



Radiohybrid prostate-specific membrane antigen ligand: new frontier in prostate cancer imaging and therapy

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The recently presented results of the LIGHTHOUSE phase 3 trial reinforce the clinical utility of detecting prostate-specific membrane antigen (PSMA) in the management of prostate carcinoma. The investigators must be commended for conducting a large prospective multicenter study with this new agent. They were able to achieve the high specificity (co-primary end point), however, failed to exceed the statistical threshold for sensitivity (other co-primary end point). Thus, they have concluded that [18F] radio hybrid (rh) PSMA-7.3 has high specificity for N1 and M1 disease.

rhPSMA ligands are a new class of radioisotope that consist of three parts; a PSMA inhibitor, a fluorine label (¹⁸F or ¹⁹F), and a chelator-complexed metal [natural gallium (Ga), natural lutetium (Lu), ⁶⁸Ga, ¹⁷⁷Lu, or ²²⁵Ac] (1). This three-part concept in which the label or the metal can be radioactive (e.g., emission of photon for imaging or a beta/alpha emitter for therapy) allows for easily created theranostic pairs that are chemically identical; this has far-reaching consequences in the growing field of radiotheranostics. [18F]rhPSMA-7 is one of these new rhPSMA ligands, consisting of four diastereoisomers (7.1, 7.2, 7.3, and 7.4). Of these four diastereoisomers, [18F] rhPSMA-7.3 (rhPSMA) is the most suitable for clinical use,

having the most favorable imaging properties and a proven biosafety profile (2). rhPSMA has a glutamic-urea-lysine/ glutamic binding motif, which targets the extracellular PSMA epitope and is used in other clinically available PSMA agents, including [18F]DCFPyL and [68Ga]Ga-PSMA-11 (3). Compared to ⁶⁸Ga radiopharmaceuticals, the ¹⁸F label in rhPSMA has advantages including a longer half-life, lower positron kinetic energy, higher positron yield and larger production batch size (4), which results in improved spatial resolution, improved intrinsic detection efficiency, and easier transportation from production site to the clinic when applicable. Relative to other ¹⁸F and ⁶⁸Ga PSMA radiopharmaceuticals, rhPSMA has equal or better targeting characteristics as shown in a recent trial (1). There are ongoing trials regarding therapy and we look forward to those results.

One of the strengths of this trial is the inclusion of an unfavorable intermediate risk (UIR) group of patients in addition to the high risk and very high-risk groups. This resembles a real-world population of primary prostate cancer. Despite inclusion of the UIR group, the specificity is similar to that reported by other available PSMA ligands which were studied predominantly in high-risk patients in a recent systematic review using [68Ga]Ga-PSMA-11 (5).

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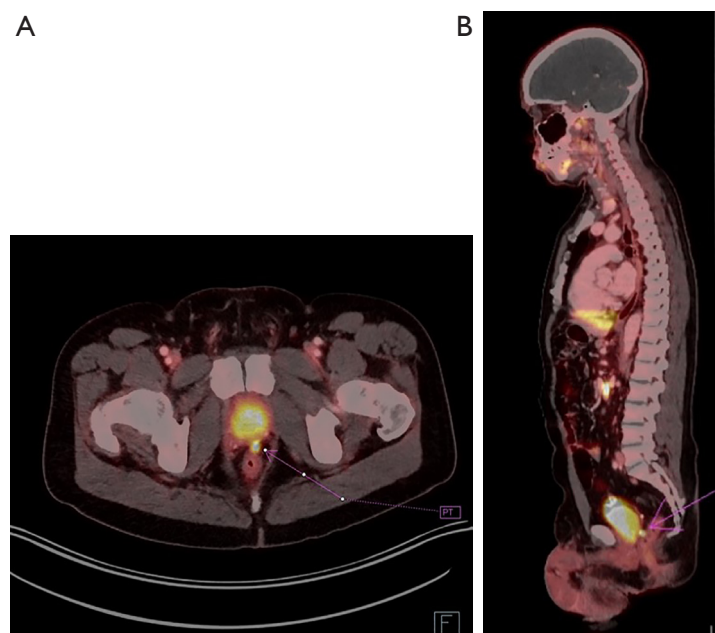


Figure 1 ^{18}F -rhPSMA-7.3 PET scan fused images in a patient with prostate carcinoma post radical prostatectomy and pelvic lymph node dissection. (A) Axial fused image demonstrating focal radiotracer uptake (arrow) in the prostatectomy bed. (B) Sagittal fused image in the same patient again demonstrating focal uptake (arrow) in the prostatectomy bed. PT, prostate tumor; rhPSMA, radiohybrid prostate-specific membrane antigen; PET, positron emission tomography.

This makes the agent more sensitive overall, considering disease detection in a lower risk group with smaller lesions and potentially less expression of PSMA protein.

A recently published retrospective single-center study using this same agent ^{18}F rhPSMA-7.3 reported a much higher sensitivity for local, pelvic, extra pelvic and metastatic disease, which may have been due to larger lesion size. Another difference was in the protocol; they used 20 mg IV furosemide and had patients void prior to scanning (2). It may be argued that using furosemide may not have much benefit as the reported urinary bladder excretion is minimal. An example can be seen in *Figure 1* where ^{18}F rhPSMA-7.3 positron emission tomography (PET) was performed without using intravenous (IV) Lasix and it demonstrates excellent visualization of tumor recurrence adjacent to the urinary bladder. This has been qualitatively shown to distinguish disease activity from urinary excretion in a recent *post hoc* analysis of the LIGHTHOUSE and SPOTLIGHT studies (6), however, the extent to which this is clinically significant enough to alter management remains to be seen. These characteristics could also potentially be advantageous in theranostics where there would be less radiation to the urinary tract during therapy as preclinical

analysis in animal model demonstrates that ^{177}Lu labelled rhPSMA has improved tumor: kidney uptake ratio and tumor growth suppression relative to ^{177}Lu LuPSMA-I&T (PLUVICTO) (7). This would allow a higher radiation dose to be delivered to the tumor with less exposure to the kidneys and urinary tract.

The detection of distant, extrapelvic metastatic lesions is similar to that reported with other agents; however, the standard of truth (SoT) in the current study was predominantly conventional imaging for confirming metastatic disease, compared to histopathology used as SoT in a recent study using ^{18}F DCFPyL PSMA (8). They reported 50% true-positive bone lesions with the ^{18}F rhPSMA-7.3; this is quite significant as it can alter management, the reported sensitivity for bone metastatic disease detection is variable ranging from 6–60% as published in a recent meta-analysis for ^{68}Ga -PSMA-11 (9).

There is a high negative predictive value reported for this new agent in pelvic lymph node detection which primarily would influence clinical decision making. The low sensitivity is in part due to limitation of PET/computed tomography (CT) resolution and in part due to microscopic metastasis only being detected on

histopathology due to patients undergoing pelvic lymph node dissection (PLND) as clinically indicated. The high false positivity of nodes can at least partly be due to not being represented in surgical dissection material. This suggests that in future clinical use, the extent of regional PLND could be planned according to PSMA PET results. Regardless, rhPSMA PET does influence surgical planning with superior performance in identifying nodal disease otherwise not seen on conventional imaging (2).

The study does not clearly define what parameters were used during interpretation to label a lesion “avid” or “not avid”, and whether mean standardized uptake value (SUV) values were used, similar to [⁶⁸Ga]Ga-PSMA-11 (9). Utilizing the previously described miPSMA score (10) might help with standardization of interpretation and reporting. Retrospective analysis of uptake parameters particularly in false negative and false positive nodes can be further investigated in future studies.

The study also reinforced the safety profile of rhPSMA with only 7.9% of participants experiencing side effects including injection site pain, diarrhea, peripheral swelling, nausea, arthralgia, dysgeusia and hypertension.

Overall, the new [18F]rhPSMA-7.3 agent has good specificity and high negative predictive value in UIR groups in addition to the high and very high risk prostate cancer groups. The additional benefit of low average urine excretion, however, does not seem to improve the sensitivity as much as that would have been expected.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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