Tumor Sink Effect: Myth or Reality?

TO THE EDITOR: We thank Prive et al. for their correspondence. As acknowledged in our publication (*1*), the main limitation of the study is the use of a single-time-point SUV measurement as a surrogate for radiation dose. Differential prostate-specific membrane antigen (PSMA) uptake patterns and tumor-to-background ratios are observed when PSMA PET image acquisition is performed at late time points in comparison to images acquired at 1 h after injection (*2–5*). Thus, it is clear that images acquired 1 h after injection cannot reflect the biologic effects of ^{177}Lu-PSMA that occur over more than 3 wk (biologic half-life). However, even if not perfectly accurate, PSMA PET imaging performed at 1 h still provides a fair estimate of the patient target expression and of the biodistribution of a PSMA-targeted radiopharmaceutical, and prior studies have reported that pretherapeutic PSMA PET measurements may be correlated with radiation dose to tumor and normal organs from ^{177}Lu-PSMA therapy (*6–8*).

Regarding the definition of low- and high-volume disease, it is important to note that CHAARTED and LATTITUDE criteria were based on conventional imaging (*9*). Applying these criteria for an analysis of PSMA PET can lead to major discordance in patient stratification, as described previously (*10*). Therefore, we recommend explicit use of the term *PSMA-VOL* in reference to the whole-body PSMA PET volumetric assessment and not just *low-volume* or *high-volume* metastatic, as follows: very low PSMA-VOL ($<25\,cm^3$), low PSMA-VOL (25–188 cm^3), moderate PSMA-VOL (189–531 cm^3), high PSMA-VOL (532–1,354 cm^3), and very high PSMA-VOL ($\geq$1,355 cm^3).

As the authors mention, we agree that patients with low-volume metastatic disease or oligometastases can safely benefit from PSMA-based radionuclide therapy without decreasing the commonly applied dose-activity level of 7.4 GBq per cycle currently in use in the ongoing trial NCT04443062 and as supported by preliminary data (*11*). On the other hand, our results suggest that the dose-activity level of ^{177}Lu-PSMA could be increased safely in patients with very high PSMA-VOL ($\geq$1,355 cm^3). Nevertheless, these findings warrant further validation by dosimetry studies and safety assessments in prospective clinical trials.

REFERENCES

1. Gafita A, Wang H, Robertson A, et al. Tumor sink effect in ^{68}Ga-PSMA-11 PET: myth or reality? *J Nucl Med.* 2022;63:226–232.
2. Rosar F, Bartholomä M, Maus S, et al. ^{89}Zr-PSMA-617 PET/CT may reveal local recurrence of prostate cancer unidentified by ^{68}Ga-PSMA-11 PET/CT. *Clin Nucl Med.* 2022;47:435–436.
3. Beheshti M, Manafi-Farid R, Geinitz H, et al. Multiphasic ^{68}Ga-PSMA PET/CT in the detection of early recurrence in prostate cancer patients with a PSA level of less than 1 ng/mL: a prospective study of 135 patients. *J Nucl Med.* 2020;61:1484–1490.
4. Hohberg M, Kobe C, Täger P, et al. Combined early and late [^{68}Ga]PSMA-HBED-CC PET scans improve lesion detectability in biochemical recurrence of prostate cancer with low PSA levels. *Mol Imaging Biol.* 2019;21:558–566.
5. Alberts I, Prenosil G, Mingels C, et al. Feasibility of late acquisition [^{68}Ga]Ga-PSMA-11 PET/CT using a long axial field-of-view PET/CT scanner for the diagnosis of recurrent prostate cancer: first clinical experiences. *Eur J Nucl Med Mol Imaging.* 2021;48:4456–4462.
6. Wang J, Zang J, Wang H, et al. Pretherapeutic ^{68}Ga-PSMA-617 PET may indicate the dosimetry of ^{177}Lu-PSMA-617 and ^{177}Lu-EB-PSMA-617 in main organs and tumor lesions. *Clin Nucl Med.* 2019;44:431–438.
7. Violet J, Jackson P, Ferdinandus J, et al. Dosimetry of ^{177}Lu-PSMA-617 in metastatic castration-resistant prostate cancer: correlations between pretherapeutic imaging and whole-body tumor dosimetry with treatment outcomes. *J Nucl Med.* 2019;60:517–523.
8. Peters SMB, Hofferber R, Privé BM, et al. [^{68}Ga]Ga-PSMA-11 PET imaging as a predictor for absorbed doses in organs at risk and small lesions in [^{177}Lu]Lu-PSMA-617 treatment. *Eur J Nucl Med Mol Imaging.* 2022;49:1101–1112.
9. Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II—2020 update: treatment of relapsing and metastatic prostate cancer. *Eur Urol.* 2021;79:263–282.
10. Barbato F, Fendler WP, Rauscher I, et al. PSMA-PET for the assessment of metastatic hormone-sensitive prostate cancer volume of disease. *J Nucl Med.* 2021;62:1747–1750.
11. Privé BM, Peters SMB, Muselaers CHJ, et al. Lutetium-177-PSMA-617 in low-volume hormone-sensitive metastatic prostate cancer: a prospective pilot study. *Clin Cancer Res.* 2021;27:3595–3601.

Andrei Gafita*
Jeremie Calais
Wolfgang P. Fendler
Matthias Eiber
**UCLA*
Los Angeles, California
E-mail: agafita@mednet.ucla.edu

Published online Apr. 28, 2022.
DOI: 10.2967/jnumed.122.264119

Thoughts on "Tumor Sink Effect in ^{68}Ga-PSMA-11 PET: Myth or Reality?"

TO THE EDITOR: We read with great interest the recent article by Gafita et al. published in *The Journal of Nuclear Medicine* (*1*). They observed that patients with a very high tumor load showed a significantly lower SUV in healthy organs on a ^{68}Ga-prostate-specific membrane antigen (PSMA) PET scan, suggesting a tumor sink effect. A comparable observation was also described by Gaertner et al. (*2*). These authors postulated that a similar effect might occur with PSMA-targeted radioligand therapy. However, dissimilar results regarding the tumor sink effect have also been reported (*3*).

Although the results of Gafita et al. may support higher treatment activities of ^{177}Lu-PSMA for those with a very high volume of disease ($\geq$1,355 mL), there were actually no significant differences in the SUV_{mean} of healthy organs between a very low volume of disease ($<$25 mL) and a high volume ($<$1,355 mL). These results are in line with what we recently observed in a therapeutic ^{177}Lu-PSMA study on patients with low-volume metastatic hormone-sensitive prostate cancer (*4,5*). We saw that the dosimetry results based on posttherapeutic SPECT imaging in patients with a maximum of 10 prostate cancer metastases—or a very low volume of metastasis following the definition of Gafita et al.—were comparable to previously reported results on patients with high-volume metastatic prostate cancer (*6–8*). This result suggests that the sink effect in the setting of low-volume metastatic disease may be of less concern than is commonly anticipated.

There are also important limitations to Gafita's study that need to be considered and also apply to the previous work investigating the sink effect. The authors did not take into account tracer pharmacokinetics or perform dosimetry but based their results on a single-time-point SUV as a surrogate for radiation dose. This choice limits the accuracy with which the radiation dose for ^{177}Lu-PSMA can be estimated, particularly as uptake in healthy organs and tumor occurs over a prolonged time (*5,9*). The observed effect could thus relate to an early differential distribution of tracer to tumors in a very high-volume setting (≥1,355 mL), which does not exist at later time points. Moreover, the precursor used for PSMA imaging (e.g., PSMA-11) and PSMA therapy (e.g., PSMA-617) generally differ and may thus confound the outcomes. The study was also prone to bias due to its retrospective multicenter design with varying local scan protocols. Therefore, the differences between a very low and a very high volume of disease may have differed using a different study strategy.

All in all, we do believe there is a relevant sink effect but want to emphasize that the present data suggest that patients with a very low volume of metastatic disease or oligometastases can safely benefit from PSMA radioligand therapy and should not be excluded after this recent report. A prospective study with a low oligometastatic volume and a high volume of disease in a homogeneous cohort of patients that includes dosimetry is awaited. Moreover, a post hoc analyses of the VISION data that compares the adverse events (e.g., xerostomia) in patients with low-volume and high-volume metastasis may lead to a better understanding. As a final note, the definition of high volume and low volume used in the studies also differs from what urooncologists think of as high and low volumes, as they generally follow the CHAARTED or LATTITUDE criteria (*10*). We therefore urge future studies to base their reports on criteria that are more commonly used.

REFERENCES

1. Gafita A, Wang H, Robertson A, et al. Tumor sink effect in ^{68}Ga-PSMA-11 PET: myth or reality? *J Nucl Med.* 2022;63:226–232.
2. Gaertner FC, Halabi K, Ahmadzadehfar H, et al. Uptake of PSMA-ligands in normal tissues is dependent on tumor load in patients with prostate cancer. *Oncotarget.* 2017;8:55094–55103.
3. Werner RA, Bundschuh RA, Bundschuh L, et al. Semiquantitative parameters in PSMA-targeted PET imaging with [^{18}F]DCFPyL: impact of tumor burden on normal organ uptake. *Mol Imaging Biol.* 2020;22:190–197.
4. Privé BM, Peters SMB, Muselaers CHJ, et al. Lutetium-177-PSMA-617 in low-volume hormone sensitive metastatic prostate cancer: a prospective pilot study. *Clinical Cancer Research.* 2021;27:3595–3601.
5. Peters SMB, Privé BM, de Bakker M, et al. Intra-therapeutic dosimetry of [^{177}Lu]Lu-PSMA-617 in low-volume hormone-sensitive metastatic prostate cancer patients and correlation with treatment outcome. *Eur J Nucl Med Mol Imaging.* 2022;49:460–469.
6. Violet J, Jackson P, Ferdinandus J, et al. Dosimetry of ^{177}Lu-PSMA-617 in metastatic castration-resistant prostate cancer: correlations between pretherapeutic imaging and whole-body tumor dosimetry with treatment outcomes. *J Nucl Med.* 2019; 60:517–523.
7. Özkan A, Uçar B, Seymen H, Yildiz Yarar Y, Falay FO, Demirkol MO. Posttherapeutic critical organ dosimetry of extensive ^{177}Lu-PSMA inhibitor therapy with metastatic castration-resistant prostate cancer: one center results. *Clin Nucl Med.* 2020; 45:288–291.
8. Delker A, Fendler WP, Kratochwil C, et al. Dosimetry for ^{177}Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43:42–51.
9. Jackson PA, Hofman MS, Hicks RJ, Scalzo M, Violet J. Radiation dosimetry in ^{177}Lu-PSMA-617 therapy using a single posttreatment SPECT/CT scan: a novel methodology to generate time- and tissue-specific dose factors. *J Nucl Med.* 2020; 61:1030–1036.
10. Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II—2020 update: treatment of relapsing and metastatic prostate cancer. *Eur Urol.* 2021;79:263–282.

Bastiaan M. Privé*
Steffie M.B. Peters
Maike J.M. Uijen
Marcel J.R. Janssen
Willemijn A.M. van Gemert
Michael C. Kreissl
Samer Ezzidin
Mark W. Konijnenberg
James Nagarajah
**Radboud University Medical Center*
Nijmegen, The Netherlands
E-mail: bastiaan.prive@radboudumc.nl

Published online Jan. 13, 2022.
DOI: 10.2967/jnumed.122.263802