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Proximal tubular trap; radiation nephropathy risks from peptide reabsorption in peptide receptor radionuclide therapy for neuroendocrine tumors

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ABSTRACT

Peptide receptor radionuclide therapy (PRRT) using radiolabeled somatostatin analogs like ^{177}Lu-DOTATATE) is highly effective for metastatic neuroendocrine tumors (NETs). However, a significant dose-limiting toxicity is radiation-induced nephropathy, primarily driven by a phenomenon termed the proximal tubular trap. Following glomerular filtration, radiolabeled peptides are avidly reabsorbed by proximal tubular epithelial cells (PTECs) via the megalin/cubilin receptor-mediated endocytosis pathway. This intracellular retention concentrates the radionuclide within the tubules, leading to prolonged, localized irradiation of renal tissue, particularly the radiosensitive proximal tubules and microvasculature. Cumulative radiation exposure causes DNA damage, oxidative stress, inflammation, and ultimately progressive tubular atrophy, interstitial fibrosis, and glomerulosclerosis, manifesting clinically as declining glomerular filtration rate (GFR), proteinuria, and potentially end-stage renal disease months to several years post-therapy.
Keywords: End-stage renal disease, Neuroendocrine tumors, Peptide receptor radionuclide therapy, Peptide reabsorption, Radiation nephropathy

Implication for health policy/practice/research/medical education:
Peptide receptor radionuclide therapy (PRRT) represents a targeted approach for treating neuroendocrine tumors (NETs) by delivering radiation specifically to somatostatin receptor-expressing cells using radiolabeled peptides like ^{177}Lu-DOTATATE. Despite its efficacy, a major limitation is radiation nephropathy arising from unintended reabsorption of these peptides in the proximal tubules of the kidney, often termed the "proximal tubular trap," where megalin-mediated endocytosis captures filtered radioligands, leading to prolonged radiation exposure and cellular damage. This phenomenon heightens risks particularly in patients with preexisting renal impairment, demanding protective strategies to mitigate long-term nephrotoxicity while preserving therapeutic benefits.

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Introduction

Peptide receptor radionuclide therapy (PRRT) represents a significant advancement in targeted cancer treatment, particularly for certain neuroendocrine tumors (NETs). This sophisticated approach leverages the biological characteristics of cancer cells to deliver radiation precisely where it is needed, minimizing damage to surrounding healthy tissues (1). At its core, PRRT combines a radioactive isotope (radionuclide) with a synthetic peptide that specifically binds to receptors abundantly present on the surface of tumor cells. The most common and well-established application targets somatostatin receptors (SSTRs), which are overexpressed in many well-differentiated NETs originating in the gastrointestinal

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tract, pancreas, and lungs (1). The process begins with meticulous patient selection using diagnostic imaging, typically a gallium-68 DOTATATE or DOTATOC PET/CT scan. This theranostic principle, using a diagnostic scan to predict therapeutic response confirms high SSTR expression on the tumors, ensuring the patient is a suitable candidate. If positive, the therapeutic phase commences (2). The most widely used radionuclide today is lutetium-177 (Lu-177), favored for its optimal emission profile (beta particles for cell kill and gamma rays for imaging) and manageable side effects compared to older isotopes like yttrium-90 (3). The Lu-177 is chelated to a somatostatin analog peptide, most commonly DOTATATE or DOTATOC. Intravenously administered radiopharmaceutical circulates through the bloodstream. Then peptide component seeks out and binds tightly to the SSTRs on the tumor cells (4). Once bound, the attached Lu-177 decays, emitting beta radiation that damages the DNA of the targeted cancer cell and its immediate neighbors, effectively destroying the tumor tissue from within (5). Previous clinical trials, most notably the NETTER-1 trial for midgut NETs, have demonstrated PRRT's efficacy. It significantly prolongs progression-free survival and overall survival compared to high-dose somatostatin analog therapy alone, while also improving quality of life by alleviating tumor-related symptoms like flushing, diarrhea, and pain (6). Treatment is usually outpatient-based, though patients receive intravenous amino acid solutions before and during infusion to protect the kidneys, the primary dose-limiting organ, from radiation damage (7). Common short-term side effects include nausea, fatigue, and mild, transient bone marrow suppression (1). Long-term risks, though relatively low with modern Lu-177 protocols, include potential kidney toxicity and a small risk of secondary myelodysplastic syndrome or leukemia, necessitating careful patient monitoring before, during, and after therapy (8). Given that, PRRT is not a cure modality, it is a powerful tool for managing advanced, inoperable, or metastatic SSTR-positive NETs, often conducted after progression on first-line therapies like somatostatin analogs. Its success has spurred research into expanding its use to other receptor-positive cancers and developing next-generation radiopharmaceuticals with different peptides, alpha-emitting radionuclides for more potent cell kill in smaller tumors, and combination strategies with other systemic therapies (9). As a paradigm of personalized, molecularly targeted oncology, PRRT exemplifies how understanding tumor biology can be harnessed to deliver effective, less toxic cancer treatments, offering renewed hope and extended survival for patients with specific hard-to-treat malignancies. Its integration into multidisciplinary cancer care continues to evolve, solidifying its role as a cornerstone therapy for eligible NET patients worldwide (10). Previous investigators found that, the pharmacokinetic profile of radiolabeled peptides used in PRRT, such as 177Lu-DOTATATE and 90Y-DOTATOC, involves rapid blood clearance and glomerular filtration due to their small molecular size (11). It should remember that, 177Lu-DOTATATE, now a Food and Drug Administration (FDA) and European Medicines Agency (EMA)-approved standard for gastroenteropancreatic NETs (12). Meanwhile, emits medium-energy beta particles with a tissue penetration of approximately 2 mm, along with low-energy gamma rays is useful for imaging and dosimetry (12). In contrast, 90Y-DOTATOC emits higher-energy beta particles with a longer tissue penetration range of about 11 mm, making it potentially more effective for larger tumor masses but also associated with a greater risk of renal toxicity due to increased off-target radiation exposure (13). Despite these differences, both radiolabeled peptides exhibit significant renal reabsorption, with studies showing 177Lu-DOTATATE still accumulating significantly in the kidneys, albeit with a better tumor-to-kidney ratio compared to 90Y-DOTATOC (14). The kidneys play a crucial and complex role in maintaining overall body homeostasis, particularly through the intricate functions of the nephron, where the proximal tubule acts as a highly specialized segment responsible for the bulk of reabsorption of filtered substances. This segment is anatomically optimized with a dense apical brush border and extensive basolateral membrane infoldings, significantly increasing its surface area to facilitate its diverse transport activities (15). Among its myriad functions, the proximal tubule is exceptionally efficient at reclaiming filtered peptides and proteins, a critical process known as the proximal tubular trap, which prevents their loss in urine and maintains systemic protein balance. This physiological mechanism, while vital for normal renal function, inadvertently becomes a central challenge in PRRT for NETs, where it contributes significantly to the risk of radiation-induced nephropathy due to the accumulation of radiolabeled peptides (15). In this review, we aimed to consider radiation nephropathy risks from peptide reabsorption in PRRT for NETs.

Search strategy

For this narrative review, the literature search was conducted across major scientific databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase. The search strategy incorporated a targeted set of domain-specific keywords—end-stage renal disease, neuroendocrine tumors, peptide receptor radionuclide therapy, peptide reabsorption, and radiation nephropathy, to capture relevant studies addressing the renal handling of radiolabeled peptides and associated nephrotoxic risks.

A short look at the neuroendocrine tumors

Neuroendocrine tumors originate from enterochromaffin cells and express high levels of SSTRs, particularly SSTR2, making them amenable to PRRT with analogs such as

DOTATATE or DOTATOC chelated to beta-emitters like lutetium-177 or yttrium-90 (16). These peptides are small, which allowing rapid glomerular filtration after intravenous administration, with plasma clearance occurring within minutes primarily by kidney excretion (4,12). However, some of the filtered load undergoes reabsorption in the proximal convoluted tubules (PCT), concentrating radioactivity there at levels, which is several times higher than in tumors (4,12,17,18). The proximal tubular trap refers to this selective retention, driven by endocytic receptors on the brush border of PCT epithelial cells, which internalize the peptides for lysosomal degradation, trapping residualizing radionuclides like ^{177}Lu-DOTATATE within the cells (4,12,17-19).

Focus on proximal tubular epithelial cells

The proximal tubule, specifically the S1 and S2 segments, is uniquely equipped with a highly efficient endocytic machinery designed for reclaiming filtered proteins and peptides to prevent their wasteful loss in urine (19). This machinery centers on two large multi-ligand receptors expressed densely on the apical (luminal) brush border membrane of proximal tubular epithelial cells (PTECs), known as megalin (also known as LRP-2) and cubilin (20). Megalin is a giant transmembrane glycoprotein belonging to the low-density lipoprotein receptor family, while cubilin is a peripheral membrane protein that functions in complex with megalin and another protein called amnionless (21). Both, megalin and cubilin form a powerful receptor system capable of binding a vast array of ligands, including albumin, vitamin-binding proteins, hormones, enzymes, and importantly, filtered peptides like radiolabeled somatostatin analogs (20). After glomerular filtration, the radiolabeled peptides in the tubular fluid bind with high affinity to megalin and cubilin on the PTEC surface. Then, this binding triggers receptor-mediated endocytosis. The receptor-ligand complexes are internalized into clathrin-coated pits, which pinch off to form early endosomes within the cell cytoplasm (21). Next, the endosomes become mature and eventually fuse with lysosomes, as the cell's digestive organelles filled with hydrolytic enzymes (21). Here, the peptide component of the radiopharmaceutical may be degraded within the lysosome over time (21); however, the radionuclide chelate complex firmly bound within a chelator molecule is often highly stable and resistant to lysosomal degradation (7). This stability becomes a liability in the PTEC; since, the radiometal-chelate complex cannot be broken down or efficiently exported from the lysosome (7,17,22,23). Consequently, it accumulates and is retained within the lysosomal compartment of the proximal tubular cell for an extended period, potentially weeks or months (7,17,22-24). During this prolonged retention, the decaying radionuclide continuously emits ionizing radiation, beta particles in the case of Lu-177 (lutetium-177), which directly within the elements of the cell (3). The short path length of beta particles means that the radiation energy is deposited almost entirely within the PTEC itself and its immediate neighbors. This results in a very high local radiation dose to the cytoplasm, nucleus, and critical organelles of the tubular cell, far exceeding the dose that would result from simple passage through the tubule or brief exposure during filtration (17,22,25). The lysosome principally becomes a radioactive reservoir, irradiating the cell from within. This mechanism of receptor-mediated uptake followed by lysosomal retention of the non-degradable radiometal-chelate complex is the defining characteristic of the proximal tubular trap (7). It explains why the kidneys receive a significantly higher radiation dose than would be predicted based solely on blood pool activity or glomerular filtration rate (GFR). Without this specific reabsorptive and retentive process, renal toxicity from PRRT would likely be minimal (11).

Role of megalin in the uptake of radiolabeled somatostatin analogs

Megalin, a 600 kDa multiligand scavenger receptor of the low-density lipoprotein receptor family, partners with cubilin to orchestrate this uptake, binding diverse positively or negatively charged peptides regardless of their net charge at physiological pH (26). Studies in megalin-deficient mice demonstrate dramatically reduced renal uptake of radiolabeled somatostatin analogs, confirming megalin's pivotal role across peptide classes used in PRRT (27). After binding, clathrin-coated pits invaginate, forming endosomes that mature into lysosomes where proteolytic enzymes cleave the peptide, but the stable metal-chelate complex of DOTA-Lu remains trapped, producing beta particles, which is sufficient to damage renal tissue (17,22,27,28). SPECT imaging and autoradiography in these models show patchy cortical retention, aligning with mosaic megalin knockout patterns, underscoring the receptor's high-capacity, low-specificity nature (27).

Radiation nephropathy following PRRT

The biological consequences of this trapped radiation are profound and form the basis of radiation nephropathy. Ionizing radiation damages cells through direct interaction with DNA and other critical molecules, and indirectly through the generation of reactive oxygen species (29). In PTECs, this condition leads to DNA double-strand breaks, mitochondrial dysfunction, disruption of cellular membranes, and activation of pro-inflammatory and pro-fibrotic signaling pathways (30). Acutely, high radiation doses can cause direct tubular cell death, leading to acute kidney injury characterized by a rapid decline in GFR, proteinuria, and sometimes enzymuria (elevated urinary enzymes like N-acetyl-β-D-glucosaminidase, NAG, indicating tubular damage) (31). However, the more insidious and clinically significant manifestation of radiation nephropathy following PRRT is chronic

progressive damage. This typically manifests months to years after therapy (11). Persistent radiation-induced injury triggers a cascade started by chronic inflammation, sustained oxidative stress, activation of fibroblasts, and excessive deposition of extracellular matrix proteins. This process, which known as tubulointerstitial fibrosis, is the hallmark of chronic radiation nephropathy (32). In the next step, fibrosis replaces functional tubular tissue and disrupts the intricate microarchitecture of the nephron. It impairs tubular reabsorptive and secretory functions and critically, compromises the peritubular capillary network, leading to chronic hypoxia which further fuels the fibrotic process (33). The end result is a progressive, often irreversible decline in overall kidney function, measured as a decrease in renal function. Patients may develop hypertension, proteinuria, anemia due to reduced erythropoietin production and electrolyte imbalances (34). In severe cases, this process can culminate in end-stage renal disease requiring dialysis or transplantation. The latency period and progressive nature make early detection and intervention crucial but challenging (35).

Renal pathology of radiation nephropathy

Histopathologically, radiation nephropathy manifests with a spectrum of acute and chronic changes in renal biopsies (31). Acute changes include epithelial cell degeneration and apoptosis in the proximal tubules, often accompanied by increased cellular proliferation with abnormally large nuclei, an early attempt at repair. This is followed by tubular atrophy and interstitial fibrosis, which is a hallmark of chronic kidney disease (31). Microvascular injury, characterized by endothelial cell swelling and rarefaction, is frequently observed and contributes to ischemic damage, sometimes progressing to thrombotic microangiopathy in the glomeruli and tubulointerstitial regions, which can lead to severe chronic kidney disease (34). Inflammatory infiltrates, composed of lymphocytes and plasma cells, may also be present, exacerbating tubular injury. Functionally, these histopathological changes lead to a gradual decline in GFR, an increase in serum creatinine, and proteinuria, reflecting the impaired reabsorptive capacity of the damaged proximal tubules (36). Patients may also experience hypertension, azotemia, and electrolyte imbalances, including hypophosphatemia due to renal phosphate loss (37). Imaging studies, such as CT and MRI, can reveal early vascular and tubular alterations, with later signs including decreased renal cortical volume, irregular corticomedullary differentiation, and cortical scarring, indicative of progressive fibrosis (38). The incidence and severity of radiation nephropathy are influenced by the choice of radiopharmaceutical and a range of patient-specific and tumor characteristics (11). Early clinical experiences with ^{90}Y-DOTATOC reported renal toxicity in some patients, especially in studies that did not consistently use amino acid protection (39). With the advent of ^{177}Lu-DOTATATE and improved protective measures, the incidence of severe renal toxicity has significantly decreased, with large trials like NETTER-1 reporting renal toxicity in few of the cases of the ^{177}Lu-DOTATATE group (17,40,41). Overall, ^{177}Lu-DOTATATE is associated with lower renal toxicity compared to ^{90}Y-DOTATOC, which is partly due to its shorter beta-energy range, leading to a more non-uniform and localized dose distribution in the kidney cortex (17).

Risk factors of radiation nephropathy

Key patient-related risk factors for radiation nephropathy include older age (especially > 60 years), pre-existing renal dysfunction (e.g., creatinine clearance < 60 mL/min), hypertension, diabetes mellitus, and previous nephrotoxic chemotherapy. These comorbidities can compromise renal reserve and heighten susceptibility to radiation damage (42). For instance, a study found that patients with more than two risk factors experienced the largest statistically significant changes in GFR. Tumor characteristics, such as extensive tumor burden or metastases near the kidneys, can also increase nephrotoxicity risk by causing post-renal obstruction, which delays ^{177}Lu-DOTATATE excretion and elevates renal radiation exposure (43). Additionally, the cumulative administered activity of the radiopharmaceutical directly correlates with the renal absorbed dose, increasing the risk with higher total doses (44). In fact, the dose-response relationship in PRRT is distinct from external beam radiotherapy due to the continuous, low-dose-rate internal radiation delivery, making traditional external beam radiotherapy thresholds (e.g., 23 Gy) less directly applicable (45). Radiobiological models, particularly the linear quadratic (LQ) model adapted for radionuclide therapy, are used to calculate the biological effective dose, which accounts for dose rate, repair kinetics, and fractionation (46). Recent studies suggest a safe renal biological effective dose threshold of approximately 40 Gy for patients without risk factors and a lower threshold of 28 Gy for those with comorbidities like hypertension and diabetes (31). However, individual patient dosimetry reveals significant variability in kidney absorbed doses, for example around 2–10 Gy per cycle for ^{177}Lu-DOTATATE, demonstrating the need for personalized treatment planning (47,48).

Strategies to mitigate nephrotoxicity

To minimize renal uptake and mitigate nephrotoxicity, several strategies are employed, with the co-infusion of amino acids being the most established clinical standard (7). A solution of L-lysine and L-arginine, typically 2.5% arginine and lysine in 1 L saline, is infused intravenously 30–60 minutes before and continuing for approximately 4 hours during ^{177}Lu-DOTATATE administration (12). This competitive inhibition reduces renal reabsorption of radiolabeled peptides, effectively lowering the renal radiation dose without compromising tumor targeting (49). Though transient side effects such as nausea and

vomiting can occur (49,50). Other nephroprotective agents, like succinylated gelatin (Gelofusine), have also been investigated and can further reduce kidney uptake through competitive binding to megalin (51,52). Molecular modifications of radiolabeled peptides are also being explored. Altering peptide charge by incorporating negatively charged residues or by PEGylation (polyethylene glycol conjugation) can reduce renal retention by influencing glomerular filtration and tubular reabsorption (7). PEG-coated PLGA [poly(lactic-co-glycolic) acid (PLGA)] nanoparticles encapsulating ^{177}Lu-DOTATATE have demonstrated significant reductions in renal uptake (from 37.89% ID/g to 5.27% ID/g) in preclinical models, potentially offering a targeted delivery system that minimizes kidney exposure (53). Additionally, the use of metabolizable linkers that are enzymatically cleaved in the renal brush border could allow for rapid excretion of the radiolabel before tubular reabsorption occurs (54). Radionuclide selection itself is a protective strategy; the shorter beta-particle range of ^{177}Lu compared to 90Y inherently leads to less diffuse renal radiation and lower nephrotoxicity (11). Moreover, rigorous patient selection, personalized renal dosimetry to limit cumulative dose, aggressive management of comorbidities, especially hypertension with RAAS inhibitors, avoidance of nephrotoxins, and lifelong monitoring of renal function (31).

Focus of patient's safety

Current clinical guidelines emphasize a multidisciplinary approach for patient selection and management of renal risks in PRRT (35). Eligibility criteria include a creatinine clearance greater than 40 mL/min (18), adequate hematological and liver function, and a Karnofsky Performance Scale of at least 60 (55). Patients with moderate renal impairment warrant closer monitoring with frequent serum creatinine measurements (56). Regular pre- and post-PRRT monitoring protocols involve assessing full blood count, renal and liver function, typically after each cycle and then at 1-, 3-, 6-, and 12-month post-treatment, with long-term follow-up continuing for several years (57). Imaging follow-up, usually 2–3 and 6 months after the last cycle, is crucial for assessing tumor response and differentiating true progression from pseudo-progression (58). Long-term renal outcomes for patients treated with PRRT, particularly ^{177}Lu-DOTATATE with amino acid protection, show a median annual decline in GFR of approximately 3.0–4.5 mL/min/1.73 m^2, which is comparable to the age-associated decline in healthy individuals or that observed in other chronic kidney diseases (59). While studies report few cases of severe renal failure (grade 3–4) with current protocols, long-term surveillance is vital due to the insidious nature of radiation-induced renal malfunction and its potential to appear several years post-PRRT (59). Cumulative renal radiation dose remains a critical factor, and while a BED of 28 Gy is suggested for high-risk patients, individualized dosimetry is increasingly recognized as crucial for optimizing treatment without exceeding organ tolerance (60).

Conclusion

In summary, the proximal tubular trap is not merely a biological curiosity; it is the fundamental mechanism underpinning the most serious long-term toxicity of an otherwise highly effective therapy for NETs. The elegant but unfortunate efficiency of the megalin/cubilin receptor system in reabsorbing filtered radiolabeled peptides, such as those used in PRRT, ensures that significant amounts of radioactivity are internalized by PTECs. Once internalized, the stable radiometal-chelate complexes resist lysosomal degradation and become effectively "trapped," delivering sustained, high-dose internal irradiation over days to weeks. This prolonged radiation exposure induces double-strand DNA breaks, impairs mitochondrial function, and triggers pro-inflammatory and profibrotic signaling cascades. Over time, these processes culminate in tubular atrophy, interstitial inflammation, and progressive fibrosis as the hallmarks of chronic radiation nephropathy, which can lead to irreversible loss of kidney function. Although co-infusion of cationic amino acids (e.g., lysine and arginine) competitively inhibits megalin/cubilin-mediated uptake and significantly reduces renal radiation burden, it does not eliminate risk. Individual susceptibility varies widely based on comorbidities such as pre-existing chronic kidney disease, hypertension, or diabetes, all of which exacerbate renal vulnerability. Furthermore, cumulative administered activity, dosing intervals, and concurrent exposure to other nephrotoxic agents like NSAIDs or contrast media critically influence outcomes.

Authors' contribution

Conceptualization: Naeem Nikpour, Zahra Eydizadeh, and Rasoul Jafari Arismani.
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Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language

style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the accuracy and content of the publication.

Ethical issues

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