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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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 intrapatient 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 (SUVmax). 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 SUVmax (rs = 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 SUVmax response at the biopsy site, but three experienced overall progression. The histoscore was unable to predict the lesion-specific change in SUVmax (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 SUVmax and overall progression (rs = 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-671.

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
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.

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 SUVmax and the PSA decline. Correlation between the single-lesion PSMA SUVmax and the overall change in PSMA SUVmax 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 SUVmax were determined by an experienced nuclear medicine physician (S.R.) and classified as responsive (SUVmax ≤30%), progressive (SUVmax >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] 12.5–26.6). The median interval between the [68Ga]-PSMA PET assessment or death.

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between single-lesion PSMA SUV\textsubscript{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\textsubscript{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 $^{68}$Ga-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\textsubscript{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 $^{177}$Lu-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 $\beta$-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.

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

| Parameter | Patient ID |
|-----------|------------|
| Chemotherapy | 5 6 8 9 10 12 13 17 19 |
| NAAI | Yes No Yes Yes Yes No Yes Yes Yes |
| ADT | Yes Yes Yes Yes Yes Yes Yes Yes Yes |
| Radical prostatectomy | Yes No Yes Yes Yes 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 |
| 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 |
| 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 |
| PSA SUV\textsubscript{max} before RLT | 12.5 21.8 14.9 32.4 26.6 7.9 2.3 48.7 24.8 |
| PSA SUV\textsubscript{max} after RLT | 11.3 12.7 8.5 24.1 17.6 14.1 6.6 28.1 16.7 |
| Change in SUV\textsubscript{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 $^{177}$Lu-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 [\(^{177}\text{Lu}\)]-PSMA-617 is a relatively new therapy. Thus, our study provides a unique preliminary insight into the responsiveness of metastatic prostate cancer lesions to [\(^{177}\text{Lu}\)]-PSMA-617 therapy according to measurable pretreatment factors (ie, PSMA expression on IHC and SUV\(_{\text{max}}\) on \(^{68}\text{Ga}\)-PSMA PET imaging). To the best of our knowledge, this is the first study to assess single-lesion PSMA IHC and response to [\(^{177}\text{Lu}\)]-PSMA-617 therapy. These findings should motivate prospective studies to optimize patient selection and improve the efficacy of [\(^{177}\text{Lu}\)]-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.

**Study concept and design:** Stangl-Kremser, Salami, Zaslavskyy, Palapattu, Rasul.

**Acquisition of data:** Hassler, Pozo-Salido, Steinbach.

**Analysis and interpretation of data:** Stangl-Kremser, Mazal.

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**Supervision:** Palapattu.

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**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.

**References**

[1] Liu H, Rajasekaran AK, Moy P, et al. Constitutive and antibody-induced internalization of prostate-specific membrane antigen. Cancer Res 1998;58:4055–60.

[2] Emmett L, Willovson K, Violet J, Shin J, Blanksby A, Lee J. Lutetium \(^{177}\)PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. J Med Radiat Sci 2017;64:52–60. http://dx.doi.org/10.1002/jmrs.227.

[3] Wright GL, Grob BM, Haley C, et al. Upregulation of prostate-specific membrane antigen after androgen-deprivation therapy. Urology 1996;48:326–34. http://dx.doi.org/10.1016/s0090-4295(96)00184-7.

[4] Heck MM, Tauber R, Schweiger S, et al. Treatment outcome, toxicity, and predictive factors for radioigand therapy with \(^{\text{177}}\text{Lu}\)-PSMA-I&T in metastatic castration-resistant prostate cancer. Eur Urol 2019;75:920–6. http://dx.doi.org/10.1016/j.eururo.2018.11.016.

[5] Emmett L, Crumbaker M, Ho B, et al. Results of a prospective phase 2 pilot trial of \(^{\text{177}}\text{Lu}\)-PSMA-617 therapy for metastatic castration-resistant prostate cancer including imaging predictors of treatment response and patterns of progression. Clin Genitourin Cancer 2019;17:15–22. http://dx.doi.org/10.1016/j.clgc.2018.09.014.

[6] Rasul S, Hartenbach M, Wollenweber T, et al. Prediction of response and survival after standardized treatment with 7400 Mbiq \(^{\text{177}}\text{Lu}\)-PSMA-617 every 4 weeks in patients with metastatic castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging 2021;48:1650–7. http://dx.doi.org/10.1007/s00259-020-05082-5.

[7] Stenger M. Calculating H-score. The ASCO Post. April 10, 2015. https://ascopost.com/issues/april-10-2015/calculating-h-score/.

[8] O’H, Lodge MA, Wahl RL. Practical PERCIST: a simplified guide to PET Response Criteria in Solid Tumors I.D. Radiology 2016;280:576–84. http://dx.doi.org/10.1148/radiol.2016142043.

[9] Scher HI, Morris MJ, Stadler WM, 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;34:1402–18. http://dx.doi.org/10.1200/JCO.2015.64.2702.

[10] Paschalis A, Sheehan B, Riismaa R, et al. Prostate-specific membrane antigen heterogeneity and DNA repair defects in prostate cancer. Eur Urol 2019;76:469–78. http://dx.doi.org/10.1016/j.eururo.2019.06.030.