Exploratory Study of [18F]fluciclovine PET/CT for Response Assessment to Docetaxel in Patients with Metastatic Castration Resistant Prostate Cancer

Akinyemi A Akintayo
Emory University School of Medicine https://orcid.org/0000-0002-6864-350X
Mehmet A Bilen
Emory University School of Medicine
Olayinka A Abiodun-Ojo
Emory University School of Medicine
Omer Kucuk
Emory University School of Medicine
Bradley Carthon
Emory University School of Medicine
Zhengjia Chen
Emory University School of Public Health
Ashesh B Jani
Emory University School of Medicine
Ephraim E Parent
Mayo Clinic's Campus in Florida
David M Schuster (dschust@emory.edu)
https://orcid.org/0000-0003-3077-742X

Original research

Keywords: Prostate cancer, [18F]fluciclovine, docetaxel, metastatic castration resistant prostate cancer, therapy response

Posted Date: April 3rd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-20377/v1

Abstract

Background The ability to accurately monitor response to treatment in patients with metastatic castration resistant prostate cancer (mCRPC) on chemotherapy has been a challenge. Conventional methods of therapy response assessment have limitations and molecular imaging has been explored as an important alternative. We set out t o determine if anti-1-amino-3-anti-1-amino-3-[18F]-fluorocyclobutane-1-carboxylic acid ([18F]fluciclovine) positron emission tomography/computed tomography (PET/CT) changes reflect response to docetaxel chemotherapy in mCRPC.

Results Seven patients with mCRPC were enrolled. Each patient was scheduled to have [18F]fluciclovine PET/CT at baseline, and after 1 and 6 cycles of chemotherapy. Uptake parameters were recorded in the prostate/bed and up to 10 metastatic lesions. Decrease in uptake of ≥30% was considered response (R); appearance of new lesions or >30% increase in uptake was progressive disease (PD); and change of < 30% uptake was stable disease (SD). Prostate specific antigen (PSA) was obtained at baseline and before each cycle. Bone scintigraphy and CT were acquired at baseline and after the 6th cycle. Assessment of response was based on Prostate Cancer Clinical Trial Working Group 3 recommendations. Correlation between [18F]fluciclovine uptake and time to PSA progression was also determined. All patients completed the 1 st and 2 nd [18F]fluciclovine PET/CT, while 4/7 patients completed all 3 scans. PET response correlated with PSA response in 3/7 (42.9%) patients and 3/4 (75%) patients after 1 and 6 cycles of docetaxel, respectively. Bone scan and CT correlated with PSA response in 1/4 (25%) patients. Mean SUVmax and SUVmean were significantly higher in patients with progressive disease versus non-progressive disease after 6 cycles of docetaxel ($p<0.05$), but not at baseline or after 1 cycle of docetaxel. There was non-significant correlation of changes in [18F]fluciclovine uptake with changes in PSA after 1 and 6 cycles of docetaxel. There was no significant correlation between PET parameters and time to PSA progression.

Conclusion [18F]fluciclovine PET/CT has better correlation than CT or bone scan with PSA response for patients with mCRPC treated with docetaxel. [18F]fluciclovine PET/CT did not predict time to PSA progression. Larger studies exploring the utility of [18F]fluciclovine PET for response assessment are recommended.

Background

Androgen deprivation therapy is widely used in the treatment of patients with prostate cancer. While most patients with prostate cancer will respond to androgen deprivation, many will eventually progress to metastatic castrate-resistant prostate cancer (mCRPC) with poor prognosis. Chemotherapy regimens for mCRPC improve overall survival in patients with mCRPC [1–3]. Docetaxel is a first line chemotherapy regimen for mCRPC with good overall response rates [4], and is more recently employed in the management of newly diagnosed metastatic hormone sensitive prostate cancer. With advances in options for the treatment of prostate cancer, including chemotherapy and novel hormonal agents in newly

diagnosed patients, it has become increasingly important to monitor treatment response. Yet, therapy response assessment remains a challenge [5].

Monitoring therapeutic response has traditionally been accomplished using serum biomarkers such as prostate specific antigen (PSA), and imaging biomarkers such as bone scanning for skeletal disease and computed tomography (CT) for nodal and soft tissue disease [6]. Bone scans are limited by high false positivity due to the flare effect [7]. Anatomic imaging such as CT is also limited by the inability of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 to reliably assess response in soft tissue and bone metastasis in which metabolic response may be decoupled from morphologic characteristics. Molecular imaging has become important in the evaluation of response, with several studies demonstrating that molecular imaging provides an independent assessment of response to therapy and prognostic information [8–11].

Amino acid metabolism is upregulated in many tumors including prostate carcinoma. Anti-1-amino-3-F-18-fluorocyclobutane-1-carboxylic acid ([18F]fluciclovine) is a synthetic amino acid analog which has demonstrated utility for staging of prostate carcinoma compared to conventional imaging [12–15], and has been approved by the United States Food and Drug Administration for imaging of suspected recurrent prostate cancer [16]. In-vitro studies with [18F]fluciclovine have shown uptake correlates with amino acid transporter expression in castration resistant prostate cancer cells [17]. Therefore we hypothesized that [18F]fluciclovine PET would reflect cancer cell metabolism via amino acid transport activity in metastatic castrate-resistant prostate cancer as well as response to therapy as the cancer is treated with cytotoxic chemotherapy. In this exploratory study, we set out to understand if [18F]fluciclovine PET/CT would better reflect response to docetaxel chemotherapy in patients with mCRPC compared with conventional imaging biomarkers, and to also assess the correlation between [18F]fluciclovine uptake and time to PSA progression.

Methods

Patients

This study was a prospective Institutional Review Board approved trial requiring written informed consent. Inclusion criteria was castration resistant metastatic prostate carcinoma (castrate serum testosterone < 50 ng/dl or 1.7 nmol/l and three consecutive rises in PSA one week apart, resulting in two 50% increases over the nadir, and PSA > 2 ng/ml) with radiologic evidence of skeletal metastases and/or nodal involvement eligible to commence chemotherapy utilizing standard regimen of docetaxel 75 mg/m^2 administered intravenously every 21 days with appropriate pre-medications (steroids and anti-emetics) given over 4–6 cycles.

Conventional Imaging and PSA Biomarkers

Each patient had standard of care conventional staging per institutional protocol including Technetium 99 m ([99 m Tc]-methylene diphosphonate (MDP)) bone scanning and CT or MR within 60 days of the

PET/CT at baseline, after the 6th cycle and at one year if able. Each patient also had serum PSA assays at baseline and prior to administration of each cycle of chemotherapy.

[18F]fluciclovine PET/CT

Each patient had baseline [18F]fluciclovine PET/CT prior to commencement of chemotherapy, and after the 1st and 6th cycle of chemotherapy.

[18F]fluciclovine was administered under FDA Investigational New Drug (IND) 72,437 and was synthesized using the FastLab Cassette System (GE Healthcare). Safety monitoring during the drug infusion was performed and no adverse events were recorded. All subjects were required to fast for four hours to normalize their neutral amino acid levels.

PET/CT were acquired on a GE Discovery-690 16 slice integrated PET/CT scanner (GE Healthcare, Waukesha, WI) with oral contrast, without intravenous contrast. [18F]fluciclovine (367.0 ± 21.1 MBq) was administered as an intravenous bolus injection. Subsequently, a low dose CT scan (120 kV, automA, maximum 160 mA) was completed from skull base to thighs for anatomic correlation and attenuation correction of emission data. At 4 minutes after radiotracer infusion, PET image acquisition of 7 consecutive 2 minutes per frame beds were completed starting from the thighs and extending superiorly to the skull base. This was immediately repeated to obtain dual time point (early and delayed) data.

Images were reconstructed with iterative technique and interpreted on a MimVista workstation (MIM Software, Cleveland, OH). Reconstruction parameters utilized VUE point FX with 3 iterations/24 subsets and 6.4 mm filter cutoff, and reconstructed slice thickness was 3.75 mm.

Image Analysis

Conventional Imaging

All conventional imaging were interpreted per usual standard of care but a targeted research interpretation was utilized for this study.

On CT or MR, bi-dimensional measurements of up to five soft-tissue lesions were recorded. These were used to determine Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria [18]. There were no bone lesions with a soft tissue component.

Bone scans findings were interpreted based on recommendations from Prostate Cancer Clinical Trial Working Group 3 (PCCTWG3) and a specialized Bone Scan Assessment Tool include in the appendix of the following reference was utilized [19].

[18F]fluciclovine PET/CT

Three dimensional regions of interest (ROI) were drawn at a MimVista workstation (MIM Software, Cleveland, OH) using the PET-Edge tool when possible, or otherwise conformational ROIs were utilized to record uptake in regions of physiologic and abnormal [18F]fluciclovine uptake.

[18F]fluciclovine uptake parameters [SUV (mean, maximum (max), and peak)] were recorded in the prostate/bed and up to 5 metastatic bone and soft tissue lesions each.

Therapy Response Assessment

Imaging response to treatment were evaluated independently for [18F]fluciclovine PET/CT and conventional imaging. Each was compared to PSA response.

Conventional Imaging and PSA Biomarkers

Assessment of response on CT or MR followed RECIST 1.1 criteria [18]. Response on PSA and bone scan were based on recommendations from the PCCTWG3 [19]. A decrease in serum PSA ≥ 50% was defined as response, while change in PSA < 50% reduction or < 25% increase was considered stable. For additional analysis, patients were also dichotomized as either having progressive disease (≥ 25% increased PSA) or non-progressive disease (decreasing or stable PSA).

[18F]fluciclovine PET/CT

Summation of [18F]fluciclovine uptake parameters from all indexed lesions per patient was recorded from each PET scan, and the same lesions were evaluated on subsequent scans. The presence of new lesions were also recorded. A decrease in summed uptake parameters of ≥ 30% was considered response (R), while appearance of new lesions or > 30% increase in summed uptake parameters was considered progressive disease (PD). Stable disease was defined as change of < 30% summed uptake parameters between scans. To also achieve a modified PET response criteria for solid tumors (PERCIST) 1.0 analysis [20], the SUVpeak of the single hottest lesion from each PET scan was also assessed for response using the above criteria.

Statistical analysis

Differences in [18F]fluciclovine uptake between the baseline PET and the measurements at each time point during the two follow-up PET scans (after one cycle and after 4–6 cycles of chemotherapy) were compared using two–sided paired t-test. Correlation between the response on [18F]fluciclovine PET scan after 1 and 6 cycles of chemotherapy (or sooner at end of chemotherapy per patient condition) and the clinical response after 6 cycles of chemotherapy (or sooner at end of chemotherapy per patient condition) as measured by standard parameters including PSA and routine radiologic objective measurements (bone scan and RECIST 1.1) was done. Association was determined using Spearman's correlation coefficient and Chi-square test. Significance level was set at $p < 0.05$ for all tests. All analyses were done using SPSS version 23 (IBM, Amonk, NY)

Results

Patients

Seven patients with metastatic castration resistant prostate cancer were recruited. Average age was 79.0 ± 5.5 years. Median PSA was 63.43 ng/ml (range 6.67–1300.00 ng/ml) and median Gleason score (Grade group) was 4 + 4 (4), with a range of 7–8 Gleason score. All patients in the study completed the 1st and 2nd [18F]fluciclovine PET/CT, while 4/7 patients completed all 3 PET/CT scans. One of the patients died during the study period from causes related to disease progression, one patient did not tolerate docetaxel after the second dose, while one patient was switched after cycle 3 from docetaxel to carbazitaxel and carboplatin due to disease progression. Baseline bone scans and conventional imaging (CT and/or magnetic resonance imaging (MRI)) were done within 2 weeks of PET scans, which was well within the specified 60 days.

Evaluation Of Therapy Response

Biochemical (PSA) response

Based upon PCCTWG 3 criteria, 1/7 (14.3%) patients had PSA response, 4/7 (57.1%) patients had stable PSA, while 2/7 (28.6%) had progression after the first cycle of docetaxel. Of the four patients that completed 6 cycles of docetaxel, 2/4 (50%) had PSA response, 1/4 (25%) had stable PSA, while 1/4 (25%) had PSA progression.

Imaging Biomarkers

CT Abdomen and pelvis

In the 4/7 patients who completed cycle 6, stable disease was present in all patients per RECIST 1.1 criteria.

Bone Scan

In the 4/7 patients who completed cycle 6, 2/4 (50%) patients were adjudged to have progressive disease, while 2/4 (50%) had stable disease per PCCTWG 3 criteria.

[18F]fluciclovine PET/CT

Baseline: All patients recruited in this study had bone metastasis detected on PET/CT; 6/7 (85.7%) patients had soft tissue disease including 4/7 (57.1%) with nodal disease

PET after first cycle (n = 7): Based on the differences in the summed SUVmax, SUVmean or SUVpeak either at early or delayed time-points, stable disease was found in 6/7 (85.7%) patients, while progresion

was noted in 1/7 patients.

Based on SUVpeak in the hottest lesion (PERCIST-like analysis), 1/7 patients had response, 4/7 patients had stable disease and 2/7 patients had disease progression.

PET after sixth cycle (n = 4): Based on the differences in the summed SUVmax, SUVmean or SUVpeak either at early or delayed time-points; 3/4 (75%) patients had response to therapy, while one of four (25%) patients had disease progression.

Based on SUVpeak in the hottest lesion (PERCIST-like analysis), response was present in 2/4 (50%) patients and stable disease in 2/4 (50%) patients.

Correlation Of Imaging With Biochemical (psa) Response

Conventional imaging

After completion of 6 cycles of docetaxel, CT response based on RECIST 1.1 revealed stable disease in all 4 patients irrespective of increasing or decreasing PSA, thus correlating with PSA response in 1/4 (25%) patients.

Therapy response based on bone scan and PCCTWG3 criteria suggested progressive disease in 2/4 (50%) patients despite reducing PSA, while despite rising PSA in one patient, bone scan suggested stable disease. Thus, bone scan correlated with biochemical response in only 1/4 patients.

[18F]fluciclovine PET

Baseline: SUVmax, SUVmean and SUVpeak did not correlate with the baseline PSA at the time of baseline scan.

PET after first cycle (n = 7): PET correlated with PSA response after the first cycle in 3/7 (42.9%) patients using the sums of either SUVmax, SUV mean or SUV peak.

PET after sixth cycle (n = 4): PET response was concordant with PSA response after the sixth cycle in 3/4 (75%) patients using summed differences of SUV max, SUV mean or SUV peak. In addition, PET after the first cycle did not predict response after cycle 6.

Progressive versus Non-progressive disease: After 6 cycles of chemotherapy the mean SUVmax and SUVmean were significantly higher in patients with progressive disease (≥ 25% increased PSA) versus non-progressive ($p < 0.05$). These difference was not seen with SUVpeak. (Table 3)

Table 1

[18F]fluciclovine uptake parameters

Summed lesions					
PET parameters	Baseline PET (n = 7)	After 1st cycle (n = 7)	After 6th cycle (n = 4)	Δ after 1st cycle (n = 7)	Δ after 6th cycle (n = 4)
SUVmax	47.6 ± 16.0	48.1 ± 20.4	36.3 ± 17.3	0.4 ± 11.5	-9.8 ± 11.5
SUVmean	30.7 ± 10.3	31.8 ± 13.2	23.3 ± 9.7	1.1 ± 8.3	-6.4 ± 7.1
SUVpeak	36.8 ± 13.3	37.8 ± 17.3	29.1 ± 13.7	1.0 ± 8.7	-6.2 ± 7.5
Hottest Lesion					
SUVmax	8.1 ± 2.3	8.8 ± 3.7	7.4 ± 3.3	0.8 ± 3.5	-1.6 ± 2.8
SUVmean	5.3 ± 1.5	5.7 ± 2.3	5.0 ± 2.8	0.3 ± 2.0	-0.8 ± 2.0
SUVpeak	6.2 ± 2.1	6.9 ± 3.2	5.8 ± 2.8	0.7 ± 2.7	-1.0 ± 2.0

Table 2

Changes in SUVmax and PSA after 1 and 6 cycles of Docetaxel

Patient	**% Δ after 1st cycle**	**% Δ after 6th cycle**	**% Δ PSA after 1st cycle**	**% Δ PSA after 6th cycle**
1	26.3	-	0.0	-
2	-28.6	-47.2	-51.7	-84.2
3	-11.9	-13.2	-20.7	-28.5
4	-20.6	-34.4	-6.1	-75.8
5	-6.2	-	100	-
6	-2.2	0.8	68.3	62.5
7	65.8	-	22.4	-

Table 3
[18F]fluciclovine uptake in patients with progressive versus non-progressive mCRPC

Parameters	Progressive Disease	Non-Progressive Disease	p-value
Mean SUVmax			
Baseline	59.5 ± 1.4	43.0 ± 16.9	0.09
Post-cycle 1	57.1 ± 3.0	44.5 ± 23.8	0.31
Post-cycle 6	61.0	28.1 ± 6.4	0.05
Mean SUVmean			
Baseline	37.3 ± 1.7	28.1 ± 11.3	0.15
Post-cycle 1	36.0 ± 0.4	30.1 ± 15.8	0.46
Post-cycle 6	37.1	18.7 ± 3.7	0.05
Mean SUVpeak			
Baseline	46.4 ± 1.1	33.0 ± 14.2	0.10
Post-cycle 1	45.6 ± 1.6	30.1 ± 20.2	0.30
Post-cycle 6	48.2	22.7 ± 6.0	0.07

Correlation with PSA trends: The changes in [18F]fluciclovine uptake correlated with changes in PSA after 1 and 6 cycles of docetaxel. This however was a non-significant trend.

Correlation Between [18f]fluciclovine Pet And Conventional Imaging Response

[18F]fluciclovine PET response criteria using the SUVmax, SUVmean and SUV peak after the 6 cycles of docetaxel correlated with RECIST 1.1 and bone scan in 2/4 (50%) patients.

An overview of the correlation between biochemical response and imaging is provided in Table 4.

Table 4

a: After one cycle

Patient	[18F]fluciclovine PET (SUVmax, SUVpeak)	PET(SUVmean)	PSA
1	SD	PD	S
2	SD	SD	R
3	SD	SD	S
4	SD	SD	S
5	SD	SD	P
6	SD	SD	P
7	PD	PD	S

Table 4

b: After six cycles

Patient	[18F]fluciclovine PET (SUVmax, SUVmean, SUVpeak)	RECIST	Bone scan	PSA
1	-	-	-	-
2	R	SD	PD	R
3	SD	SD	SD	S
4	R	SD	PD	R
5	-	-	-	-
6	SD	SD	SD	P
7	-	-	-	-
Key: R: response				
S: stable				
P: progression				
SD: stable disease				
PD: progressive disease				

Figures 1 and 2 are representative images from patients with response and non-response to docetaxel.

Time To Psa Progression

The median time to PSA progression in the evaluable patients (n = 5) was 199 days (interquartile range 115.5–321.0 days); see supplementary table. Baseline [18F]fluciclovine uptake parameters had no correlation with time to progression. Also, there was no correlation between time to PSA progression and change in PET parameters after 1 and 6 cycles of chemotherapy. (Table 5)

Table 5
Correlation of time to PSA progression with change in summed PET-parameters

Difference in PET parameter after 1st cycle	Pearson Correlation	p-value	Difference in PET parameter after 6th cycle	Pearson Correlation	p-value
SUVmax	0.51	0.25	SUVmax	0.70	0.10
SUVmean	0.67	0.16	SUVmean	0.83	0.23
SUVpeak	0.74	0.13	SUVpeak	0.74	0.10

Discusssion

Determining response to chemotherapy in patients with metastatic castration resistant prostate cancer with current conventional imaging modalities such as CT and bone scan remains a challenge [6, 7]. In this exploratory study, we set out to determine the value of [18F]fluciclovine PET/CT in the assesssment of response to the first line chemotherapeutic agent docetaxel, and its correlation with time to PSA progression.

We found 43% correlation of [18F]fluciclovine PET parameters (SUVmax, SUVmean, SUVpeak) with PSA response after a single cycle of docetaxel; however, after completion of 6 cycles of docetaxel, [18F]fluciclovine PET parameters correlated with standard of care biochemical (PSA) response in 75% of patients. In comparison to RECIST 1.1 and bone scan, [18F]fluciclovine PET correlated better with biochemical response to therapy in patients with mCRPC. The changes in [18F]fluciclovine uptake correlated with changes in PSA after 1 and 6 cycles of docetaxel. This however was a non-significant trend. There was no significant correlation of uptake parameters with time to PSA progression.

Currently, assessment of therapy response in prostate cancer is based on changes in serum PSA, clinical assessment and imaging using RECIST 1.1 and bone scans. The role of molecular imaging in assessment of therapy response has been gaining attention. Studies making use of 2-deoxy-2-[18F]fluoro-D-glucose (FDG) [8], carbon-11 choline ([11C]choline) [9, 21], 18F-fluorocholine ([18F]choline) [10] and Gallium-68 prostate specific membrane antigen ([68 Ga] PSMA) [11, 22] in the evaluation of therapy response in the setting of metatastaic prostate cancer have reported varying results.

Our finding that PET parameters correlated better with biochemical response than RECIST 1.1 or bone scan is similar to the findings of previous similar studies making use of molecular imaging in the

evaluation of response to chemotherapy in patients with mCRPC. Jadvar reported that FDG uptake decreases concordantly with PSA and contributes independent prognostic information on overall survival in men with mCRPC[8]. Studies done by Ceci et al [9] and Caroli et al [10] making use of [11C]choline and [18F]choline, respectively, reported promising results in evaluation of therapy response in patient with mCRPC. Yet, Schwarzenbock did not find correlation between change in choline uptake in [11C]choline PET/CT and response assessment in patients with mCRPC treated with docetaxel chemotherapy [21]. Seitz et al in a study of 16 patients with mCRPC undergoing docetaxel chemotherapy, reported that [68Ga] PSMA-11 PET/CT correlated better with PSA response, with 56% correlation in patients with mCRPC compared to 33% using RECIST 1.1 [11]. Other molecular imaging studies making use of [68Ga]PSMA-11 PET/CT for the assessment of therapy response in patients with metastatic prostate cancer have reported similar findings of significant correlation between response to chemotherapy and PET parameters [23, 22].

After a single cycle of docetaxel, there was limited correlation between PSA response and [18F]fluciclovine PET response and there was no statistical difference in the PET parameters between patients with progressive disease versus those who had non-progresive disease. This trend was however different after completion of 6 cycles, with correlation of 75% using PET paramters and significant difference in SUVmax and SUVmean between patients with progressive disease versus non progresive disease. The finding of 75% corelation of PET with PSA response in patients with mCRPC treated with docetaxel is higher than 56% reported by Seitz [11] and 64% reported by Ceci [9]. This disparities may be related to differences in sample size and study design. Based on the current thresholds, [18F]fluciclovine PET may have limited value in the assessment of early therapy response after a single cycle of docetaxel, therefore PET may be better employed for assessment of response after six cycles of docetaxel.

There was no correlation between [18F]fluciclovine uptake parameters at the baseline or after 6 cycles of chemotherapy and the time to PSA progression. The role of PET in evaluation of time to progression or overall survival in patients with mCRPC has not been widely reported. Jadvar et al in a study of 87 patients with mCRPC demonstrated that the sum of SUVmax derived from FDG PET/CT is a useful imaging biomarker for predicting overall survival in men with mCRPC [8]. De Giorgi et al reported in the study evaluating [18F]choline in a study of 36 patients with mCRPC treated with enzalutamide that PET/CT was an independent predictor of progression free survival, but not overall survival [24]. The disparity with [18F]fluciclovine PET from the above studies may be related to the small sample size in this exploratory study. Overall survival was not assessed in this small cohort of patients, as the study was not powered to demonstrate this.

The small sample size is an obvious limitation of this study, as only 4 patients could complete the study. This is was an exploratory study designed to assess the possible role of [18F]fluciclovine PET as a marker of therapy response in patients with mCRPC. It is practically difficul to recruit these cohort of patients with extensive metatstatic disease who also served as controls for themselves over a prolonged period of time. This study may prove useful in the design of future studies. Serum PSA was used as the reference standard for therapy response in this study; however, there have been questions raised about

the consistent applicability of PSA levels with treatment response [25, 9]. PSA levels however remains the reference method of objective assesment of patients with prostate cancer.

[18F]fluciclovine PET using the SUVmax, SUV mean or SUV peak correlated better with PSA response than conventional imaging in the assessment of treatment response in patients with metastatic castration resistant prostate cancer after 6 cycles of docetaxel. While PERCIST 1.0 criteria has been established for evaluation of response to therapy in FDG PET [20], it has not been evaluated for [18F]fluciclovine therefore we employed modified PERCIST in the assessment of response to therapy in this study.

Conclusion

This exploratory study suggests that [18F]fluciclovine PET/CT seems to better correlate with PSA response than CT or bone scan for assessment of treatment response in patients with metastatic castration resistant prostate cancer on docetaxel. The changes in [18F]fluciclovine uptake correlated with changes in PSA after 1 and 6 cycles of docetaxel. After 6 cycles of chemotherapy the mean SUVmax and SUVmean were significantly higher in patients with progressive disease versus non-progressive disease. [18F]fluciclovine PET/CT may however be limited in the prediction of time to PSA progression in this population. Larger studies are required to confirm the value of [18F]fluciclovine PET as an imaging biomarker for response assessment. Future studies evaluating therapy response in a different cohort of patients, on androgen deprivation therapy, are encouraged.

Abbreviations

mCRPC
Metastatic Castration Resistant Prostate Cancer
PET
Positron Emission Tomography
CT
Computed Tomography
PSA
Prostate Specific Antigen
PCTWG3
Prostate Cancer Clinical Trial Working Group 3
SUV
Standardized Uptake Value
RECIST
Response Evaluation Criteria in Solid Tumors
IND
Investigational New Drug
PERCIST

PET response criteria for solid tumors
R
Response
PD
Progressive Disease
SD
Stable disease

Declarations

Ethical approval and consent to participate

All procedures performed in this study were in accordance with ethical standards of the Institutional Review Board (IRB00073616) and with the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from each study participant according to institutional guidelines.

Consent for publication

Written informed consent was obtained from each study participant according to institutional guidelines.

Availability of data and materials

All data generated or analyzed during this study are available from the corresponding author on request.

Competing interests

Emory University: Blue Earth Diagnostics Ltd. provided [18F]fluciclovine synthesis cassettes to Emory University. Entitled to royalties derived from the sale of products related to the research described in this manuscript. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies.

AAA, OAA: Funding is or has been received from Blue Earth Diagnostics Ltd. and Nihon Medi-Physics Co., Ltd. through the Emory University Office of Sponsored Projects for other clinical trials using [18F]fluciclovine.

DMS: Funding is or has been received from Blue Earth Diagnostics Ltd. and Nihon Medi-Physics Co., Ltd. through the Emory University Office of Sponsored Projects for other clinical trials using [18F]fluciclovine. Participates through the Emory Office of Sponsored Projects in sponsored grants including those funded

or partially funded by Telix Pharmaceuticals (US) Inc. and Advanced Accelerator Applications. Consultant, Syncona, Global Medical Solutions (Taiwan) and AIM Specialty Health.

Funding

Funding was received from Blue Earth Diagnostics Ltd, Nihon Medi-Physics Co., Ltd and Emory University School of Medicine Catalyst and Seed funding program.

Authors' contributions

Principal investigators: Mehmet A Bilen, David M. Schuster

Patient selection and recruitment: Mehmet A Bilen, Omer Kucuk, Bradley Carthon

Imaging Interpretation: David M. Schuster, Ephraim E Parent

Data collection: Akinyemi A. Akintayo, Olayinka A. Abiodun-Ojo, David M. Schuster

Original draft preparation: Akinyemi A. Akintayo, Olayinka A. Abiodun-Ojo, Mehmet A Bilen, David M. Schuster

Statistical analysis: Akinyemi A. Akintayo, Olayinka A. Abiodun-Ojo, Zhengjia Chen

Grant recipient: David M. Schuster

Supervision: David M. Schuster

Review of manuscript: All authors

Approval of final version: All authors

Acknowledgements

We acknowledge Bridget Fielder, RN, Kathy Vaughn, Fenton G. Ingram, RT(R), CNMT, PET, Seraphinah Lawal, RT(R), CNMT, PET, Ronald J. Crowe, RPh, BCNP, and the cyclotron/synthesis team from Emory University Center for Systems Imaging.

References

1. Delanoy N, Hardy-Bessard AC, Efstathiou E, Le Moulec S, Basso U, Birtle A et al. Sequencing of Taxanes and New Androgen-targeted Therapies in Metastatic Castration-resistant Prostate Cancer: Results of the International Multicentre Retrospective CATS Database. Eur Urol Oncol. 2018;1(6):467-75. doi:10.1016/j.euo.2018.05.009.
2. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol. 2008;26(2):242-5. doi:10.1200/jco.2007.12.4008.
3. Oudard S, Fizazi K, Sengelov L, Daugaard G, Saad F, Hansen S et al. Cabazitaxel Versus Docetaxel As First-Line Therapy for Patients With Metastatic Castration-Resistant Prostate Cancer: A Randomized Phase III Trial-FIRSTANA. J Clin Oncol. 2017;35(28):3189-97. doi:10.1200/jco.2016.72.1068.
4. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(5):479-505. doi:10.6004/jnccn.2019.0023.
5. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017;71(4):630-42. doi:10.1016/j.eururo.2016.08.002.
6. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65(2):467-79. doi:10.1016/j.eururo.2013.11.002.
7. Cook GJ, Azad G, Padhani AR. Bone imaging in prostate cancer: the evolving roles of nuclear medicine and radiology. Clin Transl Imaging. 2016;4(6):439-47. doi:10.1007/s40336-016-0196-5.
8. Jadvar H, Desai B, Ji L, Conti PS, Dorff TB, Groshen SG et al. Baseline 18F-FDG PET/CT parameters as imaging biomarkers of overall survival in castrate-resistant metastatic prostate cancer. J Nucl Med. 2013;54(8):1195-201. doi:10.2967/jnumed.112.114116.
9. Ceci F, Castellucci P, Graziani T, Schiavina R, Renzi R, Borghesi M et al. (11)C-Choline PET/CT in castration-resistant prostate cancer patients treated with docetaxel. Eur J Nucl Med Mol Imaging. 2016;43(1):84-91. doi:10.1007/s00259-015-3177-4.
10. Caroli P, De Giorgi U, Scarpi E, Fantini L, Moretti A, Galassi R et al. Prognostic value of 18F-choline PET/CT metabolic parameters in patients with metastatic castration-resistant prostate cancer treated with abiraterone or enzalutamide. Eur J Nucl Med Mol Imaging. 2018;45(3):348-54. doi:10.1007/s00259-017-3866-2.
11. Seitz AK, Rauscher I, Haller B, Kronke M, Luther S, Heck MM et al. Preliminary results on response assessment using (68)Ga-HBED-CC-PSMA PET/CT in patients with metastatic prostate cancer undergoing docetaxel chemotherapy. Eur J Nucl Med Mol Imaging. 2018;45(4):602-12. doi:10.1007/s00259-017-3887-x.
12. Schuster DM, Votaw JR, Nieh PT, Yu W, Nye JA, Master V et al. Initial experience with the radiotracer anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid with PET/CT in prostate carcinoma. J Nucl Med. 2007;48(1):56-63.

13. Schuster DM, Taleghani PA, Nieh PT, Master VA, Amzat R, Savir-Baruch B et al. Characterization of primary prostate carcinoma by anti-1-amino-2-[(18)F] -fluorocyclobutane-1-carboxylic acid (anti-3-[(18)F] FACBC) uptake. Am J Nucl Med Mol Imaging. 2013;3(1):85-96.
14. Schuster DM, Nieh PT, Jani AB, Amzat R, Bowman FD, Halkar RK et al. Anti-3-[(18)F]FACBC positron emission tomography-computerized tomography and (111)In-capromab pendetide single photon emission computerized tomography-computerized tomography for recurrent prostate carcinoma: results of a prospective clinical trial. J Urol. 2014;191(5):1446-53. doi:10.1016/j.juro.2013.10.065.
15. Fei B, Abiodun-Ojo OA, Akintayo AA, Akin-Akintayo O, Tade F, Nieh PT et al. Feasibility and Initial Results: Fluciclovine Positron Emission Tomography/Ultrasound Fusion Targeted Biopsy of Recurrent Prostate Cancer. J Urol. 2019:101097ju0000000000000200. doi:10.1097/ju.0000000000000200.
16. Bach-Gansmo T, Nanni C, Nieh PT, Zanoni L, Bogsrud TV, Sletten H et al. Multisite Experience of the Safety, Detection Rate and Diagnostic Performance of Fluciclovine ((18)F) Positron Emission Tomography/Computerized Tomography Imaging in the Staging of Biochemically Recurrent Prostate Cancer. J Urol. 2017;197(3 Pt 1):676-83. doi:10.1016/j.juro.2016.09.117.
17. Ono M, Oka S, Okudaira H, Nakanishi T, Mizokami A, Kobayashi M et al. [(14)C]Fluciclovine (alias anti-[(14)C]FACBC) uptake and ASCT2 expression in castration-resistant prostate cancer cells. Nucl Med Biol. 2015;42(11):887-92. doi:10.1016/j.nucmedbio.2015.07.005.
18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47. doi:10.1016/j.ejca.2008.10.026.
19. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-18. doi:10.1200/jco.2015.64.2702.
20. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50 Suppl 1:122s-50s. doi:10.2967/jnumed.108.057307.
21. Schwarzenbock SM, Eiber M, Kundt G, Retz M, Sakretz M, Kurth J et al. Prospective evaluation of [(11)C]Choline PET/CT in therapy response assessment of standardized docetaxel first-line chemotherapy in patients with advanced castration refractory prostate cancer. Eur J Nucl Med Mol Imaging. 2016;43(12):2105-13. doi:10.1007/s00259-016-3439-9.
22. Schmuck S, von Klot CA, Henkenberens C, Sohns JM, Christiansen H, Wester HJ et al. Initial Experience with Volumetric (68)Ga-PSMA I&T PET/CT for Assessment of Whole-Body Tumor Burden as a Quantitative Imaging Biomarker in Patients with Prostate Cancer. J Nucl Med. 2017;58(12):1962-8. doi:10.2967/jnumed.117.193581.
23. Schmidkonz C, Cordes M, Schmidt D, Bauerle T, Goetz TI, Beck M et al. (68)Ga-PSMA-11 PET/CT-derived metabolic parameters for determination of whole-body tumor burden and treatment response

in prostate cancer. Eur J Nucl Med Mol Imaging. 2018;45(11):1862-72. doi:10.1007/s00259-018-4042-z.

24. De Giorgi U, Caroli P, Scarpi E, Conteduca V, Burgio SL, Menna C et al. (18)F-Fluorocholine PET/CT for early response assessment in patients with metastatic castration-resistant prostate cancer treated with enzalutamide. Eur J Nucl Med Mol Imaging. 2015;42(8):1276-83. doi:10.1007/s00259-015-3042-5.
25. Sandblom G, Ladjevardi S, Garmo H, Varenhorst E. The impact of prostate-specific antigen level at diagnosis on the relative survival of 28,531 men with localized carcinoma of the prostate. Cancer. 2008;112(4):813-9. doi:10.1002/cncr.23235.

Figures

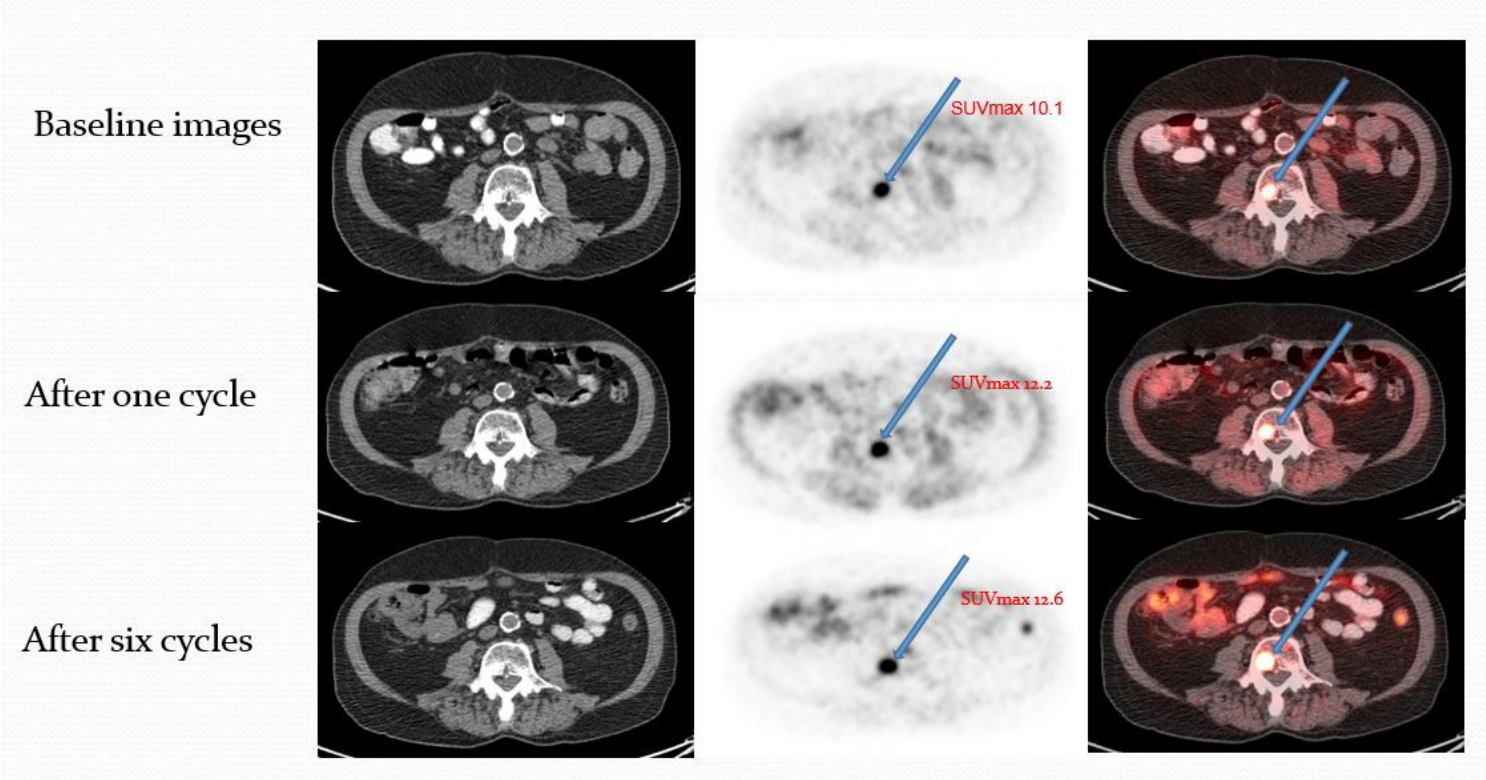

Figure 1

Non-response: 79 y/o M with mCRPC, Baseline PSA 20.79 ng/ml, summed SUVmax 60.5. Fluciclovine uptake in the L4 vertebra is a representative lesion. After 6 cycles of docetaxel, increased intensity of uptake in the same lesion was noted. There was also a corresponding increase in PSA, 33.83 ng/ml.

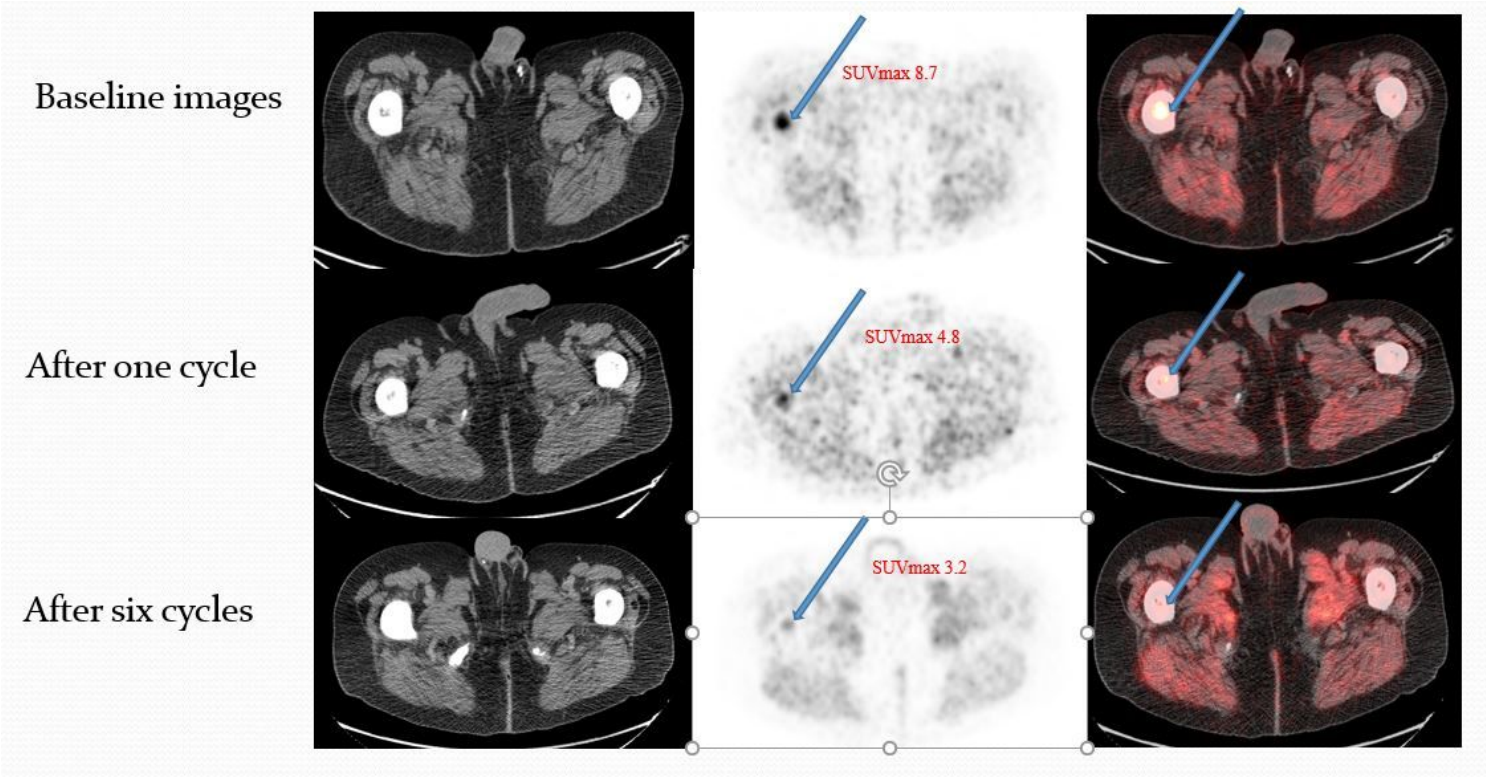

Figure 2

Response: 86 y/o M with mCRPC, Baseline PSA 63.43 ng/ml, summed SUVmax 39.2. Fluciclovine uptake shown in the right proximal femur is a representative lesion. After 6 cycles of docetaxel, decreased intensity of uptake in the same lesion was noted. There was also a corresponding decrease in PSA, 10.01 ng/ml.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementarytableTherapyresponse.docx