early state of disease or castration-sensitive prostate cancer (CSPC) and late state of disease or castration-resistant prostate cancer

(CRPC) makes ^{18}F-Fluciclovine feasible for prostate cancer at all states [3-5]. However, the only indication currently recommended by both the American College of Radiology and American College of Nuclear Medicine (ACR-ACNM) and the UK guidelines on ^{18}F-Fluciclovine PET/CT is to investigate recurrent prostate cancer based on the rise of serum PSA level following treatment. The other indications are still considered experimental [6, 7].

In the literatures, detection ability of ^{18}F-Fluciclovine PET/CT in recurrent disease following primary treatment, either radical prostatectomy (RP) with/without pelvic lymph node dissection (PLND) or radiotherapy (RT) with/without androgen deprivation therapy (ADT) closely relates to prostate-specific antigen (PSA) level [1, 2, 7-12]. Our previous work on the performance of ^{18}F-Fluciclovine PET/CT in post-RP patients who developed the first episode of recurrence with rising PSA ≤ 0.5 ng/mL reported the overall detection rate of 10.6% with 0% at PSA 0.1-0.2 ng/ml and 14.7% at PSA level 0.3-0.5 ng/mL [13]. Nevertheless, unlike post-RP patients with first recurrence who are mostly CSPC patients and hormone naïve, disease of patients with multiple episodes of treatment failures are probably progressing toward CRPC and they could be treated differently, depending on the previous treatments [5, 14]. In the light of differences in disease natures, we hypothesized that detection ability of ^{18}F-Fluciclovine PET/CT in patients with multiple episodes of treatment failures possibly differs from the patients with first episode of recurrence. This study was set to analyze the performance of ^{18}F-Fluciclovine PET/CT in this group of patients who had rising PSA level ≤ 0.5 ng/mL.

Materials and methods

Patients

After the approval of institutional review board, this retrospective study has been conducted in prostate cancer patients who underwent ^{18}F-Fluciclovine PET/CT at the MD Anderson Cancer Center from June, 30th 2017 to August, 9th 2019 (n=661). Histologically proven prostate cancer patients who experienced two or more episodes of treatment failures, specifically termed as "multiple treatment failures" were included into the study. As the definitions of PSA failure or recurrence are highly variable depending on primary, following and current treatments, we adopted clinical, radiologic and/or laboratory findings including treating physician management to determine treatment failure as follows; 1) continuous rise of PSA following treatment, 2) rise of PSA triggering re-evaluation of disease extension, 3) clinically or radiographically detected progression of residual disease or new lesion while receiving treatment with or without pathological confirmation, or 4) initiation of new local and/or systemic treatment. All recruited patients had PSA level within 2-week interval of ^{18}F-Fluciclovine PET/CT (PSA_{PET}) ≤ 0.5 ng/mL. Of note, the PSA threshold was set at ≤ 0.5 ng/mL as a considerable number of prostate cancer patients at our institution underwent ^{18}F-Fluciclovine at very low PSA levels. Furthermore, PSA level of 0.5 ng/mL was frequently applied as a reference threshold for treatment initiation. Undetectable PSA was defined as PSA level < 0.1 ng/mL.

Patient and tumor characteristics

Demographic data of all patients were collected from electronic medical record. Staging was following the American Joint Committee on Cancer (AJCC) 8th edition and risk stratification was in accordance with the National Comprehensive Cancer Network (NCCN) guidelines [15, 16]. Due to dissimilarities in natural history and possible differences in previous and subsequent treatments, we considered CRPC and CSPC as different entities. CRPC was defined by disease progression despite ADT with castrate level of testosterone < 50 ng/dL (T_{cas}) [17].

Treatment characteristics

Primary treatment was referred to either RP with/without PLND or definitive RT with/without ADT. Subsequent treatment for PSA failure or residual/recurrent disease included 1) local treatment to prostate gland or prostate bed (salvage RP, salvage RT with/without ADT, cryoablation, high-intensity focused ultrasound), 2) local treatment to metastatic site (stereotactic body radiation therapy with or without ADT) and 3) systemic treatment (first-line and second-line ADT, chemotherapy, targeted therapy, immunotherapy or Radium-223 dichloride). According to the NCCN guidelines, first-line ADT consisted of Luteinizing Hormone-Releasing Hormone (LHRH) agonists alone, LHRH antagonists alone or plus first generation anti-andro-

gens such as bicalutamide and flutamide. Second-line ADT was referred to second-generation anti-androgens, i.e., abiraterone, enzalutamide and apalutamide [16].

^{18}F-Fluciclovine imaging

The protocol of ^{18}F-Fluciclovine PET/CT imaging of our institution was following the ACR-ACNM guidelines [6]. Patient instructions prior to imaging included avoidance of strenuous activity for 24 hours and fast for at least 4 hours before ^{18}F-Fluciclovine injection. The average administered activity was 370 MBq (10 mCi). Imaging was performed from the mid-thigh to the top of skull at 5 minutes after intravenous injection of ^{18}F-Fluciclovine. PET/CT imaging were obtained from the 4 integrated PET/CT scanners, consisting of 2 GE 64-slice Discovery 710 PET/CT scanners, 1 GE Discovery MI 64-slice PET/CT scanner (GE Healthcare, Waukesha, Wisconsin, USA) and 1 Siemens 64-slice Biograph mCT PET/CT scanner (Siemens Medical Systems, Erlangen, Germany). All scanner passed the institutional routine quality control and have been tuned to the same sensitivity and specificity on the phantom studies.

Low-dose CT was performed with tube-current modulation with both intravenous and oral contrast. The CT protocol on the GE Discovery 710 or GE discovery MI scanner was X-ray collimation, 64×0.625 mm; pitch factor, 0.984; maximum mA, 560; minimum mA, 60; noise index, 30; gantry rotation time per revolution, 0.5 s; slice thickness, 3.75 mm; and slice increment, 3 mm. The CT protocol on the Siemens 64-slice Biograph mCT was X-ray collimation, 16×1.2 mm; pitch factor, 1.4; quality reference mA, 90; dose optimization index, 3; gantry rotation time per revolution, 0.5 s; slice thickness, 3 mm; and slice increment, 2 mm. Both GE and Siemens CT protocols were harmonized to radiation exposure of 3 mGy at a body mass index (BMI) of 25 kg/m^2. Low-dose CT data at the PET resolution in a 70-cm field of view were used for attenuation correction of the PET data in the matrix sizes of 128×128 for the GE scanners and 200×200 for Siemens scanners.

PET images were acquired at 3 min/bed position. Reconstruction protocol of PET data on GE Discovery MI scanner was OSEM 2 iterations, 17 subsets, time-of-flight, point-spread-function correction, 5 mm post-reconstruction Gaussian filtering, matrix size 1256×256 and reconstruction field of view 70 cm. Protocol on GE Discovery 710 scanners was OSEM 2 iterations, 18 subsets, time-of-flight, point-spread-function correction, 5 mm post-reconstruction Gaussian filtering, matrix size 192×192 and reconstruction field of view 70 cm. Protocol on Siemens Biograph mCT scanner was OSEM 2 iterations, 20 subsets, 6 mm post-reconstruction Gaussian filtering, matrix size 128×128 and reconstruction field of view 70 cm.

Imaging interpretation

Imaging interpretation was performed on the MIM version 6.6 (MIM Software Inc. Cleveland, OH). Interpretation criteria were following the ACR-ACNM guidelines and the joint European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) procedure guideline for prostate cancer imaging-version 1.0 [6, 18]. The initial interpretation of the ^{18}F-Fluciclovine PET/CT was performed by a group of 10 board certified nuclear medicine physicians. All the images were reinterpreted by 3 board certified nuclear medicine physicians, each with over 200 ^{18}F-Fluciclovine PET/CT interpretation experience. Discrepancy findings between investigators were discussed with consensus made. A boarded nuclear medicine physician with more than 300 ^{18}F-Fluciclovine PET/CT interpretation experience was the final arbiter of the imaging studies. Consensus were reached after this subsequent review and minimal 6 months follow up until February, 2020.

A positive/suspicious lesion in this study was defined as: a lesion greater than 1 cm in size with uptake intensity significantly greater than bone marrow (preferred L3 vertebra), or a lesion less than 1 cm in size with uptake intensity equal to or approaching bone marrow and significantly greater than blood pool. Other considerations for suspicious lesions included asymmetrical uptake within an intact prostate, small avid LN in typical location of recurrence and clearly visualized focal bone uptake.

Statistical analysis

Demographics characteristics and detectability of ^{18}F-Fluciclovine PET/CT were analyzed using descriptive statistics. The linear regression method using least square technique with-

Table 1. Demographic characteristics at time of initial diagnosis

	Positive study (n=7)	Negative study (n=21)	Overall (n=28)
Age, years			
Median (range)	61.1 (50.8-71.2)	59.5 (54-76.1)	60.6 (50.8-76.1)
PSA at diagnosis, ng/mL			
Median (range)	5.6 (1.4-40.0)	7.1 (3.4-24.6)	6.6 (1.4-40.0)
Gleason score, n (%)			
6-7	2 (28.6)	11 (52.4)	13 (46.4)
8-10	5 (71.4)	10 (47.6)	15 (53.6)
T classification, n (%)			
T1-T2	2 (28.6)	8 (38.1)	10 (35.7)
T3-T4	5 (71.4)	9 (42.9)	14 (50)
Tx	0	4 (19)	4 (14.3)
N classification, n (%)			
N0	5 (71.4)	12 (57.1)	17 (60.7)
N1	1 (14.3)	3 (14.3)	4 (14.3)
Nx	1 (14.3)	6 (28.6)	7 (25)
M classification, n (%)			
M0	6 (85.7)	18 (85.7)	24 (85.7)
M1	0	1 (4.8)	1 (3.6)
Mx	1 (14.3)	2 (9.5)	3 (10.7)
Extra-prostatic extension, n (%)			
Absence	1 (14.3)	5 (23.8)	6 (21.4)
Presence	4 (57.1)	9 (42.9)	13 (46.4)
Unknown	2 (28.6)	7 (33.3)	9 (32.1)
Surgical margin, n (%)			
Negative	4 (57.1)	7 (33.3)	11 (39.3)
Positive	2 (28.6)	7 (33.3)	9 (32.1)
Unknown	1 (14.3)	7 (33.3)	8 (28.6)
Seminal vesicle invasion, n (%)			
Absence	2 (28.6)	7 (33.3)	9 (32.1)
Presence	3 (42.9)	7 (33.3)	10 (35.7)
Unknown	2 (28.6)	7 (33.3)	9 (32.1)
Lymphovascular invasion, n (%)			
Absence	2 (28.6)	2 (9.5)	4 (14.3)
Presence	2 (28.6)	6 (28.6)	8 (28.6)
Unknown	3 (42.9)	13 (61.9)	16 (57.1)
Perineural invasion, n (%)			
Absence	0	0	0
Presence	4 (57.1)	8 (38.1)	12 (42.9)
Unknown	3 (42.9)	13 (61.9)	16 (57.1)
Risk classification, n (%)			
Intermediate	1 (14.3)	4 (19)	5 (17.9)
High	3 (42.9)	4 (19)	7 (25)
Very high	3 (42.9)	8 (38.1)	11 (39.3)
Unknown	0	5 (23.8)	5 (17.9)

PSA, prostate-specific antigen.

out logarithmic transformation was applied for PSA doubling time (PSADT) estimation [19]. Parametric and non-parametric continuous data were compared using independent t-test and

Table 2. Primary and subsequent treatment characteristics

	Positive study (n=7)	Negative study (n=21)	Overall (n=28)
Primary treatment, n (%)			
RP ± PLND	6 (85.7)	17 (81)	23 (82.1)
RT ± ADT	1 (14.3)	4 (19)	5 (17.9)
Subsequent treatment, n (%)			
Local treatment*, n (%)			
No	3 (42.9)	6 (28.6)	9 (32.1)
Yes	4 (57.1)	15 (71.4)	19 (67.9)
ADT, n (%)			
Naïve	2 (28.6)	5 (23.8)	7 (25)
First-line	3 (42.9)	15 (71.4)	18 (64.3)
Second-line	2 (28.6)	1 (4.8)	3 (10.7)
Chemotherapy, n (%)			
Naïve	6 (85.7)	20 (95.2)	26 (92.9)
Non-Naïve	1 (14.3)	1 (4.8)	2 (7.1)

RP, radical prostatectomy; PLND, pelvic lymph node dissection; RT, radiotherapy; ADT, androgen deprivation therapy. *Local treatment consisted of salvage RT (n=3 for positive and n=13 for negative subgroup) and cryoablation (n=1 for positive and n=2 for negative subgroup).

Table 3. Detectability of ^{18}F-Fluciclovine PET/CT by PSA and testosterone levels

	No. of patients	No. of positive	Positivity rate (%)
All patients	28	7	25
Stratified by PSA			
PSA ≤ 0.2 ng/mL	10	1	10
PSA > 0.2 ng/mL	18	6	33.3
			P=0.172*
Stratified by castration			
CRPC			
PSA ≤ 0.2 ng/mL	5	1	20
PSA > 0.2 ng/mL	4	2	50
			P=0.343*
CSPC			
PSA ≤ 0.2 ng/mL	5	0	0
PSA > 0.2 ng/mL	14	4	28.6
			P=0.179*

PSA, prostate-specific antigen; CSPC, castration-sensitive prostate cancer; CRPC, castration-resistant prostate cancer. *Comparison across 2 strata by the Fisher's Exact test.

Mann-Whitney U-test, respectively. Fisher's exact test was used for comparison of categorical data. The statistically significant *p*-value was set at 0.05. All statistical analyses were performed using the IBM SPSS Statistics software for Windows, version 21.0 (Armonk, NY: IBM Corp.).

Results

Patient and tumor characteristics at the time of initial diagnosis

There were a total of 28 eligible patients included in the analysis. Detailed demographic characteristics at the time of initial diagnosis of all patients and as stratified by positive (n=7) and negative (n=21) studies are shown in **Table 1**. The median age of all patients was 60.6 years (range 50.8-76.1) and median PSA level was 6.6 ng/mL (range 1.4-40). Proportion of GS 8-10 (71.4 vs 47.6%) and T3-T4 classification (71.4 vs 42.9%) were higher in patients with positive studies. The remaining characteristics, including N and M classification, extra-prostatic extension (EPE), surgical margin (SM), seminal vesicle invasion (SVI), lymphovascular invasion, perineural invasion and risk stratification were comparable between two subgroups.

Treatment characteristics

Table 2 displays primary and subsequent treatments (at any time during the course of disease) of all patients and as stratified by positive and negative studies. Majority of patients in both subgroups underwent RP ± PLND (85.7 vs 81%) as primary treatment. Regarding the subsequent treatment, number of patients receiving local treatment in negative subgroup was higher than that of positive subgroup (71.4 vs 57.1%). In contrast, second-line ADT (28.6 vs 4.8%) and chemotherapy (14.3 vs 3.8%) were more common in positive subgroup.

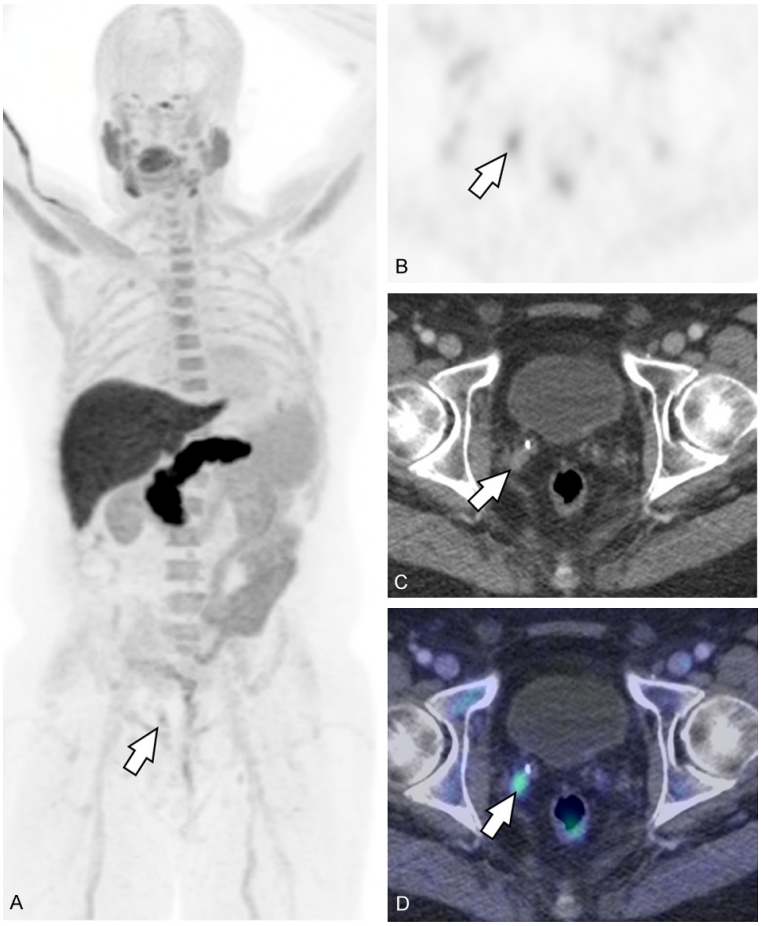

Figure 1. Recurrence tumor at prostatectomy bed with PSA level 0.3 ng/mL. A 69-year-old CRPC patient, initial staging T3bN0M0 and GS 7 (4+3) status post neoadjuvant ADT and RP + PLND, and abiraterone with intermittent ADT. Patient had PSA of 0.3 ng/mL rising from 0.1 ng/ml at time of ^{18}F-Fluciclovine PET/CT (A: MIP; B: Axial PET; C: Axial contrast enchancing CT; D: Axial fused PET/CT). The images showed a subtle enchancing 1.3×0.7 cm ^{18}F-Fluciclovine-avid nodule at superior aspect of prostatectomy bed (SUV_{max} 3.6).

PSA and castration characteristics at time of ^{18}F-Fluciclovine PET/CT

There were 9 of 28 patients who received ADT with T_{cas} (32.1%) at time of ^{18}F-Fluciclovine PET/CT performed. Nine patients were considered as CRPC (32.1%) and the remaining 19 patients were considered as CSPC (67.9%).

The median PSA_{PET} of positive and negative subgroups irrespective of castration status were 0.4 ng/mL (range 0.2-0.5) and 0.4 ng/mL (range 0.1-0.5), respectively. The median PSA_{PET} of CRPC patients with positive (n=3) and negative (n=6) ^{18}F-Fluciclovine PET/CT were 0.3 ng/mL (range 0.2-0.4) and 0.2 ng/mL (range 0.1-0.5), respectively. The median PSA_{PET} of CSPC patients with positive (n=4) and negative (n=15) studies were 0.4 ng/mL (range 0.4-0.5) and 0.4 ng/mL (range 0.1-0.5), respectively.

Regarding the PSADT estimation, 12 patients were ineligible due to receiving ADT (n=9), having only 1 PSA value (n=1) and stable PSA values for 2 or more consecutive times (n=2). The median PSADT of patient with positive (n=4) and negative (n=12) subgroups were 4.7 months (range 1.2-12.2) and 10.4 months (range 1.4-20.8), respectively.

Detection ability of ^{18}F-Fluciclovine PET/CT

Table 3 demonstrates the detection rates as stratified by PSA and testosterone levels. In brief, the overall detection rate of ^{18}F-Fluciclovine PET/CT was 25% with 10% and 33% for PSA_{PET} values ≤ 0.2 and > 0.2 ng/mL, respectively. The detection rate of CRPC and CSPC patients with PSA_{PET} values ≤ 0.2 and > 0.2 ng/mL were 20 vs 50% (*P*=0.343) and 0 vs 28.6% (*P*=0.179), respectively.

Sites of recurrence were prostate gland/bed in 3 of 7 studies (42.9%) with one case shown in **Figure 1**, pelvic LN in 3 of 7 studies (42.9%) with one case shown in **Figure 2** and multiple bone metastasis in 1 of 7 studies (14.3%) as illustrated in **Figure 3**. All nodal recurrences were ≥ 2 LNs and in 2 of 3 studies (66.7%), involved LNs were at different regions. There was no remarkable difference in site of recurrence between CSPC and CRPC patients. The full details of positive studies, including patient, tumor and treatment characteristics as well as related work-ups are demonstrated in **Table 4**.

Comparison of detection rate by clinical factors

^{18}F-Fluciclovine PET/CT tended to demonstrate recurrent disease in patients with high GS (GS

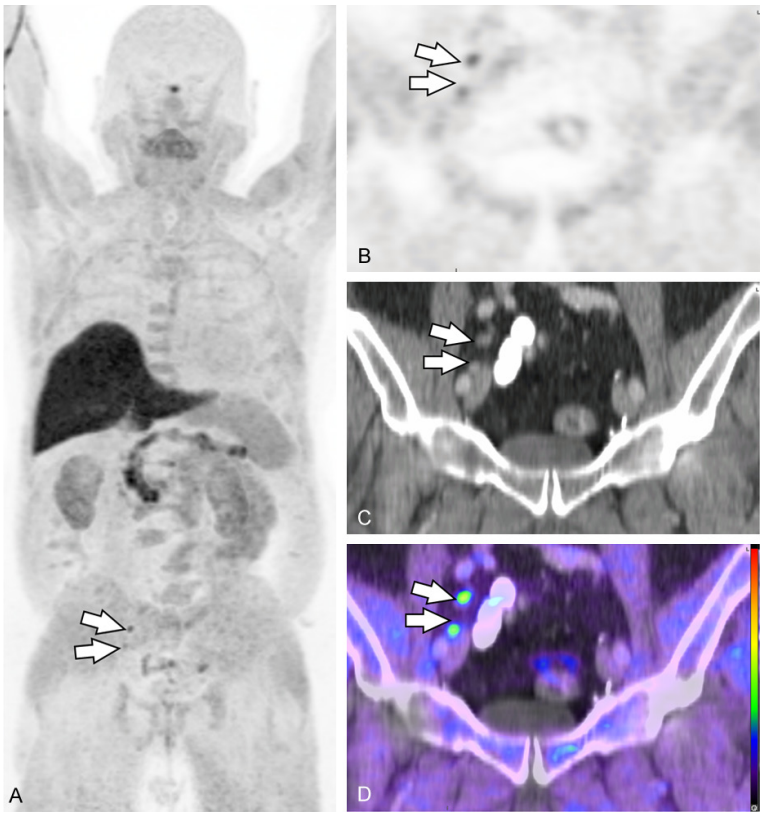

Figure 2. Pelvic lymph node metastasis with PSA level 0.2 ng/mL. A 73-year-old CRPC patient, initial staging T3aN0M0 and GS 8 (3+5) status post RP + PLND in 1997, RT for bone metastasis at T6 vertebra + chemotherapy + ADT in 1999, abiraterone in 2013 and cryoablation for surgical bed recurrence in May, 2018. At time of ^{18}F-Fluciclovine PET/CT while being on ADT in May, 2019, PSA rose from < 0.1 ng/ml to 0.2 ng/ml. The ^{18}F-Fluciclovine PET/CT images (A: MIP; B: Coronal PET; C: Coronal contrast enhancing CT; D: Coronal fused PET/CT) showed two ^{18}F-Fluciclovine-avid right external iliac lymph nodes (arrows in A-D), measures 0.9 cm (SUV_{max} 5.4) and 0.6 cm (SUV_{max} 4.1) respectively, and was later biopsy proven to be metastasis.

6-7 vs GS 8-10, 15.4 vs 33.3%) and advanced tumor stage (T1-T2 vs T3-T4, 20 vs 35.7%) at initial presentation but the differences did not reach statistical significance (P > 0.3). Use of second-line ADT (20 vs 66.7%, *P*=0.145) and chemotherapy (23.1 vs 50%, *P*=0.444) as subsequent treatment was more common in positive subgroup. In contrast, local treatment was more common in negative subgroup (37.5 vs 20%, *P*=0.371). Positivity rate of CRPC was higher than that of CSPC but was not statistically significant (33.3 vs 21.1%, *P*=0.483) (**Table 5**).

Discussion

Performance of ^{18}F-Fluciclovine PET/CT in primary treatment failure (failure after primary treatment or first recurrence) has been widely investigated for years, leading to an extensive information on the benefits of ^{18}F-Fluciclovine PET/CT in this group of patients [1, 2, 8-11]. On the contrary, studies on ^{18}F-Fluciclovine PET/CT in multiple treatment failure seemed to be very limited. We expected a distinct performance of ^{18}F-Fluciclovine PET/CT in patients with multiple treatment failure who had very low PSA level. Consequently, we conducted the current study to assess the detection ability of ^{18}F-Fluciclovine PET/CT and factors relating to positivity of ^{18}F-Fluciclovine PET/CT in such patients with PSA level ≤ 0.5 ng/mL.

The overall detection rate of ^{18}F-Fluciclovine PET/CT in post-RP failure with PSA_{PET} ≤ 0.5 ng/mL was only 10.6% [13]. In the current study, performance of ^{18}F-Fluciclovine PET/CT in multiple treatment failures with the same PSA level cut-off was twice better with overall detection rate of 25%. This finding not only supported our hypothesis that performance of ^{18}F-Fluciclovine PET/CT would be changed during the course of disease but also reassured an even better detection ability of ^{18}F-Fluciclovine PET/CT in patients with multiple treatment failures.

Linear correlation between PSA level and diagnostic performance of ^{18}F-Fluciclovine PET/CT in primary treatment failure patients has been proven by several studies [8-10, 13]. A similar trend was also noted in our multiple treatment failure patients. Detection ability of ^{18}F-Fluciclovine PET/CT was limited at PSA_{PET} level ≤ 0.2 ng/mL and was obviously failed to depict disease in non-T_{cas} patients with PSA_{PET} ≤ 0.2 ng/mL (**Table 3**). These findings might infer that disease localization could be achieved only when the PSA level was high enough and a reasonable threshold for ^{18}F-Fluciclovine PET/CT

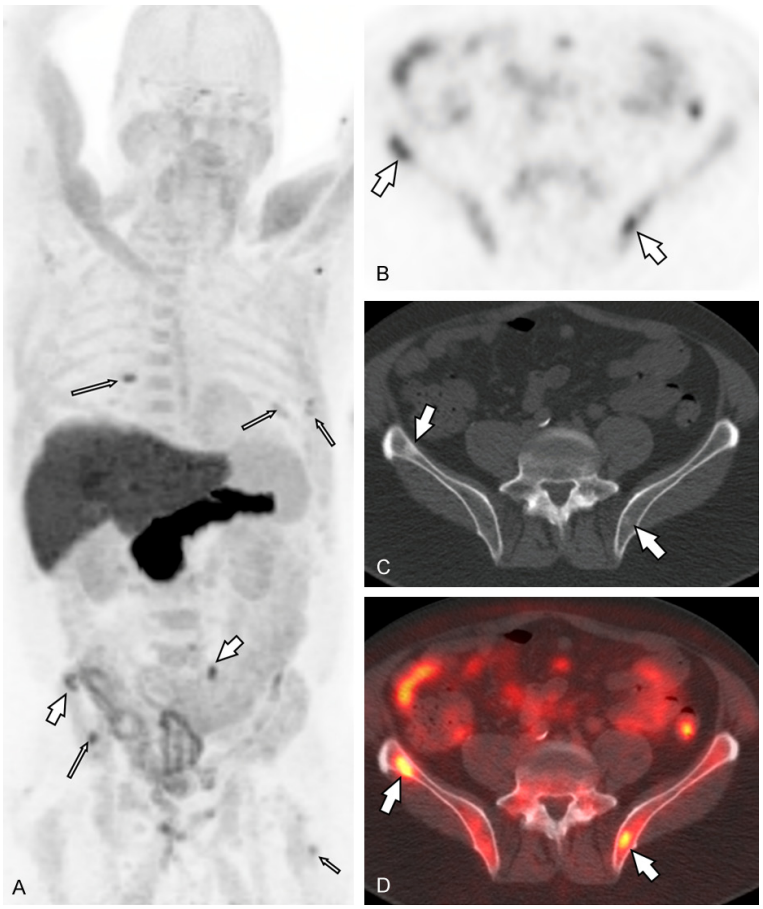

Figure 3. Bone metastases with PSA level 0.5 ng/mL. A 69-year-old patient with initial staging T3bN1M0 and GS 9 (4+5) status post RP + PLND, and ADT. At time of ^{18}F-Fluciclovine PET/CT, PSA rose from < 0.1 ng/mL to 0.5 ng/mL. The ^{18}F-Fluciclovine PET/CT images (A: MIP; B: Axial PET; C: Axial CT; D: Axial fused PET/CT) showed multiple sclerotic bone metastases at both iliac bones (block arrows in A-D), additional bone metastasis sites were marked by thin arrows on MIP image.

regardless of ADT use or castration status might be around 0.3 ng/mL.

The median PSA_{PET} of positive and negative studies of all population (0.4 vs 0.4 ng/mL), CRPC (0.3 vs 0.2 ng/mL) and CSPC (0.4 vs 0.4 ng/mL) patients were not much different. As a result, PSA_{PET} was unlikely to be a strong predictor of positive ^{18}F-Fluciclovine PET/CT. This presumption was well-supported by the independent mechanisms of ^{18}F-Fluciclovine uptake and PSA production. While ^{18}F-Fluciclovine uptake closely relates to the upregulation of LAT1 transporter in response to the proliferation of cancer cells, PSA production largely depends on the histologic subtypes of cancer cells [20-26]. Negative ^{18}F-Fluciclovine PET/CT with low PSA_{PET} might reflect truly low disease burden beyond the detection ability of ^{18}F-Fluciclovine PET/CT. Meanwhile, positive ^{18}F-Fluciclovine PET/CT with the same low PSA_{PET} level might relate to an aggressive cell proliferation with decreased PSA production resulting from histologic transformation. These examples might explain why PSA_{PET}, especially very low levels could not be a reasonable predictor of ^{18}F-Fluciclovine PET/CT findings.

The studies in primary treatment failure patients reported the association between PSADT and positivity of ^{18}F-Fluciclovine PET/CT [7, 27]. Among primary treatment failure patients with rather high PSA level (mean 7.9 ± 14.6 ng/mL), a significantly shorter PSADT was observed in patients with positive ^{18}F-Fluciclovine PET/CT (3.25 ± 2.09 vs 31.2 ± 22.0 months, P < 0.0001) [27]. Even so, effect of PSADT on detectability of ^{18}F-Fluciclovine was not strong at PSA level ≤ 0.5 ng/mL (3.3 vs 6.5 months, P=0.053) [13]. The median PSADT of positive and negative subgroups of the current study (4.7 vs 10.4 months) was rather in line with other studies. Nonetheless, correlation between PSADT and ^{18}F-Fluciclovine PET/CT findings might be inconclusive given that PSADT values were derived from a few number of patients (n=16).

Common features of positive ^{18}F-Fluciclovine PET/CT patients consisting of GS 8-10 (71.4 vs 47.6%), initial T3-T4 (71.4 vs 42.9%) and CRPC (33.3 vs 21.1%) including their treatment feature, i.e., use of second-line ADT (28.6 vs 4.8%) and chemotherapy (14.3 vs 4.8%) were corresponding with a previous study in patients with undetectable PSA level [25]. Several immunohistochemistry studies of AATs in prostate cancer were also reinforced our findings [28, 29]. LAT1 overexpression was proven to relate with

Table 4. Positive ^{18}F-Fluciclovine PET/CT

No.	Initial PSA	GS	EPE	SVI	SM	T	N	M	Risk class.	Primary Rx	PSA after primary Rx	Subsequent Rx	PSA after subsequent Rx	Castration status	PSA_{PET}	Detected lesions	Concordant work-up
1	5.1	7 (4+3)	yes	yes	no	T3b	N0	M0	high	Neoadjuvant ADT + RP + PLND	undetectable	Intermittent 1st-line ADT + Abiraterone	detectable	CRPC	0.3*	Right prostatectomy bed, size 1.4×1.0 cm., SUV_{max} 3.6	CT
2	40	8 (4+4)	n/a	n/a	n/a	T2	N0	M0	high	RT + 1st-line ADT for 2 years	undetectable	1st-line ADT for 6 years	undetectable	CRPC	0.4*	Left side of prostate bed, size n/a, SUV_{max} 4.3	MRI
3	5.8	6 (3+3)	no	no	yes	T2	N0	M0	intermediate	RP + PLND	detectable	RT	undetectable	CSPC	0.4	Left prostatectomy bed, size n/a, SUV_{max} 4.0	Biopsy
4	n/a	8 (3+5)	yes	no	no	T3a	N0	M0	high	RP + PLND	undetectable	- CMT + 1st-line ADT - Abiraterone - Cryoablation	undetectable	CRPC	0.2*	Two right external iliac LNs, size 0.9 cm., SUV_{max} 5.4 and size 0.6 cm., SUV_{max} 4.1	CT
5	1.4	8 (4+4)	yes	yes	no	T3b	N0	M0	very high	RP + PLND	detectable	RT + 1st-line ADT	undetectable	CSPC	0.4	Left pelvic LN size 1.0 cm., SUV_{max} 11.4 Left deep inguinal LN size 0.7 cm., SUV_{max} 5.5	-
6	3.4	9 (4+5)	yes	no	yes	T3a	N0	M0	high	RP + PLND	detectable	RT	undetectable	CSPC	0.4	Right external iliac LN size 1.0 cm., SUV_{max} 6.0 Left internal iliac LN size 0.7 cm., SUV_{max} 6.0	-
7	6.89	9 (4+5)	yes	yes	no	T3b	N1	M0	very high	RP + PLND	undetectable	1st-line ADT for 1 year	undetectable	CSPC	0.5	Bone metastasis at both iliac bones, few thoracic vertebrae and few ribs	MRI

*PSA during ADT; PSA, prostate-specific antigen; n/a, not available; GS, Gleason score; EPE, extra-prostatic extension; SVI, seminal vesicle invasion; SM, surgical margin; T, tumor classification; N, lymph node classification; M, metastasis; class, classification; Rx, treatment; RP, radical prostatectomy; PLND, pelvic lymph node dissection; RT, radiotherapy; 1st-line ADT, first-line androgen deprivation therapy; PSA_{PET}, PSA level at time of ^{18}F-Fluciclovine PET/CT; CSPC, castration-sensitive prostate cancer; CRPC, castration-resistant prostate cancer; SUV, standardized uptake value; LN, lymph node; CT, computerized tomography; MRI, magnetic-resonance imaging.

Table 5. Comparison of detection rate by clinical factors

Factors		No. of patients	No. of positive	Positivity rate (%)	*p*-value
Gleason score	6-7	13	2	15.4	0.396
	8-10	15	5	33.3	
T classification	T1-T2	10	2	20	0.653
	T3-T4	14	5	35.7	
Local treatment*	No	8	3	37.5	0.371
	Yes	20	4	20	
Second-line ADT	No	25	5	20	0.145
	Yes	3	2	66.7	
Chemotherapy	No	26	6	23.1	0.444
	Yes	2	1	50	
Castration status	CSPC	19	4	21.1	0.483
	CRPC	9	3	33.3	

ADT, androgen deprivation therapy; CSPC, castration-sensitive prostate cancer; CRPC, castration-resistant prostate cancer; *Local treatment consisted of salvage RT and cryoablation for residual or recurrent disease.

GS ≥ 7 (4+3), T3-T4 and poorer survival outcome of prostate cancer patients [28, 29]. Likewise, ASCT2 expression was found to have a remarkable correlation with preoperative PSA level, GS and LN status [30]. Consequently, it might presume that better performance of ^{18}F-Fluciclovine PET/CT in patients with relatively more aggressive or advanced stage prostate cancer might actually be the result of high degree of LAT1 and ASCT2 expression.

ADT has been proven to inhibit the uptake of ^{11}C- and ^{18}F-Choline by prostate cancer cell, resulting in false negative Choline PET/CT studies and a following recommendation to withdraw ADT prior to the study [31-33]. ADT was also known to regulate the expression of AATs responsible for ^{18}F-Fluciclovine uptake, thereby raising a concern that ADT might decrease the detection ability of ^{18}F-Fluciclovine PET/CT [3-5, 14, 34]. In the current study, ADT was deemed not to impair the performance of ^{18}F-Fluciclovine PET/CT as a positivity rate of patients with ADT was higher than those without ADT (33.3 vs 21.1%, *P*=0.483). In our viewpoint, this unexpected finding could be explained by the fact that our patients with ADT were coincidentally CRPC patients who generally had LAT1 overexpression, whereas patients without ADT were concurrently CSPC patients who had LAT3 as a dominant AAT [3, 4, 34]. Affinity of LAT1 for-Fluciclovine was higher than that of LAT3 [4]. Therefore, detection rate of ^{18}F-Fluciclovine PET/CT among patients with ADT or essentially CRPC patients in this study could be higher than their counterparts.

Prostate gland/bed and pelvic LN were the common sites of multiple treatment failures, similar to that of primary treatment failure [13]. However, while LN recurrence in primary treatment failure patients (post-RP patients) were all single LN, recurrent LN in multiple treatment failure patients with the equal PSA levels (≤ 0.5 ng/mL) were multiple LNs [13]. In a similar way, rate of distant metastasis in our cohort was not much different from the primary treatment failure patients (14.3 vs 10%) [13]. Nevertheless, bone metastasis in our study was multiple lesions, similar to LN metastasis. These might assume that at very low PSA level, patterns of disease recurrence/progression were the same for both first and subsequent episodes but more aggressive natures of multiple treatment failures could produce higher disease burdens.

This study was significant as one of a few works that addressed the ability of ^{18}F-Fluciclovine PET/CT in early detection (PSA_{PET} ≤ 0.5 ng/mL) of possible recurrent or progressive disease in patients who have experienced multiple episodes of treatment failure. Our notable findings included some features (GS, tumor stage, castration status and PSA_{PET}), probably relating to positive ^{18}F-Fluciclovine PET/CT that could be used as a guidance for patient selection.

Limitations of the current study mainly resulted from its retrospective nature. First, clinical data was incomplete mainly because many patients were referred from outside hospitals. Moreover, missing data during a lengthy period of follow-up from the initial diagnosis to second or subsequent recurrences (median 8 years, range 1.2-22.0) was unavoidable. Second, imaging or histopathologic confirmations were not available for all-Fluciclovine avid lesions; there were only 1 patient with histopathology and 4 patients with follow-up CT or MRI. Lastly, small number of patients with heterogeneous disease characteristics largely limited the power of statistical analysis. Further study with larger sample size and thereby more positive

^{18}F-Fluciclovine PET/CT studies may require to establish a more robust evidence.

Conclusion

Utilization of ^{18}F-Fluciclovine PET/CT in patients with multiple episodes of treatment failures who had $PSA_{PET} \leq 0.5$ ng/mL yielded an acceptable performance. Majority of detected disease were multiple lesions but still intra-pelvis, similar to primary treatment failure. $PSA_{PET} \geq 0.3$ ng/mL, CRPC, initial GS ≥ 8 or T3-T4 might enhance the detection ability of ^{18}F-Fluciclovine PET/CT.

Disclosure of conflict of interest

None.

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