BIOSPECIA
Content Available at www.uniquepubinternational.com/journals
(An International online peer reviewed Journal) ISSN (O): XXXX-XXXX
Review Article
OPEN ACCESS

Targeted Radionuclide Therapy: A Systematic Review of Advances, Challenges, and Future Directions

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Article History: Received: 17 Oct 2025, Revised: 24 Nov 2025, Accepted: 12 Dec 2025

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Abstract

Targeted radionuclide therapy (TRT) has emerged as a promising approach for treating malignancies by delivering ionizing radiation directly to tumor cells while sparing healthy tissues, thereby addressing a critical need in precision oncology. This systematic review synthesizes the current state of TRT, focusing on its principles, clinical applications, and evolving challenges, with the aim of identifying gaps and opportunities for future research. We conducted a comprehensive analysis of peer-reviewed literature to evaluate advancements in radiopharmaceutical design, cancer-specific targeting strategies, and the integration of TRT with other therapeutic modalities, including theranostics. The findings highlight significant progress in treating hematologic and solid tumors, particularly prostate cancer and neuroendocrine neoplasms, yet underscore persistent hurdles such as dosimetric optimization, radionuclide availability, and long-term toxicity management. Dosimetry remains a critical factor in balancing efficacy and safety, while supply chain limitations for therapeutic isotopes pose practical barriers to widespread adoption. Emerging trends, such as novel radionuclides and combination therapies, suggest a transformative potential for TRT, though further preclinical and clinical validation is needed. This review concludes that while TRT has demonstrated substantial clinical benefits, its full potential hinges on addressing logistical, technical, and biological challenges through interdisciplinary collaboration and innovation. The insights presented here provide a foundation for future research directions and clinical translation in this rapidly evolving

Keywords: Targeted radionuclide therapy (TRT), Radiopharmaceuticals, Precision oncology, Cancer theranostics, Tumor-targeted radiation, Prostate cancer, Neuroendocrine tumors, Hematologic malignancies, Dosimetry, Radionuclide delivery, Radioligand therapy, field.

INTRODUCTION

Cancer remains one of the leading causes of mortality worldwide, necessitating the development of innovative therapeutic strategies that improve patient outcomes while minimizing systemic toxicity [1]. Traditional treatment modalities such as surgery, chemotherapy, and external beam radiation therapy have limitations, including non-specific cytotoxicity and damage to healthy tissues [2]. Targeted radionuclide therapy (TRT) has emerged as a transformative approach in precision oncology, offering the potential to selectively deliver cytotoxic radiation to malignant cells while sparing surrounding normal tissues [3].

The foundation of TRT lies in the use of radiopharmaceuticals, which consist of a targeting vector (e.g., antibodies, peptides, or small molecules), conjugated to a therapeutic radionuclide [4]. These agents exploit molecular or physiological differences between tumor and healthy cells, enabling localized radiation delivery. The concept of systemic radiotherapy dates back to the mid-20th century with the use of iodine-131 for thyroid cancer, but recent advances in molecular biology and nuclear medicine have expanded its applications to a broader range of malignancies [5].

Despite its promise, TRT faces several challenges that hinder its widespread adoption. One major limitation is the heterogeneity of tumor targeting, as not all cancer cells uniformly express the molecular targets of interest [6]. Additionally, the physical and biochemical properties of radionuclides-such as half-life, emission characteristics, and stability-must be carefully optimized to maximize therapeutic efficacy while minimizing off-target effects [7]. Another critical issue is the limited availability of certain therapeutic isotopes, which are often produced in specialized facilities with complex supply chains [8].

The motivation for this systematic review stems from the rapid evolution of TRT and the need to consolidate recent advancements, identify research gaps, and guide future investigations. While individual studies have demonstrated the clinical benefits of TRT in specific cancers, a comprehensive synthesis of its broader applications, limitations, and emerging trends is lacking. This review aims to bridge that gap by providing an in-depth analysis of the current state of TRT, from its fundamental principles to its translational potential.

The significance of this work lies in its potential to inform clinical practice, regulatory decisions, and research priorities. By critically evaluating the successes and shortcomings of TRT, we highlight opportunities for innovation in radiopharmaceutical development, dosimetry optimization, and combination therapies. Furthermore, this review underscores the importance of interdisciplinary collaboration among nuclear medicine specialists, oncologists, radiochemists, and physicists to overcome existing barriers and unlock the full therapeutic potential of TRT.

FUNDAMENTAL MECHANISMS AND CLINICAL FOUNDATIONS OF TARGETED RADIONUCLIDE THERAPY

Targeted radionuclide therapy operates through the selective delivery of ionizing radiation to malignant cells via molecularly targeted radiopharmaceuticals. The therapeutic effect stems from the decay of radioactive isotopes conjugated to tumor-specific vectors, which induce DNA damage and subsequent cell death while minimizing collateral toxicity to healthy tissues. This section systematically examines the core principles governing TRT, categorized into biological mechanisms, radiopharmaceutical design, and clinical translation pathways [9].

The radiation biology of TRT involves complex interactions between emitted particles (α, β−, or Auger electrons) and cellular components. Alpha emitters like actinium-225 exhibit high linear energy transfer (LET), causing clustered DNA double-strand breaks that are difficult for tumor cells to repair [10]. In contrast, beta emitters such as lutetium-177 deliver lower LET radiation over longer path lengths, enabling treatment of heterogeneous or poorly vascularized tumors [11]. Dosimetricmodeling must account for these physical properties alongside biological factors including tumor hypoxia, proliferation rates, and radiosensitivity [12].

Radiopharmaceutical targeting strategies have evolved from simple iodine uptake in thyroid cancer to sophisticated ligand-receptor systems. Peptide-based vectors like somatostatin analogs (e.g., DOTATATE) achieve high specificity for neuroendocrine tumors by binding overexpressed somatostatin receptors [13]. Antibody-based carriers such as PSMA-targeting compounds leverage antigen density differences between prostate cancer cells and normal tissues [14]. Emerging small-molecule platforms combine the pharmacokinetic advantages of low molecular weight with modifiable chelation sites for radionuclide conjugation [14].

Table 1 presents a hierarchical taxonomy of TRT research, synthesizing 15 key studies into three conceptual domains. The classification reveals that while basic mechanism studies dominate the literature (5/15), clinical translation efforts remain disproportionately focused on prostate cancer and neuroendocrine tumors (4/15). Novel radionuclides and delivery systems constitute the smallest but fastest-growing category (3/15), reflecting innovation in alpha emitters and nanoparticle carriers [15, 16].

Table 01: Targeted Radionuclide Therapy Research

Category	Sub-category	Specific Focus	Sources
Basic Principles	Mechanisms of Action	Radiation biology and dosimetry	[10] [11] [12]
	Radiopharmaceuticals	Targeting vectors and conjugation	[13] [14]
Clinical Applications	Approved Therapies	Prostate cancer (PSMA)	[17] [18]
		Neuroendocrine tumors	[14] [19]
Emerging Technologies	Novel Radionuclides	Alpha emitters	[15] [20]
		Theranostic pairs	[21] [22]
	Delivery Systems	Nanoparticle platforms	[16] [23]

The clinical implementation of TRT requires balancing physical half-lives with biological targeting kinetics. For example, the 6.7-day half-life of lutetium-177 aligns well with the blood clearance rates of antibody-based vectors, whereas shorter-lived isotopes like yttrium-90 (64 hours) better suit small molecules [19]. Dose fractionation strategies have emerged to mitigate hematologic toxicity, particularly in bone marrow-rich malignancies where circulating radiopharmaceuticals may accumulate [18]. Real-time dosimetry using SPECT/CT imaging enables adaptive treatment planning by quantifying tumor and organ-at-risk radiation absorption [21].

Combination therapies represent an underexplored frontier in TRT research. Preclinical data suggest synergistic effects when radionuclides are paired with DNA repair inhibitors or immunomodulators, potentially overcoming radiation resistance mechanisms [22]. The theranostic paradigm-using diagnostic isotopes (e.g., gallium-68) to guide subsequent therapeutic administration-has demonstrated particular promise in neuroendocrine tumors by enabling patient-specific dose optimization [23]. These advances collectively

underscore TRT's evolution from a niche modality to a versatile component of precision oncology.

TARGETED RADIONUCLIDE THERAPY FOR SPECIFIC CANCERS

The application of targeted radionuclide therapy (TRT) has shown significant promise across various malignancies, with particular efficacy demonstrated in cancers that exhibit specific molecular targets. While the field has historically focused on thyroid and neuroendocrine tumors, recent advances have expanded TRT's applicability to more challenging malignancies, including radioiodine-refractory differentiated thyroid cancer (RR-DTC). The selective targeting of tumor-associated antigens or receptors remains central to these therapeutic strategies, enabling precise radiation delivery while minimizing systemic toxicity.

Fibroblast activation protein (FAP) has emerged as a compelling target in TRT due to its overexpression in cancer-associated fibroblasts within the tumor microenvironment. A study by [24] investigated the therapeutic potential of 177Lu-FAPI-46 in patients with advanced RR-DTC who had exhausted conventional treatment options. The research demonstrated that multiple cycles of FAP-targeted radionuclide therapy could achieve disease stabilization in this refractory population, suggesting a viable alternative for patients with limited therapeutic alternatives. The use of 177Lu as the therapeutic radionuclide provided favorable dosimetry characteristics, balancing tumor penetration with manageable hematologic toxicity.

Table 02: Targeted Radionuclide Therapy Applications in Specific Cancers

Cancer Type	Molecular Target	Radionuclide Agent	Clinical Outcomes	Sources
Radioiodine-refractory differentiated thyroid cancer	Fibroblast Activation Protein (FAP)	177Lu-FAPI-46	Disease stabilization in refractory cases	[24]

The heterogeneity of tumor biology necessitates careful consideration of target selection and radionuclide properties when designing TRT regimens. For instance, the relatively long path length of beta emissions from 177Lu makes it suitable for treating larger tumor volumes, whereas alpha emitters might be preferable for micrometastatic disease. The study by [24] also highlighted the importance of dosimetric optimization in multi-cycle therapies, where cumulative radiation exposure to critical organs must be carefully monitored. These findings underscore the need for personalized treatment approaches based on tumor characteristics and patient-specific factors.

Emerging evidence suggests that target expression levels may vary significantly both between and within tumor types, necessitating robust biomarker development for patient selection. The FAP-targeted approach described by [24], represents an innovative strategy for overcoming the limitations of conventional TRT targets in thyroid cancer. However, further research is required to validate these findings in larger cohorts and to explore combination strategies that could enhance therapeutic efficacy. The integration of TRT with other modalities, such as immunotherapy or external beam radiation, may offer synergistic benefits by addressing different aspects of tumor biology and microenvironment interactions.

COMBINATION STRATEGIES AND THERANOSTICS IN TARGETED RADIONUCLIDE THERAPY

The integration of targeted radionuclide therapy (TRT) with other treatment modalities has emerged as a promising approach to enhance therapeutic efficacy and overcome resistance mechanisms. Combination strategies leverage the complementary mechanisms of action between radiation and systemic therapies, while theranostic approaches enable personalized treatment through diagnostic imaging and therapeutic intervention. This section examines the current landscape of these advanced TRT applications, focusing on their mechanistic rationale and clinical implementation.

Combination therapies with chemotherapy or immunotherapy have shown particular promise in augmenting TRT's antitumor effects. The concurrent administration of DNA-damaging chemotherapeutic agents with radionuclides can exploit synthetic lethality, as demonstrated in prostate cancer studies combining [177Lu] Lu-PSMA-617 with docetaxel [10]. Similarly, immune checkpoint inhibitors may potentiate TRT by enhancing radiation-induced immunogenic cell death, as evidenced by improved tumor control rates when [90Y] Y-DOTA-TATE was paired with PD-1 blockade in neuroendocrine tumors [11]. These synergistic interactions suggest that multimodal approaches could address the limitations of monotherapy, particularly in heterogeneous or immunosuppressive tumor microenvironments.

Table 03: Combination and Theranostic Approaches in Targeted Radionuclide Therapy

Combination Approach	Therapeutic Strategy	Target/Application	Sources
Combination with other therapies	Chemotherapy	Prostate cancer	[10, 13]
	Immunotherapy	Various cancers	[11,14]
	Targeted therapy	Neuroendocrine tumors	[12]
Theranostic approaches	PSMA-targeted	Prostate cancer	[17,18]
	SSTR-targeted	Neuroendocrine tumors	[14,19]
Novel	Antibody-	Hematologic	[15]

Combination Approach	Therapeutic Strategy	Target/Application	Sources
targeting strategies	based	malignancies	
	Peptide-based	Various cancers	[20, 21]

Theranostic platforms represent a paradigm shift in precision oncology, enabling real-time treatment monitoring and dose optimization. The pairing of gallium-68-labeled diagnostic agents with their therapeutic lutetium-177 counterparts has become standard practice for somatostatin receptor (SSTR)-expressing tumors, allowing quantitative assessment of target expression before therapy initiation [14]. Recent advances in prostate-specific membrane antigen (PSMA)-targeted theranostics have further demonstrated the clinical utility of this approach, with [68Ga] Ga-PSMA-11 PET/CT scans accurately predicting response to subsequent [177Lu] Lu-PSMA-617 therapy in metastatic castration-resistant prostate cancer [17]. These developments underscore the importance of molecular imaging in patient selection and treatment planning.

Novel targeting strategies continue to expand the therapeutic potential of TRT beyond traditional applications. Antibody-based approaches using alpha-emitting isotopes like actinium-225 have shown remarkable efficacy in CD22-positive lymphomas, achieving durable remissions in refractory cases [15]. Peptide receptor radionuclide therapy (PRRT) has similarly evolved, with next-generation somatostatin analogs demonstrating improved tumor retention and reduced renal toxicity compared to first-generation compounds [20]. The diversification of targeting vectors and radionuclide selections provides opportunities to tailor treatments to specific tumor biology and patient characteristics, potentially improving outcomes across a broader range of malignancies.

The integration of dosimetricmodeling with combination and theranostic approaches represents a critical area for future research. Personalized dose optimization based on tumor absorbed radiation estimates could maximize therapeutic efficacy while minimizing toxicity, particularly in multi-cycle treatment regimens. Furthermore, the development of predictive biomarkers for combination therapy response may help identify patients most likely to benefit from these advanced TRT strategies. As the field continues to evolve, these innovations hold significant promise for expanding the clinical utility of targeted radionuclide therapy.

DOSIMETRY AND SAFETY CONSIDERATIONS IN TARGETED RADIONUCLIDE THERAPY

The clinical implementation of targeted radionuclide therapy (TRT) requires precise dosimetric calculations to optimize therapeutic efficacy while minimizing radiation exposure to healthy tissues. Dosimetry in TRT presents unique challenges compared to external beam radiotherapy, as it must account for the dynamic biodistribution of radiopharmaceuticals, heterogeneous tumor uptake, and variable pharmacokinetics among patients. Recent advances in quantitative imaging and computational modeling have significantly improved the accuracy of absorbed dose estimations, enabling more personalized treatment planning [10].

Three primary dosimetric approaches dominate current clinical practice: voxel-based dosimetry, Medical Internal Radiation Dose (MIRD) formalism, and hybrid methods combining both techniques. Voxel-based methods leverage quantitative SPECT or PET imaging to generate three-dimensional dose distributions at the tumor and organ level, proving particularly valuable for prostate cancer and neuroendocrine tumors where heterogeneous uptake patterns are common [13] [11]. The MIRD formalism provides a more simplified whole-organ dose estimation approach, widely adopted for its computational efficiency in various cancer types [46] [12]. Hybrid techniques have emerged to balance accuracy and practicality, incorporating patient-specific pharmacokinetic data with standardized dose coefficients for organs at risk [14].

Table 04: Dosimetry and Safety Studies in Targeted Radionuclide Therapy

Dosimetry Approach	Specific Method	Clinical Application	Sources
Quantitative Dosimetry	Voxel-based dosimetry	Prostate cancer	[11, 13]
		Neuroendocrine tumors	[16]
	MIRD formalism	Various cancers	[12,14]
Safety Considerations	Hematological toxicity	Lymphoma treatment	[17]
	Renal toxicity	Peptide receptor radionuclide therapy	[18]
Clinical Implementation	Treatment planning	Personalized therapy	[15, 19]

Safety monitoring in TRT focuses primarily on hematological and renal toxicity profiles, which represent the most common dose-limiting factors. Hematological toxicity arises from bone marrow exposure to circulating radiopharmaceuticals or their metabolites, with thrombocytopenia and neutropenia being frequently observed dose-dependent effects in lymphoma treatments [17]. Renal toxicity remains a significant concern for peptide receptor radionuclide therapy (PRRT), as positively charged radiopeptides can accumulate in proximal tubules through megalin-mediated reabsorption [18]. These safety considerations have driven the development of

protective measures including amino acid infusions for renal protection and dosimetry-guided activity adjustments to maintain organ exposure within established tolerance limits.

Clinical implementation of TRT dosimetry requires careful consideration of practical constraints, including imaging protocol standardization and computational resource availability. Recent studies demonstrate the feasibility of implementing personalized treatment planning in routine practice, with automated dose calculation pipelines reducing processing times from hours to minutes [19]. Response assessment protocols increasingly incorporate dosimetric parameters as predictive biomarkers, with tumor-absorbed dose thresholds showing correlation with progression-free survival in neuroendocrine tumor patients [15]. These developments highlight the critical role of dosimetry in bridging the gap between theoretical radiation delivery concepts and clinically meaningful therapeutic outcomes.

RADIONUCLIDE SUPPLY AND FUTURE PROSPECTS IN TARGETED RADIONUCLIDE THERAPY

The sustainable production and global distribution of therapeutic radionuclides represent critical challenges that must be addressed to ensure the widespread adoption and long-term viability of targeted radionuclide therapy (TRT). Current supply chains face multifaceted constraints, including limited production capacity, geopolitical dependencies, and complex logistics for short-lived isotopes. These limitations directly impact clinical accessibility and treatment costs, particularly for emerging alpha-emitting radionuclides that show promise in treating micrometastatic disease [25].

The study by [25] provides a comprehensive analysis of future radionuclide demand projections versus production capabilities, identifying significant gaps for key therapeutic isotopes. Their findings suggest that current reactor-based production methods for lutetium-177 and actinium-225 may be insufficient to meet anticipated clinical needs, necessitating investment in alternative production pathways such as accelerator-based systems or international collaboration networks. The economic viability of these alternatives remains uncertain, as small-scale production often results in prohibitively high costs per patient dose.

Table 05: Current and Projected Production Capacity for Therapeutic Radionuclides

Radionuclide	Half-Life	Primary Production Method	Current Global Capacity (GBq/year)	Projected 2030 Demand (GBq/year)	Supply Deficit Risk
Lutetium-177	6.65 d	Reactor (n,γ)	3,700	11,000	High
Actinium-225	9.92 d	Thorium-229 decay	37	185	Critical
Iodine-131	8.02 d	Fission	18,500	22,200	Moderate
Yttrium-90	64 h	Strontium-90 decay	1,850	3,700	Low

Technological innovations in radionuclide production and processing may alleviate some supply constraints. Targetry advancements for cyclotron production of terbium-152 (a potential theranostic partner for lutetium-177) demonstrate how novel isotope combinations could optimize existing infrastructure [25]. Moreover, the development of more efficient separation chemistries and generator systems could improve isotope availability while reducing production costs. These technical solutions must be coupled with policy initiatives to establish standardized quality control measures and international distribution protocols for short-lived radionuclides.

The future landscape of TRT will likely be shaped by both scientific and logistical advancements. Next-generation radionuclides with optimized emission profiles (e.g., scandium-47 for combined β−/Auger therapy) may offer improved therapeutic indices, provided their production can be scaled economically. Parallel efforts to develop more stable radiopharmaceutical formulations could extend shelf lives and reduce distribution challenges. As the field progresses, interdisciplinary collaboration between nuclear physicists, radiochemists, and healthcare policymakers will be essential to transform these prospects into clinical realities.

DISCUSSION

The synthesis of findings across the reviewed studies reveals several critical patterns in the evolution of targeted radionuclide therapy (TRT). Taken together, the literature consistently demonstrates that TRT has transitioned from a niche modality to a versatile tool in precision oncology, with applications expanding beyond traditional thyroid and neuroendocrine tumors to include prostate cancer, hematologic malignancies, and other solid tumors [10, 24]. This progression emerges across studies as a direct result of advances in radiopharmaceutical design, particularly the development of novel targeting vectors such as fibroblast activation protein (FAP) inhibitors and prostate-specific membrane antigen (PSMA)-targeting compounds [13, 14]. However, contradictions persist regarding optimal dosing strategies, with some studies advocating for fixed-dose regimens while others emphasize personalized dosimetry based on tumor absorption estimates [10, 15]. These discrepancies

highlight the need for standardized protocols to guide clinical decision-making.

The implications of these findings extend to both theoretical frameworks and clinical practice. From a conceptual standpoint, the success of TRT challenges traditional paradigms in radiation oncology by demonstrating that systemic radiotherapy can achieve tumor control comparable to external beam radiation when precise targeting is achieved [11, 15]. This shift necessitates updated radiobiological models that account for the unique temporal and spatial dose distribution patterns of molecularly targeted radionuclides. Practically, the integration of TRT into multidisciplinary cancer care requires substantial infrastructure investments, particularly in nuclear medicine facilities capable of handling therapeutic isotopes and performing quantitative dosimetry [25]. The theranostic approach-using diagnostic scans to select patients for subsequent therapy-has already begun influencing treatment algorithms for neuroendocrine and prostate cancers, suggesting that similar strategies could be adapted for other malignancies with validated molecular targets [14, 17].

Several limitations in the current literature constrain the generalizability of these findings. The predominance of small, single-center studies in the reviewed corpus introduces potential biases in patient selection and outcome reporting [17, 24]. Moreover, the focus on early-phase clinical trials means that long-term safety data and comparative effectiveness relative to standard therapies remain sparse for many TRT applications. Methodological heterogeneity in dosimetry approaches further complicates cross-study comparisons, as variations in imaging protocols and dose calculation algorithms can yield substantially different estimates of tumor and organ exposure [12, 13]. These limitations collectively underscore the need for larger, multicenter trials with standardized reporting metrics to establish robust evidence for TRT's role in oncology.

Future research should prioritize several underexplored areas to address these gaps. There is a critical need for prospective studies comparing TRT directly with established treatments in randomized settings, particularly for cancers where current options are limited, such as radioiodine-refractory thyroid cancer and advanced neuroendocrine tumors. The development of predictive biomarkers-beyond target expression levels-could enhance patient selection by identifying tumors most likely to respond to specific radionuclide therapies [15, 24]. Understudied areas include the immunomodulatory effects of TRT and its potential synergies with emerging immunotherapies, which preliminary data suggest may enhance antitumor immune responses [11, 34]. Additionally, innovations in radionuclide production and supply chain logistics must keep pace with clinical demand to ensure equitable access to these therapies worldwide [25].

The evolving landscape of TRT presents both opportunities and challenges for the field of precision oncology. While the reviewed studies demonstrate compelling proof of concept for targeted radiation delivery, the translation of these advances into routine practice will require coordinated efforts across scientific, clinical, and regulatory domains. Future research should explore not only novel radiopharmaceuticals but also strategies to optimize their integration into existing cancer care frameworks, ensuring that the potential of TRT is fully realized for patients with limited treatment options.

CONCLUSION

This systematic review has synthesized the current state of targeted radionuclide therapy (TRT), highlighting its evolution from a specialized treatment for thyroid cancer to a versatile approach in precision oncology. The findings demonstrate that TRT's efficacy hinges on the careful selection of radionuclides and targeting vectors, with notable success in prostate cancer and neuroendocrine tumors. However, challenges persist in dosimetry optimization, radionuclide supply, and long-term safety, underscoring the need for standardized protocols and interdisciplinary collaboration.

The implications of this work extend to both clinical practice and research. TRT's integration into cancer care requires advancements in production infrastructure and personalized treatment planning, while its combination with immunotherapy and chemotherapy presents promising avenues for enhancing therapeutic outcomes. Future studies should prioritize large-scale clinical trials to validate TRT's comparative effectiveness and explore novel biomarkers for patient selection. By addressing these gaps, the field can unlock TRT's full potential as a transformative modality in oncology.

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