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Unraveling the Impact of ^{177}Lu-PSMA Radioligand Therapy on Renal Impairment: Distinguishing Causation from Correlation

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Prostate-specific membrane antigen (PSMA) radioligand therapy (RLT) is transforming prostate cancer management and nuclear medicine practice around the world. Within the last decade, prospective clinical trials have led to widespread adoption of PSMA RLT (*1–3*). Currently, PSMA RLT is generally used in the castration-resistant phase after disease progression on an androgen-receptor–pathway inhibitor and taxane chemotherapy.

Despite [^{177}Lu]Lu-PSMA's being is a life-prolonging therapy, the typical patient undergoing it today has a limited median survival of 15–18 mo. Although safety is well described in this context, radionuclide therapies may have toxicities that may not manifest for years or decades. As theranostics matures and clinical applications emerge in patients with longer life expectancies, questions around longer-term toxicities become relevant. In this context, we congratulate Steinhelfer et al. (*4*) for their attempt to characterize the longer-term nephrotoxicity of [^{177}Lu]Lu-PSMA therapy.

The first [^{177}Lu]Lu-PSMA therapies were administered a decade ago in Germany (*5,6*); it is therefore fitting that long-term nephrotoxicity has been reported from a collaboration of 3 German tertiary referral centers. The VISION trial (*3*) reported renal toxicity in only the 30 d after treatment. Calais et al. reported acute renal toxicity in 1.5% patients in their prospective phase II trial (*7*). Violet et al.'s prospective study (*1*) included 28 of 50 patients with [^{51}Cr]Cr-ethylenediaminetetraacetic acid glomerular filtration rate measured at baseline and 12 wk after therapy, demonstrating a mean decline of 11.7 mL/min.

At first glance, the headline results of the German study of a moderate decrease (namely, a 15%–30% reduction from baseline) in creatinine clearance in 45% of patients in their study group, of whom nearly half had a severe (30%–40%) to very severe (>40%) reduction in creatinine clearance, appears alarming. Declines in renal function were not acute and were observed at time points subsequent to 6 mo after treatment. Renal function declined more in patients who received a higher number of cycles of therapy and declined more quickly than the normally expected rate with longer follow-up.

However, as with most retrospective research, caveats do emerge as acknowledged in the paper. Chief among these is that causality cannot be attributed to [^{177}Lu]Lu-PSMA in a patient cohort with other comorbidities and risk factors for renal disease and advanced progressive metastatic malignancy, with multiple prior lines of therapies and their own potential long-term impacts on renal function. This is a clinical situation in which there may be confounding complications and general functional decline ultimately leading to renal impairment. If renal function was near normal or normal at baseline, even very severe reductions in measured creatinine clearance as defined in this study may not immediately lead to clinically apparent consequences.

The number of patients with follow-up beyond 12 mo was rather small (20/474 screened patients with 2 y of follow-up and only 5 patients with 3 y of follow-up), limiting the usefulness of these data when considering the potential long-term consequences of the application of [^{177}Lu]Lu-PSMA in earlier phases of disease. Although the cause of patient drop-out is not explicit, it most likely is due to a combination of disease progression and treatment-refractory disease. It is possible some patients responded exceptionally, with longer survival, but stopped therapy before 4 cycles and thus were not eligible for study inclusion.

There are numerous reports of renal dosimetry with PSMA RLT, including early reports of application of amino acid infusions for renal protection (*8*). It is now clear that [^{177}Lu]Lu-PSMA-I&T delivers a slightly higher renal radiation dose than [^{177}Lu]Lu-PSMA-617 (*9*) and that amino acid infusions do not meaningfully reduce renal dose. From a dosimetry perspective, the lacrimal and salivary glands remain the organs most at risk from PSMA RLT.

There is emerging use of other isotopes, such as ^{161}Tb, ^{225}Ac, or ^{212}Pb-labeled PSMA therapies, which may add to the current prostate cancer theranostics landscape (*10*). Microdosimetry tools are also required to better characterize the absorbed doses from the short-range particulate emissions of these isotopes (*11*).

New therapies are typically tested in a phase 1 clinical trial in which the focus is on establishing a tolerable dose based on immediate side effects. This approach is used in oncologic drug trials but is not as well suited to radiopharmaceutical therapies. These are usually well tolerated initially, but longer-term toxicities may then emerge. Our radiation oncology colleagues deal with this issue by defining accepted maximal organ doses (*12*). These limits are extrapolated to radiopharmaceutical therapies, including by regulatory authorities.

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However, experience from theranostics in neuroendocrine tumors and long-term follow-up suggests that safe dose limits from low–dose-rate radionuclide therapies are likely to be considerably higher (*13*). Administered activities or number of cycles of therapy could also be individualized with dosimetry.

Long-term follow-up is mandatory, preferably in a rigorous prospective clinical trial setting, or with postmarketing surveillance for approved or established therapies. Importantly, in the context of prostate cancer theranostics, for which clinical trials are being conducted with combination therapies and in earlier-stage disease, standard clinical trial endpoints of response rates, metastasis-free survival, or progression-free survival are not wholly adequate, and longer-term follow-up is strongly recommended for emergent toxicities or for codependence and interactions with other therapies.

Leaving aside nephrotoxicity, a significant longer-term concern with systemically administered radionuclide therapies is hematologic toxicity, including myelodysplasia, acute leukemia, and chronic cytopenias, which may additionally limit delivery of other therapies. With longer experience, this has emerged as a previously underrecognized issue with peptide receptor radionuclide therapy (used singly or as a combination therapy) in neuroendocrine tumors (*14,15*). However, long-term follow-up of the NETTER-1 trial more reassuringly demonstrated myelodysplasia of 2% and no increase in nephrotoxicity compared with controls (*16*). Myelodysplasia has not yet been a reported issue with PSMA RLT, but as the treatment is applied to more patients and in earlier stages of prostate cancer, longer-term follow-up not only becomes feasible but also is mandatory to properly understand the benefits and risks.

The broader prostate cancer therapeutic landscape is complex and ever changing, with many new, effective therapeutic agents and combinations (*17*). Ongoing high-quality studies of PSMA-based theranostics are essential for nuclear medicine to remain an integral part of this medical success story (*18*).

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REFERENCES

1. Violet J, Sandhu S, Iravani A, et al. Long-term follow-up and outcomes of retreatment in an expanded 50-patient single-center phase II prospective trial of ^{177}Lu-PSMA-617 theranostics in metastatic castration-resistant prostate cancer. *J Nucl Med.* 2020;61:857–865.
2. Hofman MS, Emmett L, Sandhu S, et al. [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet.* 2021;397:797–804.
3. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2021;385:1091–1103.
4. Steinhelfer L, Lunger L, Cala L, et al. Long-term nephrotoxicity of ^{177}Lu-PSMA radioligand therapy. *J Nucl Med.* 2024;65:■■■–■■■.
5. Kratochwil C, Giesel FL, Eder M, et al. [^{177}Lu]lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42:987–988.
6. Ahmadzadehfar H, Rahbar K, Kurpig S, et al. Early side effects and first results of radioligand therapy with ^{177}Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Res.* 2015;5:114.
7. Calais J, Czernin J, Thin P, et al. Safety of PSMA-targeted molecular radioligand therapy with ^{177}Lu-PSMA-617: results from the prospective multicenter phase 2 trial RESIST-PC (NCT03042312). *J Nucl Med.* 2021;62:1447–1456.
8. Baum RP, Kulkarni HR, Schuchardt C, et al. ^{177}Lu-labeled prostate-specific membrane antigen radioligand therapy of metastatic castration-resistant prostate cancer: safety and efficacy. *J Nucl Med.* 2016;57:1006–1013.
9. Schuchardt C, Zhang J, Kulkarni HR, Chen X, Muller D, Baum RP. Prostate-specific membrane antigen radioligand therapy using ^{177}Lu-PSMA I&T and ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer: comparison of safety, biodistribution, and dosimetry. *J Nucl Med.* 2022;63:1199–1207.
10. Kratochwil C, Fendler WP, Eiber M, et al. Joint EANM/SNMMI procedure guideline for the use of ^{177}Lu-labeled PSMA-targeted radioligand-therapy (^{177}Lu-PSMA-RLT). *Eur J Nucl Med Mol Imaging.* 2023;50:2830–2845.
11. Hofmann W, Li WB, Friedland W, et al. Internal microdosimetry of alpha-emitting radionuclides. *Radiat Environ Biophys.* 2020;59:29–62.
12. Dawson LA, Kavanagh BD, Paulino AC, et al. Radiation-associated kidney injury. *Int J Radiat Oncol Biol Phys.* 2010;76(suppl)S108–S115.
13. Geenen L, Nonnekens J, Konijnenberg M, Baatout S, De Jong M, Aerts A. Overcoming nephrotoxicity in peptide receptor radionuclide therapy using [^{177}Lu]Lu-DOTA-TATE for the treatment of neuroendocrine tumours. *Nucl Med Biol.* 2021;102–103:1–11.
14. Goncalves I, Burbury K, Michael M, et al. Characteristics and outcomes of therapy-related myeloid neoplasms after peptide receptor radionuclide/chemoradionuclide therapy (PRRT/PRCRT) for metastatic neuroendocrine neoplasia: a single-institution series. *Eur J Nucl Med Mol Imaging.* 2019;46:1902–1910.
15. Kennedy KR, Turner JH, MacDonald WBG, Claringbold PG, Boardman G, Ransom DT. Long-term survival and toxicity in patients with neuroendocrine tumors treated with ^{177}Lu-octreotate peptide radionuclide therapy. *Cancer.* 2022;128:2182–2192.
16. Strosberg JR, Caplin ME, Kunz PL, et al. ^{177}Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol.* 2021;22:1752–1763.
17. Gillessen S, Bossi A, Davis ID, et al. Management of patients with advanced prostate cancer-metastatic and/or castration-resistant prostate cancer: report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022. *Eur J Cancer.* 2023;185:178–215.
18. Jang A, Kendi AT, Sartor O. Status of PSMA-targeted radioligand therapy in prostate cancer: current data and future trials. *Ther Adv Med Oncol.* 2023;15:17588359231157632.