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Prospective, Single-Arm Trial Evaluating Changes in Uptake Patterns on Prostate-Specific Membrane Antigen (PSMA)-Targeted ^{18}F-DCFPyL PET/CT in Patients with Castration-Resistant Prostate Cancer Starting Abiraterone or Enzalutamide

Running Title: PSMA PET Post Anti-Androgen Therapy

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Abstract

Purpose: Positron emission tomography (PET) with small molecules targeting prostate-specific membrane antigen (PSMA) is being adopted as a clinical standard for prostate cancer (PCa) imaging. In this study, we evaluated changes in uptake on PSMA-targeted PET in men starting abiraterone or enzalutamide.

Methods: This prospective, single-arm, two-center, exploratory clinical trial enrolled men with metastatic castration-resistant prostate cancer (CRPC) initiating abiraterone or enzalutamide. Each patient was imaged with ^{18}F-DCFPyL at baseline and within 2-4 months after starting therapy. Patients were followed for up to 48 months from enrollment. A central review evaluated baseline and follow-up PET scans recording change in maximum standardized uptake value (SUV_{max}) at all disease sites and classifying the pattern of change. Two parameters: the delta percent SUV_{max} (DPSM) of all lesions and the delta absolute SUV_{max} (DASM) of all lesions were derived. Kaplan-Meier curves were used to estimate time to therapy change (TTTC) and overall survival (OS).

Results: Sixteen evaluable patients were accrued to the study. Median TTTC was 9.6 months (95% confidence interval (CI), 6.9-14.2) and median OS was 28.6 months (95% CI 18.3-not available (N/A)). Patients with a mixed-but-predominantly-increased pattern of radiotracer uptake had shorter TTTC and OS. Men with low DPSM had median TTTC 12.2 months (95% CI 11.3-N/A) and median OS 37.2 months (95% CI 28.9-N/A), while those with high DPSM had median TTTC 6.5 months (95% CI 4.6-N/A, $P = 0.0001$) and median OS 17.8 months (95% CI 13.9-N/A, $P = 0.02$). Men with low DASM had median TTTC 12.2 months (95% CI 11.3-N/A) and median OS N/A (95% CI 37.2 months-N/A), while those with high DASM had median TTTC 6.9 months (95% CI 6.1-N/A, $P = 0.003$) and median OS 17.8 months (95% CI 13.9-N/A, $P = 0.002$).

Conclusions: Findings on PSMA-targeted PET 2-4 months after initiation of abiraterone or enzalutamide are associated with TTTC and OS. Development of new lesions and/or increasing intensity of radiotracer uptake at sites of baseline disease are poor prognostic findings suggesting shorter TTTC and OS.

Key Words: Anti-androgen; response assessment; CRPC; radiopharmaceutical; prognosis

Introduction

There is interest in the use of positron emission tomography (PET) radiotracers targeting the prostate-specific membrane antigen (PSMA) to improve imaging of men with prostate cancer (PCa) (*1*). PSMA is a transmembrane type II glycoprotein that is overexpressed on most PCa cells (*2*). Over the last 5 years, PSMA-targeted imaging has been used for initial staging of men with high-risk PCa (*3*), re-staging of men with biochemical failure after attempted curative local therapy (*4*), and selection of men with metastatic disease for treatment with PSMA-targeted endoradiotherapy (*5*).

There are little data on the prognostic value of PSMA-targeted PET and the use of PSMA ligands for following response to therapy in men with PCa. For first-line systemic treatment with androgen deprivation therapy (ADT), the interplay between androgen signaling and PSMA expression can lead to increased PSMA on the cell surface and a short-term flare phenomenon on PSMA-targeted PET (*6,7*). Long-term ADT tends to produce decreasing lesion conspicuity (*8*). Some studies have reported flare in castration-resistant PCa (CRPC) following initiation of second-generation anti-androgen agents (abiraterone or enzalutamide) (*9,10*), while others suggest increasing uptake on PSMA-targeted PET reflects progression and worsening disease (*11*). There is increasing interest in following patients with PCa using serial PSMA-targeted PET, and an approach to determining progression was recently introduced (*12*).

The aim of this prospective, single-arm, two-center, exploratory clinical trial was to evaluate the ability of PSMA-targeted PET to determine progression relative to conventional imaging with bone scan and computed tomography (CT). A post-hoc analysis was also used to provide pilot data on the association of metrics of response and survival between baseline and short interval follow-up PSMA-targeted PET/CT using ^{18}F-DCFPyL (*13*) in men with CRPC starting treatment with abiraterone or enzalutamide.

Materials and Methods

This study was registered with ClinicalTrials.gov (NCT02856100, NCT02691169) and was carried out under the auspices of a United States Food and Drug Administration Investigational New Drug application (IND121064) and Health Canada Clinical Trial Application (Control#190215). The study was approved by the institutional review boards at both McMaster University and Johns Hopkins Hospital.

Patients

Inclusion criteria for the study: (1) age ≥18 years; (2) histologically or cytologically confirmed prostate adenocarcinoma without neuroendocrine differentiation or small cell features; (3) planned to start abiraterone or enzalutamide within 1-7 days after baseline ^{18}F-DCFPyL PET/CT; (4) documented progressive metastatic PCa as assessed by the treating clinician with either rising serum prostate specific antigen (PSA) on 2 determinations at least one week apart and/or radiographic progression; (5) ongoing androgen deprivation with serum testosterone < 50 ng/dL; (6) Eastern Cooperative Oncology Group performance status ≤2; (7) hemoglobin ≥90 g/L; (8) platelet count >100,000/μL; (9) serum albumin ≥30 g/L; (10) serum creatinine <1.5 x upper limits of normal or calculated creatinine clearance ≥60 mL/min; and (11) serum potassium ≥3.5 mmol/L.

The exclusion criteria were: (1) abnormal liver function with serum bilirubin ≥1.5 x upper limit of normal and/or AST or ALT ≥2.5 x upper limits of normal; (2) uncontrolled hypertension; (3) active viral hepatitis or chronic liver disease; (4) history of pituitary or adrenal dysfunction; (4) clinically significant heart disease; (5) other malignancies except non-melanoma skin cancer; (6) known brain metastases; (7) history of gastrointestinal disorders that would interfere with absorption of orally administered hormonal agents; (8) unresolved acute toxicities due to prior therapy; (9) current enrollment in an investigational

drug or device study or participation in such a study within 30 days. Figure 1 shows a STARD diagram of this study.

Imaging Protocol

Baseline ^{18}F-DCFPyL PET/CT was performed within 7 days of initiating abiraterone or enzalutamide therapy. Follow-up PET/CT was done between two and four months after initiation of therapy. ^{18}F-DCFPyL was synthesized according to current good manufacturing practices as previously described (*14*). Patients were asked to be *nil per os* for 4 hours prior to radiotracer administration. 333 MBq (9 mCi) of ^{18}F-DCFPyL were administered intravenously 60±10 minutes prior to imaging. PET/CT from the mid-thighs through the skull vertex was obtained on one of several scanners: a 128-slice Biograph mCT (Siemens Healthineers, Erlangen, Germany), a 16-slice Biograph (Siemens Healthineers, Erlangen, Germany), or a 64-slice Discovery RX (General Electric, Waukesha, WI, USA). Scanners were operated in 3D emission mode with CT attenuation correction. Standard ordered-subset expectation maximization reconstructions were used. All images were transferred to a central workstation for review. The baseline PET/CT is hereafter refered to as PET1 and follow-up PET/CT scan as PET2.

Within 2 weeks of PET1 or PET2, respectively, baseline and follow-up conventional imaging (bone scan and contrast-enhanced CT chest, abdomen, and pelvis) were obtained.

Clinical Follow-Up

PSA was assessed at baseline and at the time of follow-up imaging. PSA response to therapy was considered significantly decreased (>50% PSA decrease), stable (≤ 50% decrease), or increased. Time-to-therapy change (TTTC; a surrogate for clinical progression) and overall survival (OS) were determined by review of the electronic medical

record. TTTC was calculated as the number of days the patient was on a second-generation anti-androgen therapy until the primary treating oncologist determined that progression had occurred (based on standard-of-care imaging or laboratory or clinical assessment), the patient died, or the patient was lost to follow-up. OS was calculated as the number of days from initiation of second-generation anti-androgen therapy to death, loss to follow-up, or final date of censoring. Data were censored on April 20, 2020, 48 months after the start of the study.

Image Analysis

A consensus central review was carried out with all images analyzed by 3 board-certified nuclear medicine physicians with experience in the interpretation of PSMA-targeted PET (KAZ, SYC, and SPR). Images were analyzed using a Mirada XD3 workstation (Mirada Medical, Oxford, UK). For each PET, the total number of ^{18}F-DCFPyL-positive disease sites, in addition to location, size and avidity ($SUV_{max,}$) of each lesion, was recorded. The total tumor burden was defined as the total number of sites of ^{18}F-DCFPyL-positive disease. The change in avidity (SUV_{max}) for each lesion between PET1 and PET2, and the appearance of new lesions, were determined. The overall change in avidity between PET1 and PET2 was then classified into one of five categories: (1) all-increased (all lesions increased in avidity), (2) mixed-but-predominantly-increased (>50% of lesions increased in avidity, Figure 2), (3) mixed (equal number of lesions increased as decreased in avidity), (4) mixed-but-predominantly-decreased (> 50% lesions decreased in avidity), and (5) all-decreased (all lesions decreased in avidity). We defined 2 additional ^{18}F-DCFPyL PET parameters to semi-quantitatively reflect change from PET1 to PET2: (1) delta percent SUV_{max} (DPSM) or the sum of the percent change in SUV_{max} between PET1 and PET2 for ^{18}F-DCFPyL-positive disease sites (not including new lesions):

$$DPSM = \sum \frac{(SUV_{maxPET2} - SUV_{maxPET1})}{SUV_{maxPET1}} X\ 100$$

and (2) delta absolute SUV_{max} (DASM) or the sum of the absolute SUV_{max} change between PET1 and PET2 for ^{18}F-DCFPyL-positive disease sites (not including new lesions):

$$DASM = \sum SUV_{maxPET2} - SUV_{maxPET1}$$

The conventional imaging obtained at the time of PET1 and PET2 was reviewed by the same readers. Utilizing RECIST 1.1, all patients were classified as having response, stable disease, or progression at the PET2 time point.

Statistical Methods

Continuous variables are reported as median and interquartile range (IQR). Patients were classified into high and low groups based on median values. The cutoff value for DPSM, DASM and number of lesions at baseline were 33, 556 and 13, respectively. To compare ^{18}F-DCFPyL PET/CT to conventional imaging, we treated DASM and DAPM above the median for this patient cohort as evidence of progression on PET. Kaplan-Meier curves were used to estimate TTTC and OS probabilities and the univariate Cox proportional-hazards model was used to compare differences in TTTC and OS between the high and low groups. Kaplan-Meier curves were utilized instead of cumulative probability curves for TTTC because no deaths occurred prior to changes in therapy. All statistical tests were two-sided, and statistical significance was set at $P \leq 0.05$. Analyses were performed in R 3.6.2 (*15*).

Results

Patients

Between April 2016 and December 2016, 18 Caucasian men were enrolled (8 at Johns Hopkins and 10 through McMaster University affiliated hospitals). 1/18 (6%) had no visible lesions on either ^{18}F-DCFPyL PET/CT scan and was excluded. 1/18 (6%) underwent the baseline PET1 scan but was not started on abiraterone or enzalutamide and was also excluded. For the 16 men who were analyzed, the median age (IQR) was 71.5 (66.8-72.0) years. Serum PSA at the time of PET1 was 24.0 (12.1-47.1) ng/mL. 14/16 (88%) men were started on abiraterone and 2/16 (13%) were started on enzalutamide. Although not in the exclusion criteria, none of the patients had previously received either chemotherapy or a prior second-generation anti-androgen agent. Additional details are included in Table 1.

Clinical Follow-Up

Following therapy initiation, 10/16 (62.5%) men had a serum PSA decrease, of which 8/10 (80%) had a PSA_{50} response (>50% PSA decrease). For these 10 men: median PSA at first follow-up was 8.8 (5.5 – 13.4) ng/dL and median TTTC was 16.6 (11.2-22.0) months. Six men (38%) had a rise in PSA; for these men the PSA at first follow-up was 41.2 (17.3-54.3) ng/mL and TTTC was 5.4 (3.8-6.8) months.

As of the final censoring date (April 20, 2020): 10 men had died, 4 remained alive, and 2 had been lost to follow-up. Of the 4 men who were still alive, 2 remained on therapy with abiraterone. Median time of follow-up was 28.2 (18.4-38.9) months.

^{18}F-DCFPyL PET/CT Image Analysis

Table 2 is a summary of clinical parameters with corresponding PET findings.

The majority of the men, 12/18 (67%), in our study had high baseline ^{18}F-DCFPyL-avid metastatic tumor burden (5 or more ^{18}F-DCFPyL-positive lesions on PET1). Based on the categories noted above, 5/16 (31%) men had an all-increased pattern, 6/16 (38%)

had a mixed-but-predominantly-increased pattern, 3/16 (19%) had a mixed pattern, 1/16 (6%) had a mixed-but-predominantly-decreased pattern, and 1/16 (6%) had an all-decreased pattern. A waterfall plot depicting percentage change in PSA that occurred relative to change in patterns of ^{18}F-DCFPyL uptake between PET1 and PET2 is shown in Figure 3.

Nine of 16 (56%) men had new sites of radiotracer uptake on PET2; 5/9 (56%) had increased PSA. The median in TTTC for the 9 men with new ^{18}F-DCFPyL PET-positive metastases was 7.0 (4.6-9.3) months. In comparison, for the seven men without new ^{18}F-DCFPyL PET-positive metastases, only 1/7 (14%) had an increased PSA and the median TTTC was 12.8 (11.2-28.3) months. All men (6/6, 100%) with increased PSA had either a mixed-but-predominantly-increased pattern (5/6, 83%) or an all-increased pattern (1/6, 17%) of PSMA-avid disease.

There were six men with mixed-but-predominantly-increased uptake on PET2, and this finding was associated with unfavorable response to therapy, median TTTC 5.4 (3.8-6.8) months. All had high baseline tumor burden, positive DPSM and DASM. Most subjects, 5/6 (83%), with a mixed-but-predominantly-increased pattern had increased PSA and new ^{18}F-DCFPyL PET-positive sites of suspected metastases on follow-up. However, one man with an all-decreased pattern and high metastatic tumor burden on baseline PET1, had favorable therapy response with prolonged TTTC (43.6 months), negative DPSM (-462.5), and negative DASM (-29.9).

Across all men, the median TTTC was 9.6 months [95% confidence interval (CI) 6.9-14.2 months]. Men with a positive and high (increasing avidity from PET1 to PET2) DPSM and DASM had an unfavorable therapy response with shorter TTTC. As illustrated in Figure 4, there was a significant difference (P = 0.0001) in TTTC for men with ^{18}F-DCFPyL PET-positive disease burden above the median DPSM (6.5 months, 95% CI 4.6-N/A) versus those below the median (12.2 months, 95% CI 11.3-N/A). The Cox model

hazard ratio (HR) for high DPSM was 23.9 (95% CI 2.8-203.1). In regards to DASM, for those men above the median, the TTTC was 6.9 months (95% CI 6.1-N/A) versus 12.2 months, (95% CI 11.3-N/A) for those below the median (P = 0.003). The Cox model HR for high DASM was 8.2 (95% CI 1.7-40.5).

DPSM and DASM were also associated with OS (Figure 5). Median OS across all patients was 28.6 months (95% CI 18.3-N/A). However, the median OS for men with ^{18}F-DCFPyL PET-positive disease burden above the median DPSM was 17.8 months (95% CI 13.9-N/A), while the median OS for men below the median DPSM was 37.2 months (95% CI 28.9-N/A, P = 0.02, Figure 5). The median OS for men with ^{18}F-DCFPyL PET-positive disease burden above the median DASM was 17.8 months (95% CI 13.9-N/A), while for those below the median DASM it was N/A (95% CI 37.2 months-N/A), which was significant (P = 0.002). The Cox model HR for high DASM was 9.3 (95% CI 1.8-47.9).

Stratifying patients by tumor burden suggests the number of lesions at baseline was not associated with TTTC (Figure 6). Although the separation of the survival curves suggests a longer OS based on a low number of lesions at baseline, this did not reach significance (P = 0.35).

Comparison to Conventional Imaging

Seven of 16 (44%) patients had progression by both RECIST 1.1 and PCWG3 criteria on conventional imaging contemporaneous with PET2, while 7/16 (44%) had stable disease and 2/16 (13%)) had partial response. Of the 6 patients with rising PSA at the time of PET2, 4/6 (67%) had progression on conventional imaging. Of the 10 patients with decreasing PSA at the time of PET2, 3/10 (30%) had progression on conventional imaging.

For patients who had all-increased pattern of uptake on PET2, 1/5 (20%) demonstrated evidence of progression on conventional imaging. For patients with mixed-

but-predominantly-increased uptake on PET2, 5/6 (83%) had progression on conventional imaging. None of the patients with mixed pattern of uptake had progression on conventional imaging. The one patient with a mixed-but-predominantly-decreased pattern of uptake on PET2 had progression on conventional imaging and the one patient with an all-decreased pattern of uptake did not have progression on conventional imaging.

For patients with TTTC longer than the median, 1/8 (13%) had evidence of progression on conventional imaging at the time of PET2. For patients with TTTC shorter than the median, 6/8 (75%) had progression on conventional imaging. For patients with OS longer than the median, 1/8 (13%) also had progression on conventional imaging. Finally, for patients with OS shorter than the median, 6/8 (75%) had progression on conventional imaging.

We considered TTTC below the median as evidence of early progression. For detecting early progression, ^{18}F-DCFPyL PET had a sensitivity of 88%, specificity of 88%, and overall accuracy of 88%. For detecting early progression, conventional imaging had a sensitivity of 63%, specificity of 75%, and overall accuracy of 69%.

Discussion

PSMA-targeted PET is being increasingly used for evaluation of PCa at the time of staging (*3*), biochemical recurrence (*4*), and therapy guidance (*5*). However, to date, there is mixed data on the meaning of patterns of changing uptake with therapy on PSMA-targeted PET. The available data suggests there can be a complex interplay between androgen-targeted therapy, androgen receptor signaling, PSMA expression, and patient response to therapy in some imaging contexts (*10*,*11*, Table 3).

Most of our subjects with CRPC had a mixed PET response 2-4 months following initiation of a second-generation anti-androgen agent, suggesting biological heterogeneity between metastatic sites. We found imaging biomarkers associated with unfavorable

response to therapy on short interval follow-up ^{18}F-DCFPyL PET/CT included: 1) new sites of ^{18}F-DCFPyL PET-positive metastatic disease and 2) overall increasing lesion uptake. The derived metrics DPSM and DASM were both associated with TTTC and OS – men with a net increase in ^{18}F-DCFPyL uptake across sites of disease on short interval follow-up PET had shorter TTTC and OS. Baseline ^{18}F-DCFPyL-avid tumor burden alone was not associated with outcomes. We also found the sensitivity, specificity, and overall accuracy of ^{18}F-DCFPyL for detecting early progression (as defined by short TTTC) was superior to conventional imaging.

The subset of 6 men with mixed but predominantly increasing ^{18}F-DCFPyL uptake at sites of disease from PET1 to PET2 had the worst outcomes. These patients all had positive DPSM and DASM parameters, most had new lesions as well as increasing PSA at follow-up. 5 of the next 6 patients with the shortest TTTC were men with increasing uptake at all sites of disease. Most of those men presented with concurrently decreased PSA at follow-up. This suggests that while some sites of disease may be increasing in avidity due to flare, overall, increasing uptake suggests disease progression. Granted, there do appear to be men who have increased uptake on PSMA-targeted PET after therapy initiation, in the context of an initial decrease in PSA, who may have a flare phenomenon (*10*). However, increased uptake and/or more conspicuous lesions on PSMA-targeted PET after the initiation of a second-generation anti-androgen must be interpreted with caution. Lastly, patients with a mixed or mixed-but-predominantly-decreasing pattern of uptake had relatively prolonged TTTC and OS.

Interval changes in PSMA-targeted PET avidity and metastatic pattern in patients starting second-generation anti-androgen agents are likely multi-factorial. The changes may be due to modulation of PSMA expression by androgen receptor signaling (*6*), tumor cell death as a result of response to therapy (*8*), loss of PSMA expression as cells differentiate towards a neuroendocrine phenotype (*16*), loss of PSMA expression in

advanced adenocarcinoma (*17*), or alternative splicing variants and other aberrations that limit the interaction of androgen signaling with PSMA (*18*). Due to this inherent complexity, correlation with pathology and tissue sampling may be helpful in future studies.

The primary limitation of this study was the relatively small sample size. Additional larger, prospective studies with long-term follow-up are needed to more definitively address the causes of the uptake patterns observed with PSMA-targeted PET. Further, the endpoint of TTTC does not necessarily reflect progression, although it should be a reliable surrogate for clinical progression barring an intolerable toxicity. The use of both DPSM and DASM could be viewed as overly-complex, however both of these metrics can be derived with relative ease with modern software and we were unable to statistically demonstrate that one was superior to the other. Lastly, given the exposure limitations allowed by the FDA for investigational radiotracers, only two time points could be obtained in this study. Additional PET scans at later time-points would be helpful to understand the prognostic implications of changes in PSMA-targeted radiotracer uptake with time.

Conclusions

Short interval follow-up PET (2-4 months) after initiation of treatment with a second-generation anti-androgen improves detection of progression. Men with increased uptake or new lesions on early interval PET may be experiencing progression rather than flare and may require alternative therapy.

Conflict-of-Interest

M.G.P. is a coinventor on a US patent covering ^{18}F-DCFPyL and as such is entitled to a portion of any licensing fees and royalties generated by this technology. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. S.P.R. and S.Y.C. are consultants for

Progenics Pharmaceuticals, Inc., the licensee of ^{18}F-DCFPyL. M.A.G. has served as a consultant for Progenics Pharmaceuticals, Inc. M.G.P, M.A.G., and S.P.R. have received research funding from Progenics Pharmaceuticals, Inc. Funding for this study was received from the Movember Foundation, the Prostate Cancer Foundation Young Investigator Award and National Institutes of Health grants CA134675, CA184228, EB024495, and CA183031.

Key Points:

Question: Can PSMA-targeted PET detect early progression and provide prognostic information about men starting abiraterone or enzalutamide?

Pertinent Findings: PSMA-targeted PET improves detection of progression relative to conventional imaging. New lesions or increasing apparent tumor burden on PSMA-targeted PET are poor prognostic findings.

Implications for Patient Care: Men starting treatment with abiraterone or enzalutamide who have an increasing number of lesions or increased uptake in existing lesions on PSMA-targeted PET may need alternative therapy.

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Tables and Table Legends

Table 1. Selected demographic and clinical information for the patients included in the analysis.

Parameter	Data
Age (years)	71.5 (66.8-72.0)
Race - Caucasian	100%
PSA (ng/mL) - PET1 - PET2	 24.0 (12.1-47.1) 11.0 (6.1-27.0)
Interval between PET1 and PET2 (days)	84 (70-91.5)
Therapy initiated - abiraterone - enzalutamide	 88% 13%

Continuous variables are given as median and IQR. Otherwise, values listed are percentages based on a 16-patient sample size.

Table 2. Selected clinical and imaging data for patients in this study.

Patient	Change in PSA (%)	DASM	DAPM	Overall Change in Avidity Between PET1 and PET2	Conventional Imaging Radiologic Progression	TTTC (Months)	OS (Months)
1	-71.8	+227.6	+3558.4	Mixed but Predominantly Increased	Yes	10.3	18.6
2	-1.6	-29.9	-462.5	All Decreased	No	43.6	43.6
3	-53.3	-4.3	-38.4	Mixed	No	42.2	42.2
4	+146.5	+29.5	+1637.9	Mixed but Predominantly Increased	Yes	3.5	33.3
5	+63.5	+98.8	+1124.3	Mixed but Predominantly Increased	Yes	4.6	17.7
6	+146.9	+74.8	+2517.7	Mixed but Predominantly Increased	Yes	3.3	7.1
7	-57.7	+16.0	+87.2	All Increased	No	12.8	37.8
8	-88.5	+40.5	+804.0	All Increased	Yes	7.1	14.1
9	+87.5	+4.5	+13.2	All Increased	No	11.9	47.8
10	-65.5	+13.4	+87.3	Mixed	No	14.4	45.8
11	-93.7	+3.5	+114.2	Mixed	No	11.4	29.1
12	+135.7	+171.8	+3107.9	Mixed but Predominantly Increased	Yes	6.2	13.4
13	-44.4	+36.6	+308.6	All Increased	No	10.4	29.4
14	-88.4	-138.4	-566.3	Mixed but Predominantly Decreased	Yes	9.3	26.6
15	+75.0	+275.1	+3223.7	Mixed but Predominantly Decreased	No	7.0	22.5
16	-68.2	+76.6	+1542.2	All Increased	No	7.0	27.4

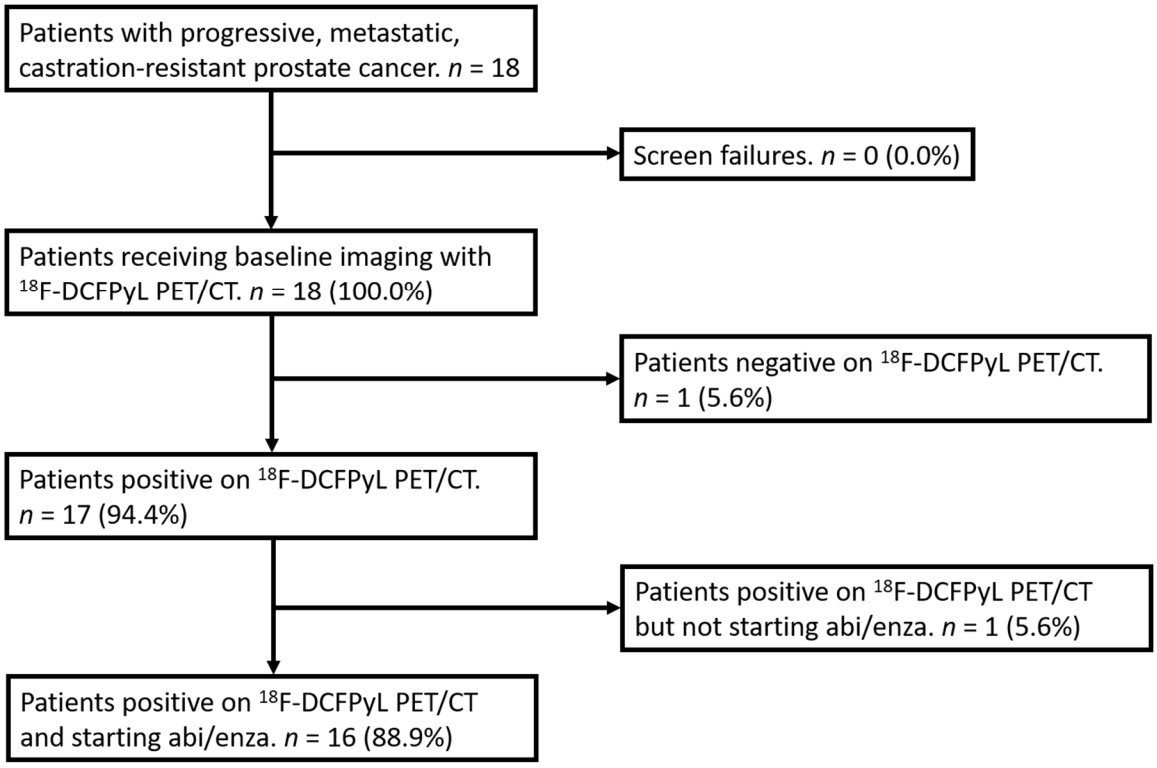
Table 3. Key findings from the literature regarding the presence or absence of the flare phenomenon on PSMA-targeted PET upon the initiation of androgen-axis targeted therapeutic agents.

First Author (Year), (*Reference*)	Number of Patients	Therapy Initiated	Key Results
Hope, et al (2017), (*7*)	1	ADT	Flare observed on 4-week follow-up scan
Afshar-Oromieh, et al (2018), (*8*)	10	ADT	Long-term ADT decreased conspicuity of lesions
Aggarwal, et al (2018), (*10*)	8	ADT in 4 patients, enzalutamide in 4 patients	Variably-observed, heterogeneous flare
Emmett, et al (2018), (*19*)	15	ADT in 8 patients, enzalutamide or abiraterone in 7 patients	Mix of flare and true progression observed
Plouznikoff, et al (2019), (*11*)	26	Enzalutamide or abiraterone	No evidence of flare was observed

ADT = androgen deprivation therapy

Figures and Figure Legends

Figure 1. A STARD diagram of the study described in the text.



Abi = abiraterone, enza = enzalutamide

Figure 2. Examples of patterns of change of ^{18}F-DCFPyL uptake. (A) 72-year-old man with extensive metastatic CRPC who developed a mixed-but-predominantly-decreased pattern of uptake on PET2. This patient had TTTC of 9.3 months and OS of 26.6 months. (B) 52-year-old man with more limited metastatic CRPC in whom a pattern of all-increased uptake on PET2 was observed. This patient had TTTC of 7.1 months and OS of 14.1 months.

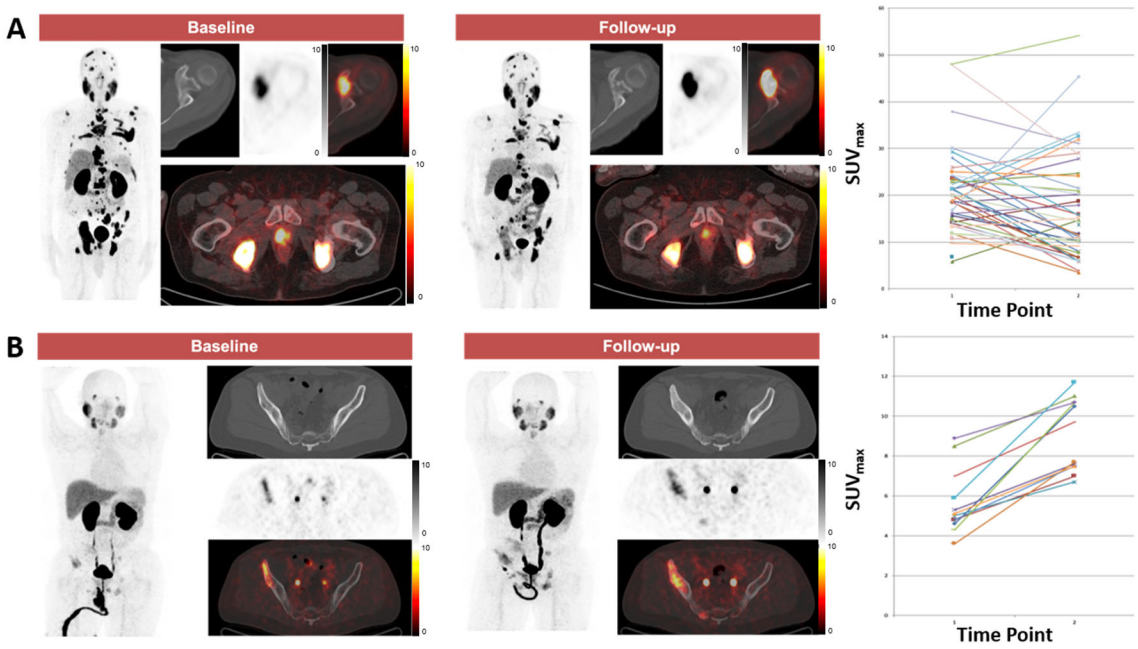


Figure 3. Waterfall plot demonstrating changes in PSA that occurred in the patients in this study, color-coded according to the changes in patterns of uptake on PET. The patient with the smallest percentage change in PSA from baseline (seventh patient from the left) is coded “all-decreased”.

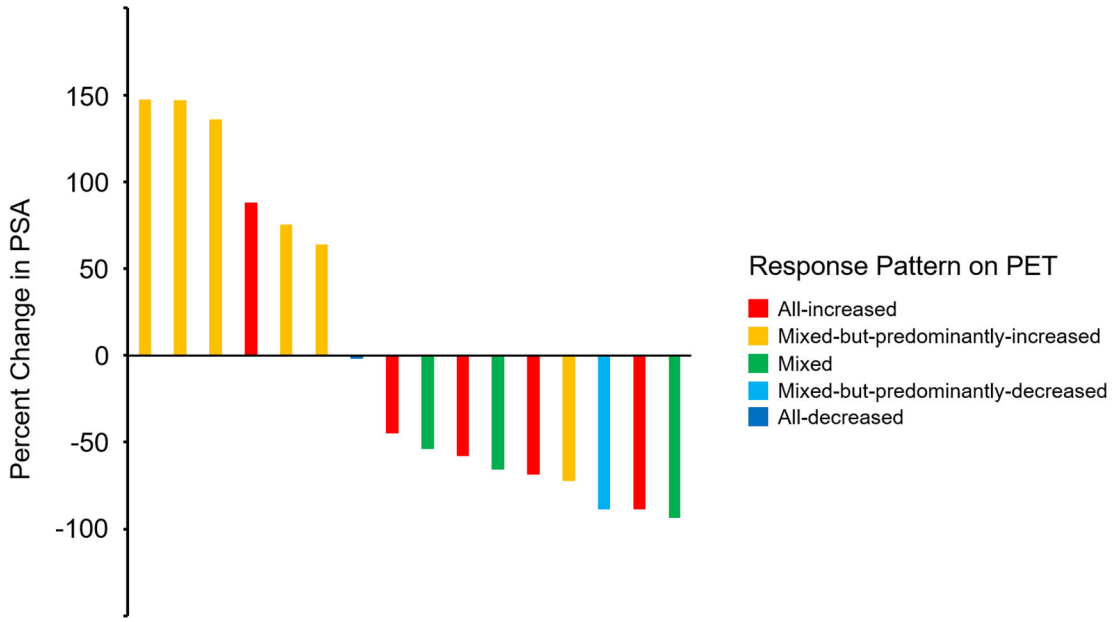


Figure 4. (A) Kaplan-Meier curve demonstrating that DPSM is associated with TTTC, with high DPSM corresponding to patients with shorter TTTC (blue curve) and low DPSM corresponding to patients with longer TTTC (orange curve). (B) Similar results were found in the Kaplan-Meier analysis with DASM.

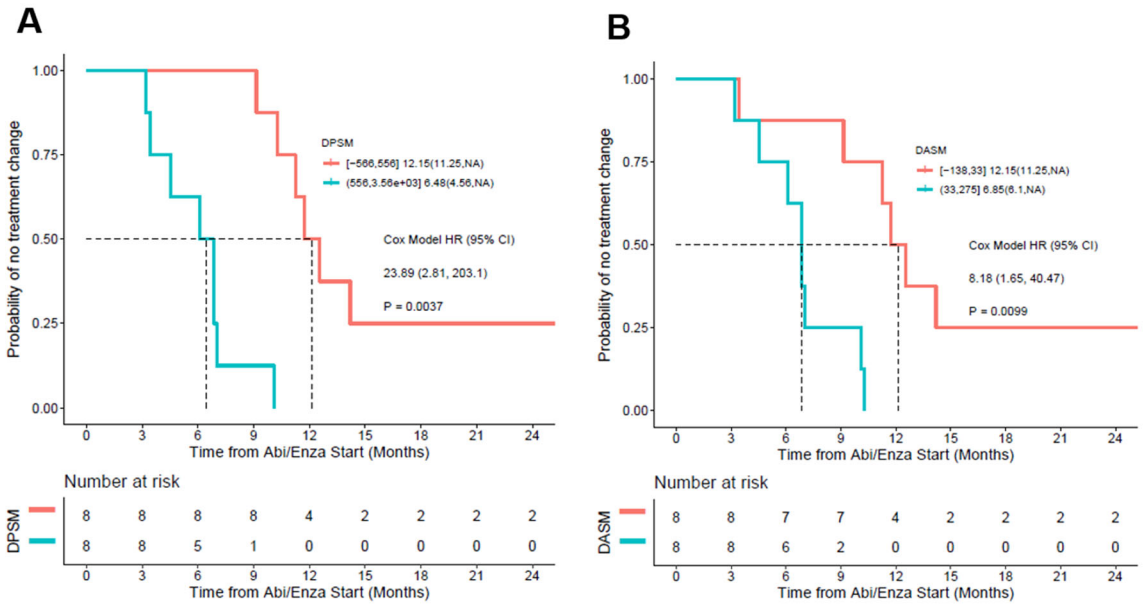


Figure 5. (A) Kaplan-Meier curve demonstrating DPSM is associated with OS, with high DPSM corresponding to patients with shorter OS (blue curve) and low DPSM corresponding to patients with longer OS (orange curve). (B) Similar results were found with DASM.

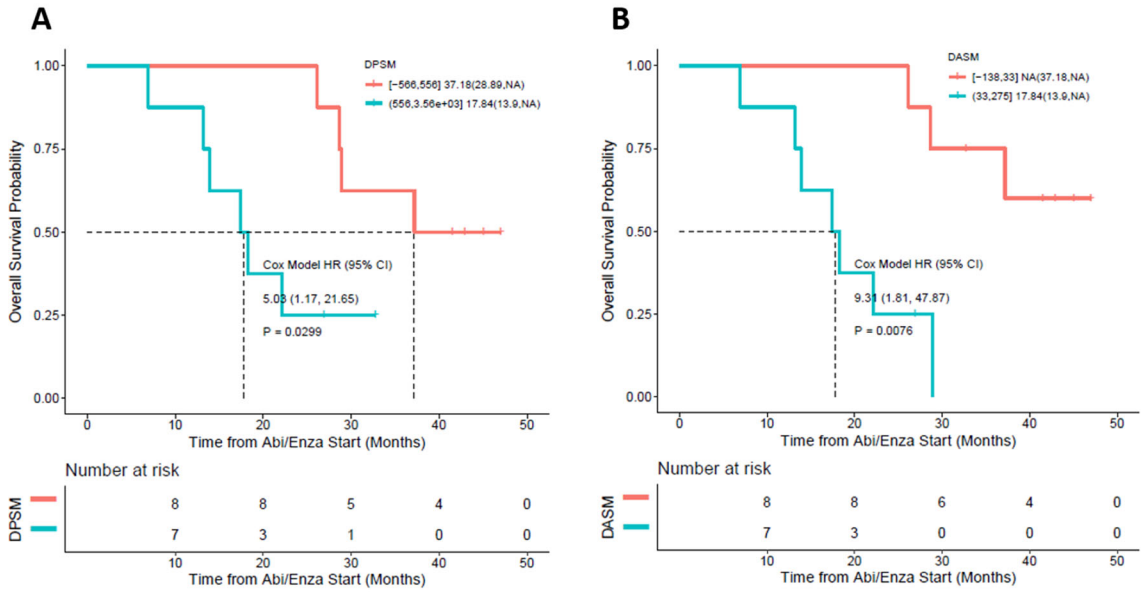


Figure 6. (A) Kaplan-Meier curves showing no difference in TTTC in patients with high PSMA-avid tumor burden at baseline (blue curve) and low PSMA-avid tumor burden at baseline (red curve). (B) Patients with lower baseline tumor burden also did not have significantly better OS.