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Brief Correspondence

Single-lesion Prostate-specific Membrane Antigen Protein Expression (PSMA) and Response to [¹⁷⁷Lu]-PSMA-ligand Therapy in Patients with Castration-resistant Prostate Cancer

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Article info

Article history:

Accepted June 14, 2021

Associate Editor:

Guillaume Ploussard

Keywords:

Biomarker
 Prostate cancer
 Prostate-specific membrane antigen

Abstract

Initial reports of a clinical response in patients treated with the radioligand [¹⁷⁷Lu]-PSMA-617 for castration-resistant prostate cancer (CRPC) are promising, despite known inter- and inpatient heterogeneity. In metastatic CRPC, we examined the association of baseline immunohistochemical (IHC) expression of prostate-specific membrane antigen (PSMA) in a single lesion and responsiveness to [¹⁷⁷Lu]-PSMA-617 therapy, measured as the PSMA maximum standardized uptake value (SUV_{max}). Between 2015 and 2020, 19 patients with multiple metastases underwent single-lesion biopsy, [⁶⁸Ga]-PSMA positron emission tomography (PET) imaging, and treatment with [¹⁷⁷Lu]-PSMA-617. A monoclonal anti-PSMA antibody was used to semiquantitatively assess PSMA IHC in the biopsy specimen. Imaging evaluation of the biopsied single lesion and overall response was performed according to Positron Emission Tomography Response Criteria in Solid Tumors. The PSMA IHC histoscore correlated positively with pretreatment same-site PSMA SUV_{max} ($r_s = 0.6$). Nine patients had imaging after three cycles of [¹⁷⁷Lu]-PSMA-617 and were included in the lesion-specific analysis. Of these, five patients (55.6%) had an SUV_{max} response at the biopsy site, but three experienced overall progression. The histoscore was unable to predict the lesion-specific change in SUV_{max} (95% confidence interval [CI] –44.2 to 69.2) or PSA (95% CI –125.2 to 17.2). There was no correlation between single-lesion SUV_{max} and overall progression ($r_s = 0.1$) on [⁶⁸Ga]-PSMA PET imaging. Additional studies need to interrogate the clinical consequence of PSMA expression heterogeneity in metastases and the association with response to [¹⁷⁷Lu]-PSMA-617.

Patient summary: Treatment with a radioactive binding molecule called [¹⁷⁷Lu]-PSMA-617 for men with prostate cancer resistant to castration (CRPC) is showing promise. We investigated the association between the presence of PSMA protein in metastatic lesions at biopsy and response to [¹⁷⁷Lu]-PSMA-617 among men with metastatic CRPC. We found that assessment of PSMA presence at biopsy is not a



reliable predictor of response to [¹⁷⁷Lu]-PSMA-617. Additional studies are needed to better determine which CRPC metastatic sites will respond to this therapy.

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Castration-resistant prostate cancer (CRPC) is a lethal disease. Prostate-specific membrane antigen (PSMA) is a particularly promising target for prostate cancer molecular imaging and therapy based on radiopharmaceuticals (eg, [⁶⁸Ga]-PSMA and [¹⁸F]-PSMA). PSMA is a transmembrane receptor that functions as a folate hydrolase-carboxypeptidase that internalizes ligands on binding [1]. The level of PSMA protein expression, assessed via immunohistochemistry (IHC), correlates with parameters of prostate cancer aggressiveness, including Gleason score, propensity to metastasize, and development of castration resistance [2]. Numerous studies have shown high PSMA expression in CRPC [3]. Considering this and the generally limited amount of PSMA expression observed in benign tissues, targeting of PSMA in advanced prostate cancer has been aggressively pursued. Radionuclide therapy combining PSMA-targeted approaches with the β-emitter lutetium-177 have recently been proposed. While exciting responses have been observed in some cases, up to one-third of patients do not respond [2].

To better select patients for treatment with [¹⁷⁷Lu]-labeled PSMA ligands, there is a need for predictive biomarkers of treatment response. Existing data suggest that platelet count, a regular need for analgesics, and the presence of visceral metastases, as well as hemoglobin, age, lactate dehydrogenase, and the [⁶⁸Ga]-PSMA standardized uptake value (SUV) on positron emission tomography (PET), may serve this purpose to varying degrees [4–6]. The association of tumor PSMA IHC with response to [¹⁷⁷Lu]-PSMA radioligand treatment is currently unknown.

After institutional review board approval (#1217/2020), we performed a retrospective, single-center analysis of 19 patients with multifocal CRPC metastases (Supplementary Fig. 1). Patients underwent [⁶⁸Ga]-PSMA-HBED-CC PET, biopsy of a single metastatic lesion, and subsequent [¹⁷⁷Lu]-PSMA-617 therapy at 4-wk intervals from 2015 to 2020. Clinicopathological data including longitudinal PSA values were collected from patient records (Table 1). A monoclonal anti-PSMA antibody (Epitomics, Burlingame, CA, USA; rabbit monoclonal antibody, 1:50 dilution) was used to semiquantitatively assess PSMA expression via IHC. Experienced genitourinary pathologists scored immunohistochemical results as the staining intensity (on a scale from 0 to 3) and the percentage of positively stained cells to generate a histoscore between 0 and 300 according to the following equation [7]:

$$\text{IHC histoscore} = 1 \times (\% \text{ cells } 1^+) + 2 \times (\% \text{ cells } 2^+) + 3 \times (\% \text{ cells } 3^+)$$

We first assessed the association between SUV on [⁶⁸Ga]-PSMA PET imaging and IHC expression of PSMA from a single CRPC metastatic site before [¹⁷⁷Lu]-PSMA-617 therapy. Univariate linear regression analysis was used to measure the potential association between baseline PSMA on IHC and the single-lesion change in PSMA SUV_{max} and the PSA decline. Correlation between the single-lesion PSMA SUV_{max} and the overall change in PSMA SUV_{max} was assessed using Spearman correlation. Follow-up time was defined from treatment initiation to the date of most recent assessment or death.

Lesion-specific changes in PSMA SUV_{max} were determined by an experienced nuclear medicine physician (S.R.) and classified as responsive (SUV_{max} ≤30%), progressive (SUV_{max} ≥30%), or stable (lesions not meeting the criteria for response or progression) [8]. [⁶⁸Ga]-PSMA PET assessment was quantified according to Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) [8]. PSA response was defined as an absolute negative change in PSA from baseline to second imaging [9].

A PSMA histoscore could be determined for 12 of the 19 patients (median histoscore 280, interquartile range [IQR] 175–290). Baseline characteristics are shown in Supplementary Table 1. PSMA expression on IHC correlated with pretreatment same-site SUV_{max} ($r_s = 0.6$). Of these 12 patients, nine underwent a second PSMA PET evaluation after three cycles of [¹⁷⁷Lu]-PSMA-617 therapy and were included in the lesion-specific analysis. Clinicopathological and imaging data for these patients are shown in Table 1. Among the nine patients, the median number of previous systemic CRPC therapies was three (IQR 3–4) and median pretreatment PSA was 482 μg/l (IQR 42.7–911.8). The median pretreatment biopsy-site PSMA SUV_{max} was 21.8 (IQR 12.5–26.6). The median interval between the imaging studies was 5.2 mo (IQR 4.9–5.6). Median radioactivity of 22 505 MBq (IQR 18 220–44 801) was delivered during radionuclide therapy. Four patients (44.4%) died during follow-up at a median time of 8.2 months (IQR 6.0–11.4) after treatment initiation.

A single-lesion SUV_{max} response was observed in five of nine patients, while two had a stable lesion and two others experienced progression. Among the responders, the change in SUV_{max} for the biopsied lesion ranged from –33% to –43% on consecutive [⁶⁸Ga]-PSMA PET imaging (Fig. 1). In the overall [⁶⁸Ga]-PSMA PET assessment, five patients experienced progression according to PERCIST. Interestingly, three of these five patients had a single-lesion SUV_{max} response at the biopsy site. There was no correlation

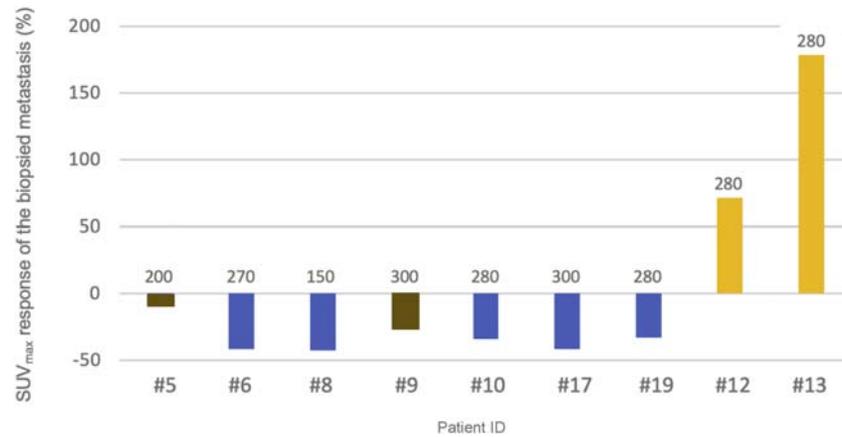


Fig. 1 – Percentage change in PSMA SUV_{max} in biopsied metastases after ¹⁷⁷Lu-PSMA-617 therapy for individual patients. Blue bars = lesion responded; brown bars = lesion stable; yellow bars = lesion progressed according to Positron Emission Tomography Response Criteria in Solid Tumors. The x-axis shows the individual patients with the number above the columns describing the PSMA protein expression assessed by immunohistochemistry of the investigated lesion at baseline. PSMA = prostate-specific membrane antigen; SUV_{max} = maximum standardized uptake value on ⁶⁸Ga-PSMA positron emission tomography imaging.

between single-lesion PSMA SUV_{max} and overall progression ($r_s = 0.1$). A PSA decline was observed in four of the nine patients (44.4%). The PSMA histoscore was unable to predict the lesion-specific change in PSMA SUV_{max} (95% confidence interval [CI] –44.2 to 69.2; $p = 0.6$) or PSA decline (95% CI –125.2 to 17.2; $p = 0.1$) on univariate analysis. Supplementary Figure 2 shows PSMA IHC results for biopsied metastases as well as baseline and consecutive ⁶⁸Ga-PSMA PET images in three representative patients.

For patients with prostate cancer bone lesions, we found that PSMA expression on IHC correlated with the SUV_{max} for the biopsied metastatic lesions at baseline ($r_s = 0.6$). However, single-lesion PSMA expression on IHC was not an accurate predictor of response to ¹⁷⁷Lu-PSMA-617 therapy. Furthermore, we found that while PSMA avidity on

imaging may substantially decrease in some metastatic lesions following therapy, new lesions can emerge during this time (Supplementary Fig. 3).

There are several potential explanations for our findings. These initial observations could be explained by heterogeneous PSMA expression both within and between specific tumor foci [10]. Furthermore, altered vascularity and tissue permeability, along with other factors, may alter radiopharmaceutical delivery to cancer cells. In addition, it is possible that some areas may possess features that render them resistant to β -emission-based therapy. Mixed therapeutic responses could also be reflective of tissue-specific effects of the therapy [10].

The current study has several limitations, including its retrospective approach and limited sample size. These

Table 1 – Clinicopathological and imaging data for the nine patients who underwent two consecutive ⁶⁸Ga-PSMA-PET imaging studies

Parameter	Patient ID								
	5	6	8	9	10	12	13	17	19
Chemotherapy	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
NAAI	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
ADT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Radical prostatectomy	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Gleason score	NA	6	8	9	9	NA	8	8	9
Platelets (10 ⁹ cells/l)	76	296	178	183	197	248	232	199	298
Baseline PSA (μg/l)	911.8	42.7	162.8	29.3	1693	1521	684	25.2	482
PSMA IHC (histoscore)	200	270	150	300	280	280	280	300	280
Metastatic site	OID	L1	OIS	L1	OIS	OIS	OIS	L3	OIS
Baseline PSA (μg/l)	911.8	42.7	162.8	29.3	1693	1521	684	25.2	482
PSA on 2nd imaging (μg/l)	520.9	16.8	128.9	34.4	1624	1527	1475	8.8	976
Change in PSA (μg/l)	-390.9	-25.9	-33.9	5.1	-69	6	791	-16.4	494
PSMA SUV _{max} before RLT	12.5	21.8	14.9	32.4	26.6	7.9	2.3	48.7	24.8
PSMA SUV _{max} after RLT	11.3	12.7	8.5	24.1	17.6	14.1	6.6	28.1	16.7
Change in SUV _{max} (%)	-10	-42	-43	-26	-34	78	187	-42	-33
Overall ⁶⁸ Ga-PSMA-PET assessment	PR	PR	PR	PD	PD	PR	PD	PD	PD

PET = positron emission tomography; NA = not available; NAAI = new androgen-axis inhibitor; ADT = androgen deprivation therapy; PSA = prostate-specific antigen; IHC = immunohistochemistry; PSMA = prostate-specific membrane antigen; OID = os ilium dexter; L1 = lumbar vertebra 1; OIS = os ilium sinister; L3 = lumbar vertebra 3; SUV = standardized uptake value; RLT = radioligand therapy with ¹⁷⁷Lu-PSMA-617; PR = partial response; PD = progressive disease.

limitations notwithstanding, such data are rare, given that biopsies of PSMA-avid CRPC metastatic lesions are not commonly performed and [¹⁷⁷Lu]-PSMA-617 is a relatively new therapy. Thus, our study provides a unique preliminary insight into the responsiveness of metastatic prostate cancer lesions to [¹⁷⁷Lu]-PSMA-617 therapy according to measurable pretreatment factors (ie, PSMA expression on IHC and SUV_{max} on [⁶⁸Ga]-PSMA PET imaging). To the best of our knowledge, this is the first study to assess single-lesion PSMA IHC and response to [¹⁷⁷Lu]-PSMA-617 therapy. These findings should motivate prospective studies to optimize patient selection and improve the efficacy of [¹⁷⁷Lu]-PSMA-617 therapy for men with CRPC.

Author contributions: Ganesh S. Palapattu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Statistical analysis: Stangl-Kremser, Tosoian.

Obtaining funding: None.

Administrative, technical, or material support: Rasul, Mitterhauser, Comperat, Mazal, Kain.

Supervision: Palapattu.

Other: None.

Financial disclosures: Ganesh S. Palapattu certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.euros.2021.06.007>.

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