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Original Article

Exploratory study of ^{18}F-fluciclovine pet/ct for response assessment to docetaxel in patients with metastatic castration-resistant prostate cancer

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Abstract: Monitoring therapeutic response in patients with metastatic castration-resistant prostate cancer (mCRPC) can be challenging. We set out to determine if ^{18}F-fluciclovine PET/CT could be a useful imaging biomarker for response to docetaxel chemotherapy in patients with mCRPC. Seven patients with mCRPC had ^{18}F-fluciclovine PET/CT scheduled at baseline and after 1 and 6 cycles of chemotherapy. The sum of SUVmax from the prostate/bed and up to 5 metastatic bone and soft tissue/visceral lesions were recorded. The SUVpeak of the hottest lesion (PERCIST-like) was also recorded. In comparison to the baseline scan, a decrease of ≥30% was considered response; new lesions or >30% increase was progressive disease; change of <30% was stable disease. Bone scintigraphy and CT were acquired at baseline and after the 6th cycle. Response assessment was based on the Prostate Cancer Clinical Trial Working Group 3 recommendations. All (7/7) enrolled patients completed the 1st and 2nd scans, while 4/7 patients completed all 3 scans. PET response correlated with PSA response in 3/7 (42.9%) patients after 1 cycle of docetaxel, and 3/4 (75%) patients after 6 cycles of docetaxel, respectively. Bone scan and CT correlated with PSA response in 1/4 (25%) patients. There was no significant correlation between baseline ^{18}F-fluciclovine PET parameters or changes in PET parameters and time to PSA progression. In conclusion, this exploratory study showed that ^{18}F-fluciclovine PET/CT has better correlation with PSA response than CT or bone scan in patients with mCRPC treated with docetaxel. ^{18}F-fluciclovine PET/CT however did not predict time to PSA progression.

Keywords: Prostate cancer, ^{18}F-fluciclovine, docetaxel, metastatic castration-resistant prostate cancer, therapy response

Introduction

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 (^{18}F-fluciclovine) is a synthetic amino acid analog that has demonstrated utility for the 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 ^{18}F-fluciclovine have shown uptake correlates with amino acid transporter expression in castration-resistant prostate cancer cells [17]. ^{18}F-fluciclovine PET activity has been shown to reflect cancer cell metabolism, therefore, ^{18}F-fluciclovine PET activity in metastatic castrate-resistant prostate cancer may correlate with tumor burden as well as the response of the cancer cells to cytotoxic chemotherapy. In this exploratory study, we set out to understand if ^{18}F-fluciclovine PET/CT would better reflect the response to docetaxel chemotherapy in patients with mCRPC compared with conventional imaging biomarkers and to also assess the correlation between ^{18}F-fluciclovine uptake and time to PSA progression.

Materials and methods

Patients

This study was a prospective Institutional Review Board-approved trial requiring written informed consent. Inclusion criteria were 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 the 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 before administration of each cycle of chemotherapy.

^{18}F-fluciclovine PET/CT: Each patient had a baseline ^{18}F-fluciclovine PET/CT before the commencement of chemotherapy and after the 1st and 6th cycle of chemotherapy. ^{18}F-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 was acquired on a GE Discovery-690 16 slice integrated PET/CT scanner (GE Healthcare, Waukesha, WI) with oral contrast, without intravenous contrast. ^{18}F-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 was completed starting from the thighs and extending superiorly to the skull base. This was immediately repeated to obtain dual time point (initial 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 the 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].

^{18}F-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 ^{18}F-fluciclovine uptake.

^{18}F-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 was evaluated independently for ^{18}F-fluciclovine PET/CT and conventional imaging. Each was compared to the 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]. For additional analysis, patients were also dichotomized as either having progressive disease (≥ 25% increased PSA) or non-progressive disease (decreasing or stable PSA).

^{18}F-fluciclovine PET/CT: The summation of ^{18}F-fluciclovine uptake parameters (SUVmax, SUVmean) 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 was also recorded. A decrease in summed uptake parameters of ≥30% was considered response (R), while the appearance of new lesions or >30% increase in summed uptake parameters was considered progressive disease (PD). Stable disease was defined as a change of <30% summed uptake parameters between scans.

To also achieve a modified PET response criteria for solid tumors (PERCIST) 1.0 analysis, the SUVpeak of the single hottest lesion from each PET scan was also assessed for response using the above criteria.

Statistical analysis

Differences in ^{18}F-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 ^{18}F-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, Armonk, NY).

Results

Patients

Seven patients with metastatic castration-resistant prostate cancer were recruited. The average age was 79.0±5.5 years. Median PSA was 63.43 ng/ml (range 6.67-1300.00 ng/ml) and the median Gleason score (Grade group) was 4+4 (4), with a range of 7-8 Gleason score (**Table 1**). All patients in the study completed the 1st and 2nd ^{18}F-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 cabazitaxel and

Table 1. Patients' characteristics

ID	Age	PSA 1	Gleason score	SUVmax of hottest lesion (baseline)	PSA 2	SUVmax of hottest lesion (after cycle 1)	PSA 3	SUVmax of hottest lesion (after cycle 6)
1	74	>1300	4+4=8	7.6	>1300	14.5	-	-
2	86	63.43	4+4=8	8.7	53.08	4.8	10.01	5.0
3	70	70.18	4+4=8	5.1	50.94	5.1	50.23	6.1
4	84	270.29	4+4=8	10.5	253.69	8.9	64.54	6.1
5	78	16.89	4+4=8	6.5	26.09	6.4	-	-
6	79	20.79	4+3=7	11.5	35.02	12.6	33.76	12.2
7	78	6.67	4+3=7	6.5	5.87	9.6	-	-

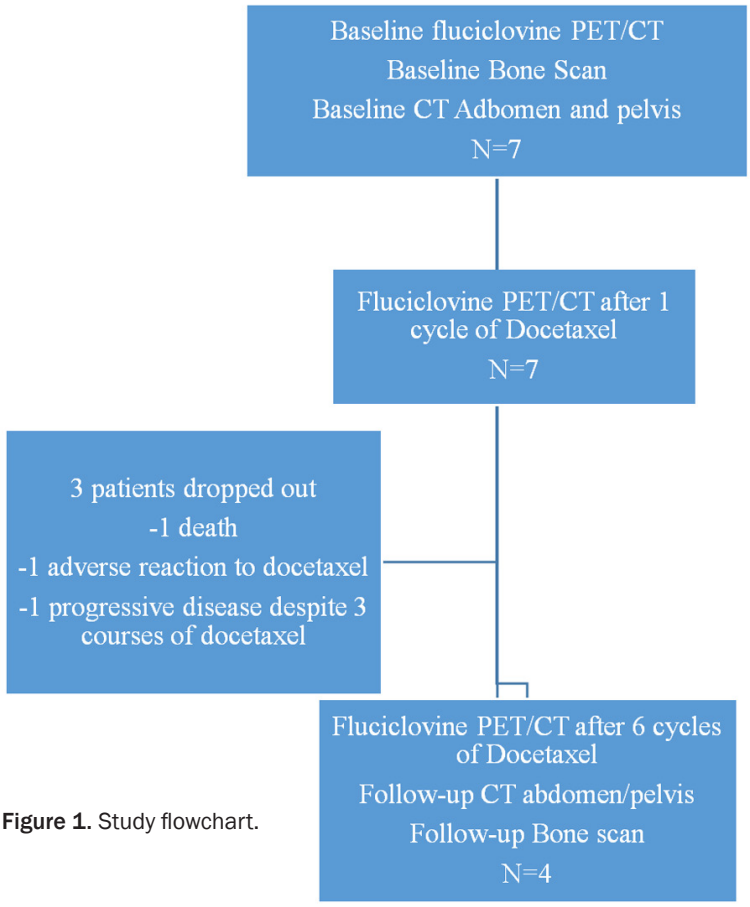

Figure 1. Study flowchart.

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 (**Figure 1**).

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 (**Table 3**).

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.

^{18}F-fluciclovine PET/CT: All PET results given are based on the initial time point. Delayed time point data did not improve on initial time point data.

Table 2 presents a summary of the mean of summed PET parameters at baseline, after the first and sixth cycles of chemotherapy. All patients recruited in this study had bone metastasis detected on baseline PET/CT; 6/7 (85.7%) patients had soft tissue disease including 4/7 (57.1%) with nodal disease.

After one cycle of Docetaxel (n=7), based on the differences in the summed SUVmax, stable disease was found in 6/7 (85.7%) patients, while progression was noted in 1/7 patients.

Table 2. ^{18}F-fluciclovine uptake parameters in patients with mCRPC

Sum of lesions (mean ± SD)					
PET parameters	Baseline PET (n=7 patients/ 49 lesions)	After 1st cycle (n=7 patient/49 lesions)	After 6th cycle (n=4 patients/23 lesions)	Δ after 1st cycle (%)	Δ after 6th cycle (%)
Summed SUVmax	47.6±16.0	48.1±20.4	36.3±17.3	0.4±11.5 (0.8)	-9.8±11.5 (-20.6)
Summed SUVmean	30.7±10.3	31.8±13.2	23.3±9.7	1.1±8.3 (3.6)	-6.4±7.1 (-20.8)
SUVpeak hottest lesion PERCIST-like (mean ± SD)					
SUVpeak*	6.2±2.1	6.9±3.2	5.8±2.8	0.7±2.7 (11.3)	-1.0±2.0 (16.1)

*n=1, single hottest lesion; Δ= change.

Table 3. Changes in summed SUVmax and PSA in individual patients with mCRPC after 1 and 6 cycles of Docetaxel

Patient	% Δ after the 1st cycle	% Δ after the 6th cycle	% Δ PSA after 1st cycle	% Δ PSA after the 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	-

Δ= change.

Using summed SUVmean, 5/7 (71.4%) patients had stable disease and progressive disease in 2/7 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.

After the sixth cycle of chemotherapy (n=4), based on the differences in the summed SUVmax, and SUVmean, 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.

^{18}F-fluciclovine PET: There was no significant correlation of summed SUVmax or SUVmean, with the baseline PSA at the time of the baseline scan.

After the first cycle (n=7), PET response using the difference in sums of either SUVmax, compared to parameters at baseline PET correlated with PSA response after the first cycle in 3/7 (42.9%) patients, while PET response using summed SUVmean correlated with PSA response in 2/7 (28.6%) patients.

Using SUVpeak of the hottest lesion (PERCIST-like), there was correlation with PSA response in 3/7 (42.9%) patients after the first cycle.

After the sixth cycle (n=4), PET response using summed differences of SUVmax, SUVmean compared to baseline PET was concordant with PSA response after the sixth cycle in 3/4 (75%) patients.

SUVpeak of the hottest lesion had a similar correlation with PSA response after the sixth cycle.

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 ($P< 0.05$). This difference was also seen with SUVpeak of the hottest lesion (**Table 4**).

Table 4. ^{18}F-fluciclovine uptake in patients with progressive versus non-progressive mCRPC

Parameters	Progressive Disease	Non-Progressive Disease	*p*-value
Mean SUVmax (summed)			
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	0.04
Mean SUVmean (summed)			
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	0.04
SUVpeak hottest lesion			
Baseline	7.0±2.1	5.6±2.2	0.14
Post-cycle 1	9.0±3.8	5.3±1.9	0.42
Post-cycle 6	9.8	4.5±1.0	<0.04

Table 5. Correlation of imaging with PSA for assessment of therapy response in patients with mCRPC on Docetaxel

A. After one cycle

Patient	^{18}F-fluciclovine PET			PSA
	SUVmax	SUVmean	SUVpeak hottest lesion	
1	SD	PD	PD	S
2	SD	SD	R	R
3	SD	SD	SD	S
4	SD	SD	SD	S
5	SD	SD	SD	P
6	SD	SD	SD	P
7	PD	PD	PD	S

B. After six cycles

Patient	^{18}F-fluciclovine PET (Summed SUVmax, SUVmean, SUVpeak hottest lesion)	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.

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

Correlation between ^{18}F-fluciclovine PET and conventional imaging response

^{18}F-fluciclovine PET response criteria using the summed SUVmax, SUVmean, and SUVpeak of the hottest lesion 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 5**.

Figures 2 and **3** are representative images from patients with non-response. **Figures 4** and **5** are representative images from a patient with 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 1. Baseline ^{18}F-fluciclovine uptake parameters did not correlate 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 6**).

Discussion

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 ^{18}F-fluciclovine PET/CT in the assessment of response to the first-line chemotherapeutic agent docetaxel, and its correlation with time to PSA progression.

We found a 43% correlation of response assessment using ^{18}F-fluciclovine PET parameters (SUVmax, and SUVpeak of the hottest lesion) with PSA response after a single cycle of docetaxel; however, after completion of 6 cycles of docetaxel, ^{18}F-fluciclovine PET parameters correlated with the standard of care biochemical (PSA) response in 75% of patients. In comparison to RECIST 1.1 and bone scan, ^{18}F-fluciclovine PET correlated better with the biochemical response to therapy in patients with mCRPC. The changes in ^{18}F-fluciclovine uptake correlated with changes in PSA after 1 and 6 cycles of docetaxel. This however was a

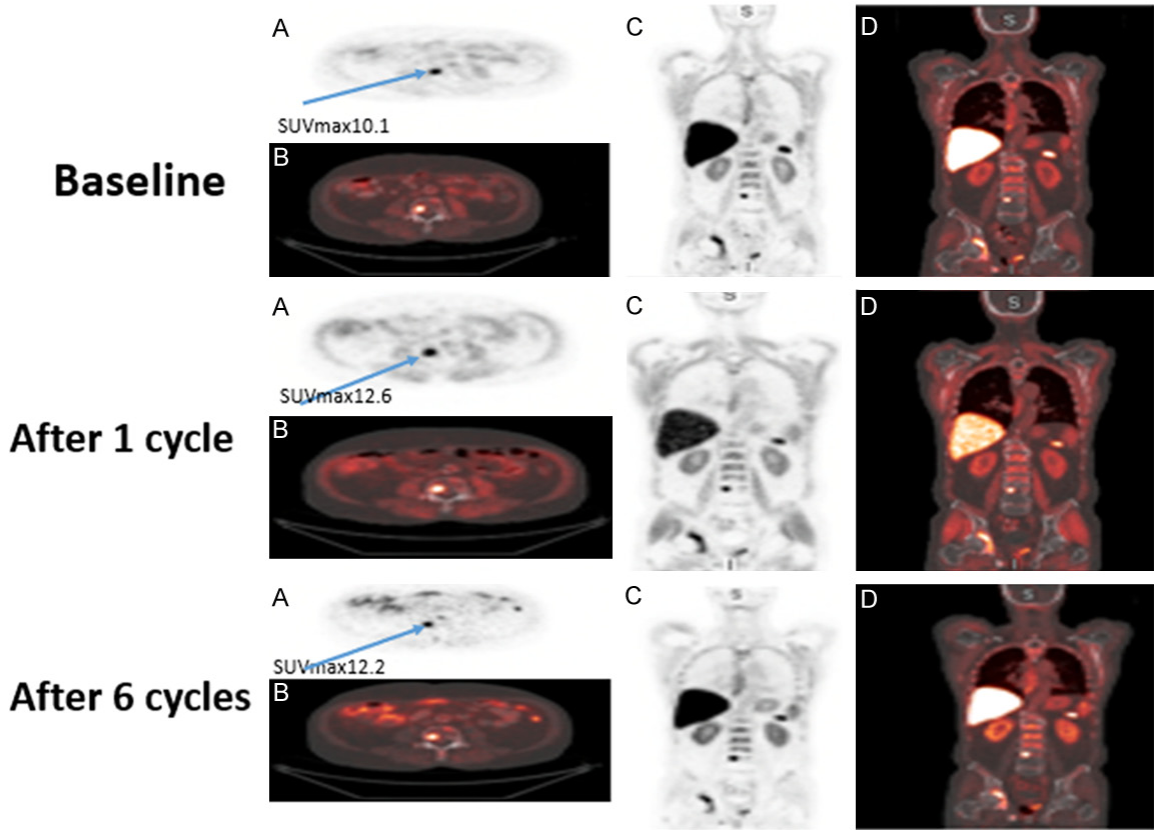

Figure 2. Representative case of non-response. A 79-year-old male with metastatic castration-resistant prostate cancer, Gleason score 4+3, baseline PSA 20.79 ng/ml which increased to 33.83 ng/ml after 6 cycles of chemotherapy. A. Axial image of fluciclovine PET with abnormal uptake in the L4 vertebra. B. Axial image of fused fluciclovine PET/CT with abnormal uptake in the L4 vertebra. C. Coronal image of fluciclovine PET. D. Coronal image of fused fluciclovine PET/CT. Images demonstrate increased intensity of fluciclovine uptake in the same lesion on subsequent imaging after chemotherapy.

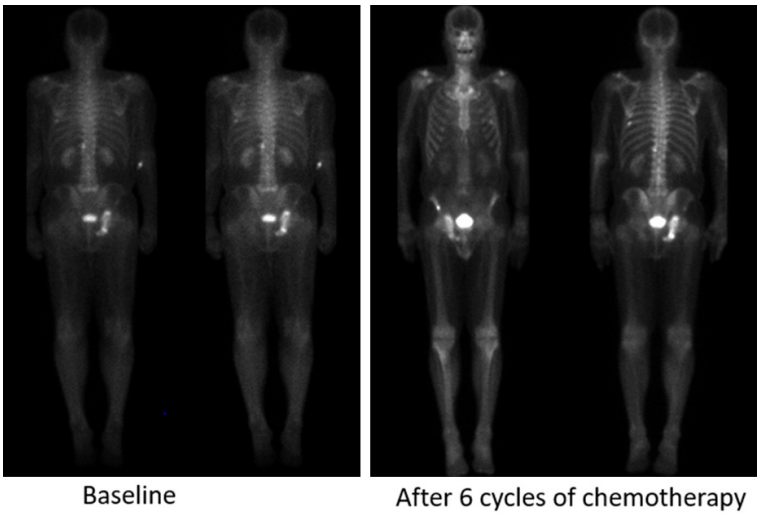

Figure 3. Technituium-99 bone scans in a 79-year-old male with metastatic castration-resistant prostate cancer, Gleason score 4+3, baseline PSA 20.79 ng/ml showing progressive disease after 6 cycles of chemotherapy in comparison to baseline scan.

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 the assessment of therapy response has been gaining attention. Studies making use of 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) [8], carbon-11 choline (^{11}C-choline) [9, 20], ^{18}F-fluorocholine (^{18}F-choline) [10] and Gallium-68 prostate-specific membrane antigen (^{68}Ga-

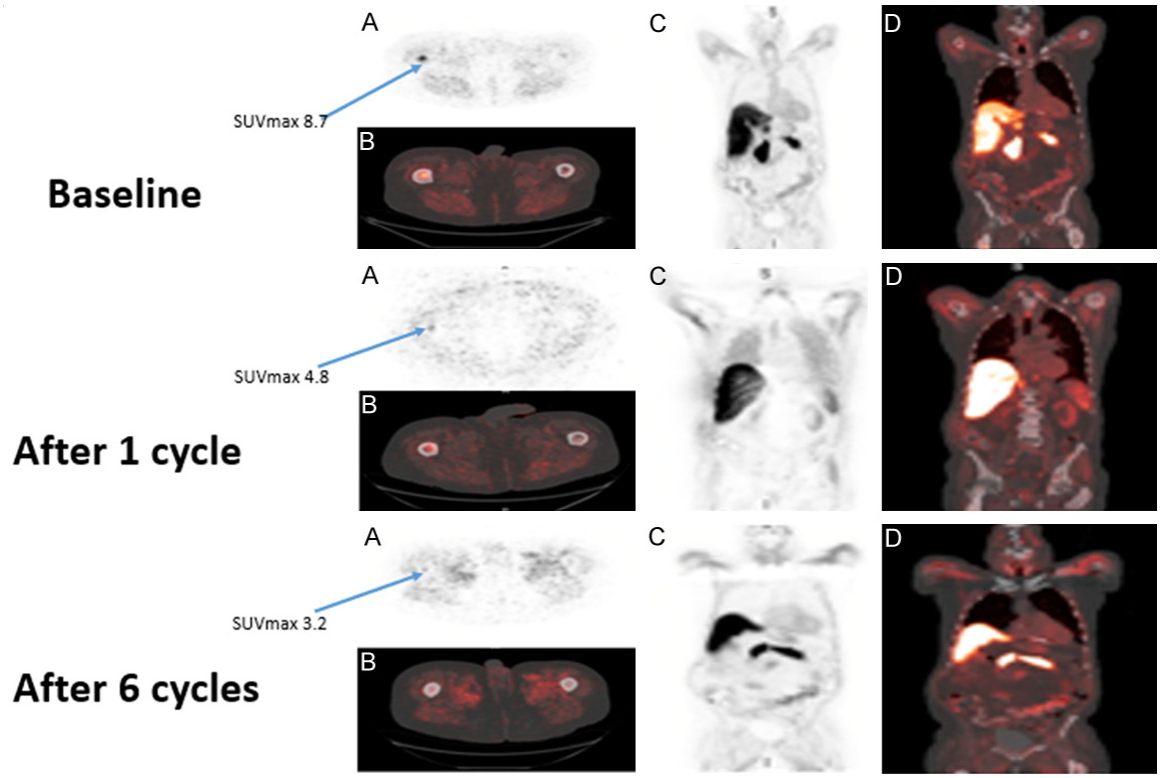

Figure 4. Representative case of response. 86 y/o M with metastatic castration-resistant prostate cancer, Gleason score 4+4, baseline PSA 63.43 ng/ml, which decreased to 10.01 ng/ml after 6 cycles of chemotherapy. A. Axial image of fluciclovine PET with abnormal uptake in the right proximal femur. B. Axial image of fused fluciclovine PET/CT with abnormal uptake in the right proximal femur. C. Coronal image of fluciclovine PET. D. Coronal image of fused fluciclovine PET/CT. Images demonstrate decreased intensity of fluciclovine uptake in the same lesion on subsequent imaging after chemotherapy.

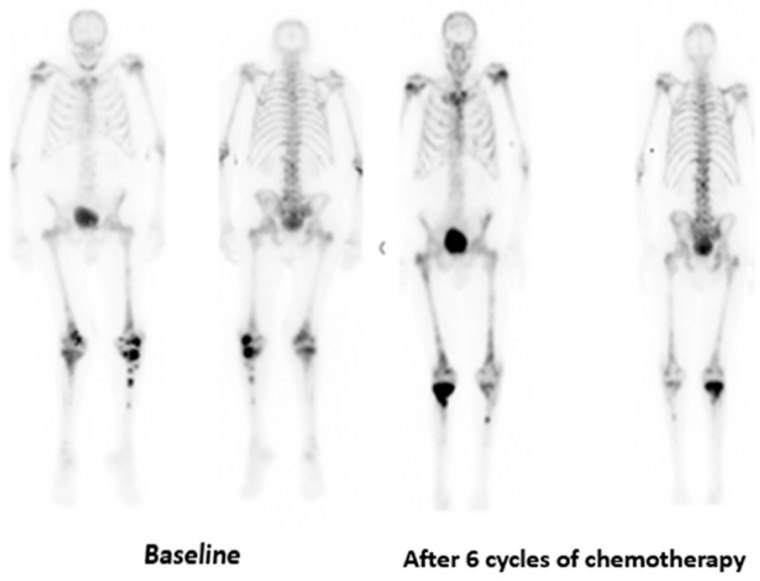

Figure 5. Technituium-99 bone scans in an 86-year-old male with metastatic castration-resistant prostate cancer, Gleason score 4+4, baseline PSA 63.43 ng/ml showing stable disease after 6 cycles of chemotherapy in comparison to baseline bone scans.

PSMA) [11, 21] in the evaluation of therapy response in the setting of metastatic 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 Ca-

Table 6. Correlation of time to PSA progression with change in summed PET-parameters

Δ PET parameter after the 1st cycle	Pearson Correlation	*p*-value	Δ PET parameter after the 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 hottest lesion	0.74	0.13	SUVpeak hottest lesion	0.74	0.10

Δ= change.

roli et al [10] making use of ^{11}C-choline and ^{18}F-choline, respectively, reported promising results in the evaluation of therapy response in patients with mCRPC. Yet, Schwarzenbock did not find a correlation between change in choline uptake in ^{11}C-choline PET/CT and response assessment in patients with mCRPC treated with docetaxel chemotherapy [20]. Seitz et al in a study of 16 patients with mCRPC undergoing docetaxel chemotherapy, reported that ^{68}Ga-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 ^{68}Ga-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 [21, 22].

After a single cycle of docetaxel, there was limited correlation between PSA response and ^{18}F-fluciclovine PET response, however, there was no statistical difference in the PET parameters between patients with progressive disease versus those who had non-progressive disease. This trend was however different after the completion of 6 cycles, with a correlation of 75% using PET parameters and a significant difference in SUVmax, SUVmean, and SUVpeak of the hottest lesion between patients with progressive disease versus non-progressive disease. The finding of a 75% correlation 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]. These disparities may be related to differences in sample size and study design. Though speculative, ^{18}F-fluciclovine PET may be a valuable tool in the assessment of early therapy response after a single cycle of docetaxel, and overall response after completing six cycles of docetaxel.

There was no correlation between ^{18}F-fluciclovine uptake parameters at the baseline or after 6 cycles of chemotherapy and the time to PSA progression. The role of PET in the 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 ^{18}F-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 [23]. The disparity with ^{18}F-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 determine this. Further evaluation in larger prospective studies is encouraged.

The small sample size is an obvious limitation of this study. This was an exploratory study designed to assess the possible role of ^{18}F-fluciclovine PET as a marker of therapy response in patients with mCRPC. It is practically difficult to recruit this cohort of patients with extensive metastatic disease who also served as controls for themselves over a prolonged period. As noted only 4 patients could complete the study. 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 [9, 24]. PSA levels however remain a primary reference method of objective assessment of patients with prostate cancer. Finally, while PERCIST 1.0 criteria has been established for evaluation of response to therapy in FDG PET [25], it has not been evaluated for ^{18}F-fluciclovine; therefore, we employed a modified PERCIST with SUVpeak in the assessment of response to therapy in this study.

Conclusion

This exploratory study suggests that ^{18}F-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 ^{18}F-fluciclovine uptake correlated with changes in PSA after 1 and 6 cycles of docetaxel. After 6 cycles of chemotherapy, the mean SUVmax, SUVmean, and SUVpeak of the hottest lesion were significantly higher in patients with progressive disease versus non-progressive disease. ^{18}F-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 ^{18}F-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.

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Disclosure of conflict of interest

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Supplementary Table 1. Changes in SUVmax and PSA and time to PSA progression

Patients	% Δ SUVmax after 1st cycle	% Δ SUVmax after 6th cycle	% Δ PSA after 1st cycle	% Δ PSA after 6th cycle	Time to PSA progression (days)
1	26.3	-	0.0	-	-
2	-28.6	-47.2	-51.7	-84.2	199
3	-11.9	-13.2	-20.7	-28.5	397
4	-20.6	-34.4	-6.1	-75.8	175
5	-6.2	-	100	-	56
6	-2.2	0.8	68.3	62.5	245
7	65.8	-	22.4	-	-

Δ= change.