

Tumor sink effect in ⁶⁸Ga-PSMA-11 PET: Myth or Reality?

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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 very high tumor load showed a significantly lower standardized uptake value (SUV) of healthy organs on a ^{68}Ga -PSMA PET scan, suggesting for a tumor sink effect. A comparable observation was also described by Gaertner et al. (2). These authors postulate that a similar effect might occur with PSMA-targeted radioligand therapy. However, dissimilar results regarding the tumor sink effect have also been reported (3).

While the results of Gafita et al. may support higher treatment activities of ^{177}Lu -PSMA for those with very high-volume disease ($\geq 1355\text{ml}$), there were actually no significant differences in SUVmean of the healthy organs between very low volume ($< 25\text{ml}$) and high volume disease ($< 1355\text{ml}$). These results are in line to what we recently observed in a therapeutic ^{177}Lu -PSMA study in low-volume metastatic hormone sensitive prostate cancer patients (4,5). We saw that the dosimetry results based on post-therapeutic SPECT imaging in patients with maximum ten prostate cancer metastases - or very low-volume metastatic following Gafita et al. definition - were comparable to previously reported results in high-volume metastatic prostate cancer patients (6-8). This suggests that the sink effect in a low-volume metastatic disease setting may be of less concern than it is commonly anticipated.

There are also important limitations to Gafita's study which needs to be considered and also applies to the previous work investigating the sink effect. The authors did not take into account tracer pharmacokinetics or performed dosimetry, but based their results on a single time-point SUV as a surrogate for radiation doses. This has limited accuracy to estimate the radiation dose for ^{177}Lu -PSMA, particularly as uptake in healthy organs and tumor occurs over a prolonged time (5,9). The observed effect could thus be related to an early differential distribution of tracer to tumors in a very high-volume setting ($\geq 1355\text{ml}$), which does not exist on later timepoints. Moreover, the precursor used for PSMA imaging (e.g. PSMA-11) and PSMA therapy (e.g. PSMA-617) generally differ which may confound the outcomes. The study is also prone to bias due to its retrospective multicenter design with varying local scan protocols. Therefore, the differences between very low- and high-volume disease may have differed (or not) 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 (very) low-volume metastatic disease or oligometastases can safely benefit of PSMA radioligand therapy, and should not be excluded following this recent report. A prospective study with low-oligometastatic volume and high-volume disease in a homogenous 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 low-volume and high-volume metastatic patients may lead to a better understanding. As a final note, the definition of high- and low-volume used in the studies also differ to what uro-oncologists think of low- and high-volumes as they generally follow the CHAARTED or LATTITUDE criteria (10). We therefore urge following studies to (also) report based on criteria that are more commonly used.

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