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Heterogeneous Flare in Prostate-specific Membrane Antigen Positron Emission Tomography Tracer Uptake with Initiation of Androgen Pathway Blockade in Metastatic Prostate Cancer

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Abstract

Background: Prostate-specific membrane antigen (PSMA)-based positron emission tomography (PET) imaging is a highly sensitive tool for the detection of prostate cancer metastases. However, the effect of primary and secondary androgen deprivation therapy (ADT) on PSMA PET uptake has not been described.

Objective: To prospectively evaluate changes in ^{68}Ga-PSMA-11 PET uptake on initiation of androgen receptor (AR)-targeted therapy.

Design, setting, and participants: Prospective single-institution study of patients with metastatic castration-sensitive ($n = 4$) and castration-resistant prostate cancer ($n = 4$) starting treatment with ADT and enzalutamide, respectively, who underwent serial ^{68}Ga-PSMA-11 PET imaging before and after treatment initiation.

Outcome measurements and statistical analysis: The percentage change in ^{68}Ga-PSMA-11 PET uptake from baseline was descriptively reported and graphically represented.

Results and limitations: Early increases in PSMA PET tracer uptake in at least one metastatic lesion were observed in six out of seven patients who achieved subsequent prostate-specific antigen declines of >50% from baseline. Overall, 22 of 45 metastatic lesions (49%) exhibited early increases in PSMA uptake that were indicative of a flare effect rather than disease progression. Considerable intra- and interpatient heterogeneity was observed in the temporal pattern of PSMA uptake on treatment initiation. Study limitations include the sample size, the variable timing for scan acquisition, and limited long-term follow up.

Conclusions: Tumor flare in PSMA PET tracer uptake in the absence of disease progression is variably observed on initiation of AR-targeted treatment. Further studies are needed to delineate the factors controlling PSMA expression to optimize the diagnostic yield.

Patient summary: Flares of increased prostate-specific membrane antigen (PSMA) tracer uptake on positron emission tomography scans are variably observed following initiation of hormone therapy for prostate cancer and do not necessarily represent disease progression. There was considerable variability in PSMA expression between patients, and further studies are needed to understand the factors controlling PSMA expression.

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1. Introduction

Prostate-specific membrane antigen (PSMA)–based positron emission tomography (PET) imaging has demonstrated enhanced sensitivity and specificity for prostate cancer detection compared to conventional imaging techniques [1,2]. PSMA-based radioligand therapies (RLT), including ^{177}Lu-PSMA-617, have promising antitumor activity in metastatic castration-resistant prostate cancer (mCRPC) [3–8]. However, PSMA uptake across metastatic lesions is variable, and progression within lesions with low PSMA avidity may contribute to a limited duration of response to PSMA-targeted RLT for some patients [8].

Methods to enhance PSMA surface expression may therefore translate into significant improvements in the diagnostic sensitivity of PSMA-based imaging and the therapeutic activity of PSMA-targeted RLT. We previously demonstrated that the androgen receptor (AR) suppresses expression of PSMA, and conversely, AR pathway blocking therapies lead to upregulation of PSMA expression [9]. This suggests the potential for "flares" of increased PSMA uptake on initiation of AR-targeted therapy, which may be used as a "priming" effect that can increase the diagnostic yield of PSMA PET and the therapeutic payload with PSMA-targeted RLT.

In the current study, we prospectively evaluated changes in PSMA uptake on PET imaging in patients with metastatic castration-sensitive (mCSPC) or mCRPC at baseline and after starting treatment with primary androgen deprivation therapy (ADT) or enzalutamide, respectively.

2. Patients and methods

Patients with metastatic prostate cancer were enrolled in an institutional review board–approved single-institution study. Eligibility criteria included at least three measurable lesions according to RECIST 1.1 criteria on conventional imaging, with a plan to initiate either primary ADT for mCSPC (consisting of a luteinizing hormone–releasing hormone [LHRH] agonist + short-term antiandrogen bicalutamide to block potential flare in serum testosterone levels) or enzalutamide for mCRPC. Patients with mCRPC were required to remain on LHRH analog treatment during the course of the study evaluation. Patients underwent ^{68}Ga-PSMA-11 PET imaging using a whole-body PET scanner before starting either primary ADT or enzalutamide. Following initiation of ADT or enzalutamide, patients were imaged at weekly and bi-weekly intervals, respectively, with ^{68}Ga-PSMA-11 PET using the same imaging parameters as the baseline scan for up to four additional scan time points.

The maximum standardized uptake value (SUV_{max}) for each metastatic lesion (up to 7 lesions per patient) visualized on ^{68}Ga-PSMA-11 PET was determined by a trained nuclear medicine physician (T.H.) blinded to the clinical outcomes. As most metastatic lesions were <1 cm in diameter, SUV_{mean} could not be reliably obtained. The absolute and percentage changes in SUV_{max} on a per-lesion basis were determined for descriptive reporting and graphical representation. Patients were subsequently followed for prostate-specific antigen (PSA) response at 12 wk (≥50% decline from baseline) and PSA nadir on treatment.

3. Results

Eight patients (four each with mCSPC and mCRPC) were enrolled between August 2016 and January 2017. Baseline patient characteristics, PSA response, and PSMA PET results at the first post-treatment imaging time point are shown in Table 1. The mean interval between baseline PSMA PET and initiation of treatment was 11 d (range 0–30). The mean interval between baseline PSMA PET and the first post-treatment PSMA PET was 25 d (range 13–40).

A total of 45 metastatic lesions detectable on PSMA PET were evaluated (median SUV_{max} 16.9, range 4.6–58.3). The median baseline uptake on PET was similar between the mCRPC and mCSPC groups (SUV_{max} 16.0 ± 13.0 vs 17.3 ± 8.7; $p = 0.55$).

3.1. mCSPC patients

A total of 22 metastatic lesions were visualized on PSMA PET in the mCSPC cohort before and after treatment with primary ADT (Fig. 1A). All four patients responded to primary ADT with a mean maximal decline from baseline serum PSA of 99% (range 97.9–100%) and mean PSA nadir of 1.26 ng/ml (range 0–4. 2). Three patients (ADT001, ADT002, and ADT004), exhibited an increase in PSMA PET tracer uptake in at least one metastatic lesion at one or more post-treatment imaging time points. Of the 22 evaluable metastatic lesions, 15 (68%) exhibited an initial increase in SUV_{max} on PSMA PET, with a mean maximal increase in SUV_{max} from baseline of 46.3% (range 0.8–127%).

Table 1 – Baseline patient characteristics, PSA response, and ^{68}Ga-PSMA PET imaging results.

Patient	Age (yr)	Gleason grade	Prior local treatment	PSA (ng/ml)		Change in PSA from baseline (%)	Mean change in SUV_{max}, % (range)
				Baseline	Nadir		
ADT001	68	4 + 3	RP, RT	10.1	0	−100	8.6 (−37.6 to 46.9)
ADT002	65	4 + 3	RP, RT	17.8	0	−100	9.6 (−0.3 to 27.0)
ADT003	52	4 + 3	None	39.6	0.83	−97.9	−41.4 (−63.2 to −28.2)
ADT004	47	4 + 5	None	1044.6	4.2	−99.6	35.7 (−24.6 to 61.8)
ENZ001	64	3 + 3	RP, RT	8.6	1.1	−87.4	−15.1 (−43.1 to 39.0)
ENZ002	75	4 + 3	RT	45.6	0	−100	−7.0 (−46.2 to 19.6)
ENZ003	70	3 + 4	RP, RT	5.7	0.2	−96.5	36.4 (−28.8 to 94.5)
ENZ004	61	4 + 5	None	12.5	12.2	−2.4	7.7 (−52.8 to 122.6)

PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RP = radical prostatectomy; RT = radiotherapy; SUV = standardized uptake value.
[a] Change in SUV_{max} on PSMA PET from baseline to first post-treatment scan.