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Theranostic in Oncology: Precision Targeting with Radioligand Therapy

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Abstract

The rapid evolution of theranostics in oncology necessitates a consolidated review to synthesize its foundational principles, current clinical applications, and future trajectory. This approach, which integrates diagnostic imaging with targeted radio nuclide therapy, represents a paradigm shift toward precision medicine but requires a clear elucidation of its mechanisms and positioning within the broader oncology landscape. This review aims to fulfill that need by providing a comprehensive overview of radioligand therapy, from its core concepts to its comparative value and emerging potential. This mini review details the fundamental 'lock and key' mechanism of theragnostic, explaining the synergy between targeting vectors and radioactive payloads. It explores the radiopharmaceutical toolkit, comparing vectors like peptides and small molecules and contrasting the properties of diagnostic and therapeutic radionuclides. The critical roles of patient selection via pre-therapeutic imaging and personalized dosimetry for safety and efficacy are examined. Furthermore, the biological and physical mechanisms of cytotoxicity, including the pivotal crossfire effect, are described. The review also analyzes the distinct safety profile of radioligand therapy and positions against other systemic and radiotherapeutic modalities, highlighting its unique value in treating disseminated disease. Looking forward, the field is poised for expansion through the investigation of novel targets, radionuclides, and combination strategies with immunotherapy. Ongoing clinical trials are expected to solidify the role of theranostics in earlier lines of treatment, moving beyond the current late-line standard. Ultimately, the continued integration of molecular profiling and nanotechnology promises to further refine these strategies, cementing theranostics as a cornerstone of personalized cancer management.

Keywords: Oncology, Prostate-specific membrane antigen, Radioligand therapy, Somatostatin receptor, Theranostics

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Introduction

Theranostics in oncology represents a transformative approach that integrates diagnostic imaging and targeted therapy, offering the promise of precision medicine tailored to individual tumor biology [1-5]. Recent advancements have focused on developing radioligand therapies that exploit specific molecular targets within tumors, enabling both visualization and eradication of malignant cells [6, 7]. The evolution of this field is underpinned by a deeper understanding of tumor heterogeneity, molecular profiling, and innovative delivery systems, as evidenced by the comprehensive reviews and studies available in recent literature.

One of the foundational concepts in theranostics is the identification of specific molecular targets expressed predominantly or exclusively on tumor cells. For instance, neuroendocrine neoplasms and prostate cancer have been at the forefront of radioligand theranostics, with high levels of somatostatin receptor and prostate-specific membrane antigen (PSMA) expression, respectively. Ferdinandus et al. [8] highlights the clinical success of imaging and therapy targeting these receptors, demonstrating how high receptor expression facilitates effective patient selection and response assessment through radioligand scintigraphy and positron emission tomography (PET). These approaches exemplify the core principle of theranostics: using molecular imaging to guide targeted radionuclide therapy, thereby improving outcomes.

The development of novel radioligands targeting other tumor-associated proteins further expands the theragnostic landscape. Lindner et al. [9] discussed fibroblast activation protein as a promising target, emphasizing that fibroblast activation protein targeted radiopharmaceuticals do not require extensive patient preparation, unlike traditional tracers such as fluorine-18 fluorodeoxyglucose [^{18}F] FDG. This attribute simplifies clinical workflows and enhances the feasibility of theranostic applications across various tumor types. The versatility of radioligands is also demonstrated by the development of agents like [I]GD1, a radiolabeled poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor designed for Auger electron therapy, as presented by Destro et al. [10]. This agent exemplifies the integration of diagnostic imaging with therapeutic potential, leveraging the radiolabeling of molecules involved in deoxyribonucleic acid (DNA) repair pathways to achieve targeted cytotoxicity.

The clinical translation of theranostics has been accelerated by landmark approvals such as Lutathera and Pluvicto, which have demonstrated the efficacy of radioligand therapy in neuroendocrine tumors and prostate cancer, respectively. Tran et al. [11] reviews the evolving landscape, emphasizing how these successes have catalyzed research into novel radionuclides, targeting strategies, and combination therapies. The integration of radiotheranostics with other treatment modalities, including immunotherapy and molecular targeted agents, is increasingly recognized as a promising avenue to overcome resistance and tumor heterogeneity. Bristow et al. [12] advocate for combining precision radiotherapy with molecular targeting and immunomodulatory agents, underscoring the importance of a multimodal approach in personalized cancer treatment. The role of molecular profiling in guiding theranostic strategies is well documented. Miklja et al. [13] demonstrate how comprehensive genomic and transcriptomic analyses facilitate the identification of actionable targets in pediatric gliomas, enabling tailored therapeutic interventions. Similarly, Sicklick et al. [14] propose that personalized combination therapies, informed by molecular profiling, can address the complexity and heterogeneity of refractory cancers, thereby improving clinical outcomes. These studies underscore the importance of integrating molecular diagnostics with theranostic approaches to realize the full potential of precision oncology.

Nanotechnology has emerged as a complementary platform to enhance theranostic efficacy. Al-Thani et al. [15] reviews how nanoparticles, such as gold, iron oxide, and liposomes, can be engineered to serve as both imaging agents and drug delivery vehicles. These nanoplatforms offer advantages including improved targeting, controlled release, and reduced systemic toxicity, making them highly suitable for personalized theranostic applications. The combination of nanotechnology with radioligand therapy holds promise for overcoming current limitations related to tumor penetration and off-target effects. Emerging radionuclides and innovative targeting strategies continue to shape the future of theranostics. Watabe et al. [16] discussed the development of novel radionuclides and tumor targets, such as trophoblast cell-surface antigen 2 (TROP-2) and nectin-4, which are under clinical investigation. The ability to switch radionuclides—using diagnostic isotopes for imaging and therapeutic isotopes for treatment—embodies the essence of theranostics, allowing for real-time monitoring and adaptive treatment planning. Turner [17] emphasizes that the timing of theranostic interventions is critical, advocating for personalized scheduling based on tumor response and progression.

In summary, the current state of theranostics in oncology is characterized by significant progress in target identification, radioligand development, and clinical implementation. The integration of molecular diagnostics, advanced imaging, and targeted radionuclide therapy exemplifies the shift toward precision medicine, aiming to improve efficacy while minimizing toxicity. As research continues to evolve, the combination of nanotechnology, novel radionuclides, and comprehensive molecular profiling is poised to further refine theranostic strategies, ultimately transforming cancer management into a more personalized and effective discipline.

The Fundamental Principle: Lock and Key with a Radioactive Payload

The foundational paradigm of theranostics in oncology is elegantly conceptualized as a 'lock and key' mechanism, where precision targeting is achieved through the specific molecular recognition between a disease-associated target and a designed radiopharmaceutical [18-20]. This approach merges diagnostic capability with therapeutic intervention into a single, cohesive strategy, fundamentally shifting the treatment paradigm from a broad-spectrum assault to a precision-guided strike. At the core of this principle is the 'key': a targeting ligand, typically a small molecule, peptide, or antibody, engineered to bind with high affinity and specificity to a molecular 'lock' [21, 22]. These locks are specific biomarkers, such as proteins or receptors, that are overexpressed on the surface of cancer cells while demonstrating minimal presence on healthy tissues (Table 1). This selective expression is the cornerstone that enables theranostics to discriminate between malignant and normal cells.

Prominent examples of such molecular locks include the PSMA in prostate cancer, somatostatin receptors in neuroendocrine tumors, and fibroblast activation protein in a wide array of carcinomas [23]. The overexpression of these targets on the tumor cell surface provides a unique molecular address, allowing the radiopharmaceutical to accumulate preferentially within the tumor microenvironment. The 'key' is then conjugated to a radioactive payload, creating the complete radiopharmaceutical. This payload is a radionuclide chosen for its specific emission properties, which dictates its function [24]. For diagnostic purposes, radionuclides like gallium-68 (Ga-68) or copper-64 emit positrons or gamma rays, enabling non-invasive visualization through PET or single-photon emission computed tomography (CT) [25, 26].

This diagnostic phase is the first half of the 'see and treat' approach. By administering a diagnostic radiopharmaceutical (e.g., Ga-68-PSMA-11 or Ga-68-DOTA-[Tyr^3]-octreotate (DOTATATE)), clinicians can visually confirm the presence and density of the target receptor across all metastatic sites [27, 28]. This imaging step is crucial for patient selection, ensuring that only those patients with sufficient target expression—and thus a higher likelihood of response—proceed to the therapeutic phase. Following confirmation of target availability, the therapeutic counterpart is administered. This agent uses the same or a highly similar targeting ligand but is conjugated to a therapeutic radionuclide, such as lutetium-177 (Lu-177) or actinium-225 (Ac-225) [29, 30]. These isotopes emit cytotoxic radiation—beta particles in

Table 1: Summary of the core components of the theranostic 'lock and key' model.

Component	Role in theranostics	Key examples	Examples
Targeting ligand ('key')	Binds with high specificity to a molecular target (the 'lock') on cancer cells, enabling precise delivery of the radioactive payload.	Peptides (e.g., targeting somatostatin receptors)	DOTATATE, DOTATOC
		Small Molecules (e.g., targeting PSMA)	PSMA-11, PSMA-I&T
		Antibodies/Fragments (e.g., targeting fibroblast activation protein)	Fibroblast activation protein inhibitor-46 (FAPI-46), FAPI-74
Diagnostic radionuclide	Emits signals (e.g., positrons) for non-invasive imaging to confirm target expression, stage disease, and select patients for therapy.	Ga-68	Ga-68-DOTATATE, Ga-68-PSMA-11
		^{18}F	[^{18}F]FDG, [^{18}F]DCFPyL
Therapeutic radionuclide	Emits cytotoxic radiation (beta or alpha particles) to cause lethal DNA damage in targeted cancer cells.	Lu-177 (beta emitter)	Lu-177-DOTATATE (Lutathera®), Lu-177-PSMA-617 (Pluvicto®)
		Ac-225 (alpha emitter)	Ac-225-DOTATATE, Ac-225-PSMA-617

the case of Lu-177 or alpha particles for Ac-225—designed to induce irreparable DNA damage and cell death in the targeted cancer cells.

The 'lock and key' mechanism ensures that the cytotoxic radiation is delivered with remarkable precision. Once the radiopharmaceutical binds to its target on the cancer cell, it is internalized, bringing the radioactive payload into close proximity to the cell's nucleus [31]. This localized delivery maximizes the radiation dose to the tumor while largely sparing surrounding healthy organs from significant exposure. The 'see and treat' cycle creates a closed-loop, personalized treatment system. The diagnostic scan not only selects appropriate patients but also provides critical baseline information for subsequent response assessment [32]. After therapeutic administration, follow-up diagnostic scans can be performed to monitor treatment efficacy, quantify changes in target expression, and guide decisions on further therapy cycles.

The choice of radionuclide pair is a critical consideration in this paradigm. Isotope pairs like Ga-68 for imaging and Lu-177 for therapy are considered 'matched pairs' due to their similar chemical properties and pharmacokinetics, ensuring that the imaging agent accurately predicts the biodistribution of the therapeutic agent [33]. This matching is essential for reliable dosimetry and treatment planning. Beyond simple matched pairs, the concept of 'theragnostic twins' further refines the approach. Here, the exact same targeting vector is used for both diagnosis and therapy, with only the radionuclide being switched. This guarantees near-identical biological behavior between the diagnostic and therapeutic molecules, providing the highest possible predictive value for treatment, delivery and safety. The fundamental 'lock and key' principle is not static; it is platform technology. As new tumor-specific targets are discovered, new targeting ligands can be developed and paired with appropriate radionuclides [34, 35]. This expandability makes theranostics a versatile and evolving field, capable of being adapted to a growing list of malignancies.

In summary, the 'lock and key with a radioactive payload' principle elegantly combines molecular biology with nuclear medicine. By leveraging the specific interaction between a targeting vector and a tumor-associated antigen, and coupling it with the switchable nature of radionuclides, theranostics enables a truly personalized 'see and treat' methodology that is revolutionizing precision oncology.

The Radiopharmaceutical Toolkit: Radionuclides and Vectors

The efficacy of radioligand therapy is wholly dependent on the sophisticated components that constitute the radiopharmaceutical agent. This toolkit consists of 2 fundamental parts (Figure 1) [36]: the targeting vector, which serves as the guidance system, and the radionuclide, which provides the diagnostic signal or therapeutic payload (Table 2). The careful selection and combination of these elements are critical for achieving optimal tumor targeting, imaging quality, and cytotoxic effects.

Targeting vectors

The targeting vector is the biological 'key' responsible for the precise delivery of the radionuclide to the tumor cell. These molecules are chosen for their high affinity and specificity to molecular targets overexpressed on cancer cells. The main classes of vectors include peptides, small molecules, and antibodies, each with distinct pharmacokinetic properties that influence their clinical application [37]. Peptides, such as those binding to somatostatin receptors (e.g., DOTATATE, DOTA-[Tyr^3]-octreotide (DOTATOC)), offer rapid tumor targeting and fast clearance from the bloodstream, which reduces background noise in

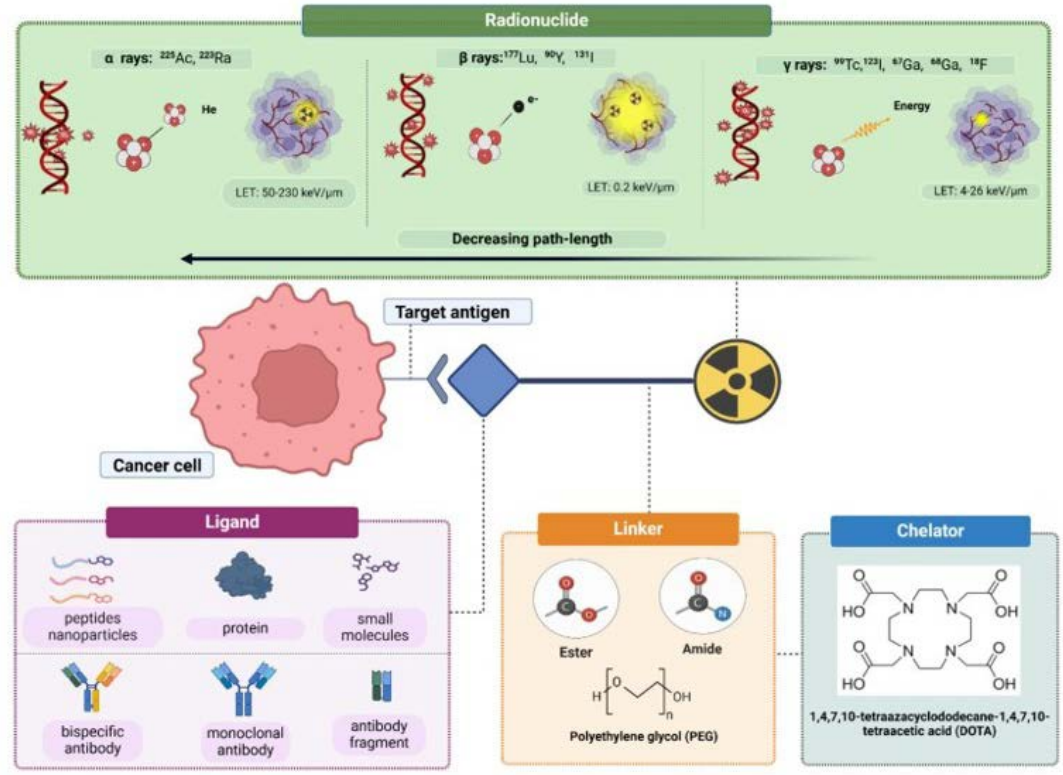

Figure 1: Components of radioligands [36].

Table 2: Comparison of the primary components of the radiopharmaceutical toolkit.

Component	Type/Class	Key characteristics	Advantages	Limitations
Targeting vectors	Peptides (e.g., DOTATATE)	Short amino acid chains targeting receptors (e.g., SSTR)	Rapid tumor targeting and blood clearance; high tumor-to-background ratio.	Limited to extracellular targets; susceptible to enzymatic degradation.
	Small molecules (e.g., PSMA-11)	Low molecular weight inhibitors	Very rapid tissue penetration and clearance; excellent for same-day imaging.	Design complexity for some targets; lower per-molecule affinity than antibodies.
	Antibodies	Full-length or engineered fragments (e.g., minibodies)	Extremely high affinity and specificity for target.	Slow blood clearance (days); delayed optimal imaging; potential immunogenicity.
Diagnostic radionuclides	Ga-68	Positron emitter (β^+)	Generator-produced (on-demand); 68 min half-life ideal for peptides/small molecules.	Lower batch activity compared to cyclotron-produced isotopes; shorter half-life limits distribution.
	^{18}F	Positron emitter (β^+)	Cyclotron-produced; 110 min half-life allows high-resolution images and distribution.	Requires a nearby cyclotron; half-life may be long for fast-clearing vectors.
Therapeutic radionuclides	Lu-177	Beta emitter (β^-) with gamma emission (γ)	Medium-energy β^- particles (1 to 2 mm range) enable crossfire effect; allows post-therapy imaging.	Lower linear energy transfer than alpha emitters; may be less effective for single cells.
	Ac-225	Alpha emitter (α)	High-energy, high-linear energy transfer α particles; short range (<0.1 mm) causes complex, irreparable DNA damage.	Potent 'sniper' effect; requires meticulous dosimetry; risk of daughter radionuclide redistribution.

imaging and minimizes radiation exposure to healthy tissues [38-40].

In contrast, small molecule inhibitors, like PSMA-11 or PSMA-imaging and therapy (I&T) used for targeting prostate cancer, are characterized by their very small size, enabling rapid tissue penetration and exceptionally fast blood clearance [41, 42]. Antibodies and their fragments, while much larger, provide an extremely high affinity and specificity for their targets, such as carcinoembryonic antigen. However, their large size results in a prolonged circulation time, often taking days to achieve optimal tumor-to-background ratios, which can be a disadvantage for same-day imaging but beneficial for delivering a sustained radiation dose [43, 44]. The choice of vector is thus a balance between targeting efficiency, pharmacokinetics, and the biological characteristics of the target itself.

Diagnostic radionuclides

Diagnostic radionuclides are selected for their ability to emit signals that can be detected by external imaging devices like PET-CT scanners, enabling non-invasive visualization of disease. Ga-68 has become a cornerstone of theranostics due to its ideal properties for PET imaging [45, 46]. It is a generator-produced isotope, meaning it can be eluted from a Germanium-68/Ga-68 generator on-site, providing a convenient and cost-effective source without the need for a nearby cyclotron [47]. Its 68 min half-life is well-suited to the pharmacokinetics of small peptides and molecules, allowing for same-day imaging. ^{18}F is another critically important PET radionuclide, most famously used in [^{18}F]FDG for metabolic imaging [48, 49]. Its key advantage is a 110 min half-life, which allows for longer synthesis and imaging protocols and produces high-resolution images due to its low positron energy. While [^{18}F]FDG is not target-specific, ^{18}F is increasingly being incorporated into novel target-specific tracers (e.g., 2-(3-{1-carboxy-5-[(6-[^{18}F] fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid ([^{18}F]DCFPyL) for PSMA imaging) [50, 51]. However, ^{18}F requires a cyclotron for production, limiting its availability compared to generator-produced Ga-68, making the choice between them often a matter of logistics, tracer chemistry, and desired image resolution.

Therapeutic radionuclides

Therapeutic radionuclides are chosen for their emission of cytotoxic radiation that can induce lethal DNA damage in cancer cells. Lu-177 is one of the most widely used therapeutic isotopes. It emits medium-energy, medium-pathlength beta particles, which travel about 1 to 2 mm in tissue [52]. This 'crossfire' effect is particularly advantageous for treating heterogeneous tumors, as it can irradiate neighboring cancer cells that may not have bound the radiopharmaceutical directly, effectively overcoming some degree of tumor heterogeneity. Lu-177 also emits low-energy gamma photons, allowing for simultaneous post-therapy imaging and dosimetry. For more aggressive or resistant tumors, alpha-emitting radionuclides like Ac-225 offer a potent alternative [53]. Ac-225 decays through a series of steps to release high-energy, high-linear energy transfer alpha particles. These particles are highly cytotoxic, causing complex, double-strand DNA breaks that are difficult for cancer cells to repair. Crucially, their extremely short path length (50 to 80 micrometers) confines the destructive power to a few cell diameters, minimizing damage to the surrounding healthy tissue. This makes Ac-225 an ideal 'microscopic sniper' for treating small clusters of cells or micrometastases, although its powerful potency requires meticulous dosimetry to manage potential off-target effects, especially from its daughter radionuclides [54-56].

In summary, the radiopharmaceutical toolkit is built upon the synergistic combination of a targeting vector and a radionuclide. The selection of the vector—be it a peptide, small molecule, or antibody—dictates the pharmacokinetics and specificity of delivery, while the choice of radionuclide determines the function, be it for high-resolution imaging or for delivering cytotoxic radiation via beta or alpha emissions. The strategic pairing of these components enables the precise 'see and treat' paradigm that defines modern theranostics.

Patient Selection and Dosimetry: The Gatekeepers of Efficacy and Safety

The success of radioligand therapy is not solely dependent on the pharmaceutical agent but is critically contingent on the meticulous processes of patient selection and dosimetry. These 2 elements act as the essential gatekeepers, ensuring that the potent cytotoxic power of theranostics is delivered to the right patients in the safest and most effective manner possible, thereby maximizing therapeutic benefit while minimizing potential harm.

The imperative of pre-therapeutic imaging

The foundational step in any theranostic protocol is pre-therapeutic imaging, which serves as a non-invasive biopsy to confirm the presence and density of the molecular target. This is typically achieved using a diagnostic radiopharmaceutical pair, such as Ga-68-PSMA-11 for

prostate cancer or Ga-68-DOTATATE for neuroendocrine tumors, imaged via PET [57, 58]. This scan visually confirms the 'lock' on the tumor cells, providing a map of disease distribution that is often more sensitive and specific than conventional imaging modalities like computed topography or magnetic resonance imaging. The qualitative and quantitative assessment of this imaging is paramount. A positive scan with high, homogeneous uptake of the tracer across all known metastatic sites is a strong predictor of therapeutic efficacy [59]. Conversely, the absence of significant target expression, or the presence of target-negative lesions, indicates that the cancer is unlikely to respond to the corresponding radioligand therapy [60]. This pre-therapeutic screening effectively stratifies patients, preventing unnecessary treatment, cost, and potential toxicity in those who would not benefit.

Defining theranostic eligibility

The concept of 'theranostic eligibility' extends beyond a simple positive scan. It represents a comprehensive clinical judgment that integrates molecular imaging findings with other patient-specific factors. Eligibility criteria often include a minimum standardized uptake value on the PET scan, confirming that target expression is sufficiently high to achieve a meaningful therapeutic index [61, 62]. This ensures that the radiation dose delivered to the tumor will be substantially higher than the dose to dose-limiting organs. This stringent eligibility criterion is a primary driver of the superior outcomes observed in clinical trials and practice. By treating a biologically selected population with tumors that are inherently susceptible to the therapy, overall response rates and progression-free survival (PFS) are significantly improved [63]. Furthermore, assessing the heterogeneity of target expression across different lesions helps in prognostication and can inform decisions on combination therapies or alternative treatments for non-responding subclones, underscoring the role of theranostic eligibility as a cornerstone of personalized oncology.

The principle of dosimetry: Personalized dose calculation

Dosimetry is the science of calculating the absorbed radiation dose, expressed in Grays, delivered to both tumors and healthy organs. It moves beyond the standardized, activity-based dosing (e.g., MBq/kg) to a more personalized approach, recognizing that individual variations in anatomy, physiology, and biokinetics can lead to vastly different radiation exposures from the same administered activity [64, 65]. The goal of dosimetry is to optimize the safety and efficacy of each treatment cycle. The process involves serial quantitative imaging—using PET-CT at multiple time points after administration of either the diagnostic or therapeutic agent—to track the radiopharmaceutical's uptake and clearance over time. These time-activity data are then fed into sophisticated mathematical models to compute the cumulative radiation dose absorbed by critical organs, most commonly the kidneys and bone marrow, as well as by the target tumors [66, 67]. This allows for a patient-specific risk-benefit assessment.

Safeguarding critical organs

The kidneys and red bone marrow are typically dose-limiting organs in systemic radioligand therapy. The kidneys are often at risk because they filter and reabsorb many small peptides and molecules, leading to significant retention and irradiation of the renal parenchyma [68]. Without careful dosimetry, this can lead to late-onset nephrotoxicity. Similarly, the bone marrow can be exposed via circulation of the radiopharmaceutical in the blood, potentially causing myelosuppression, such as thrombocytopenia and neutropenia. Dosimetry models establish safety thresholds for these organs, derived from historical data in radiobiology and external beam radiotherapy [69, 70]. By calculating the predicted dose to the kidneys and marrow before or during treatment, clinicians can personalize the administered activity for each cycle. This may involve adjusting the activity to stay within safe limits or implementing protective measures, such as amino acid solutions for renal protection, thereby proactively mitigating the risk of severe and irreversible organ damage.

Tumor dosimetry and treatment optimization

While protecting healthy organs is paramount, the ultimate goal of therapy is to deliver a lethal radiation dose to all tumor sites. Tumor dosimetry aims to quantify this, often revealing a wide variation in absorbed dose across different lesions within the same patient [71]. Larger or poorly perfused tumors may receive an insufficient dose, explaining partial responses or the emergence of treatment resistance, while smaller, well-vascularized metastases receive a sterilizing dose. This understanding is driving the next frontier of personalization: adapting therapy based on tumor dosimetry. If dosimetry indicates sub-therapeutic dosing to certain lesions, strategies such as activity escalation, switching to a more potent radionuclide (e.g., from Lu-177 to Ac-225), or combining with sensitizing agents could be employed [72, 73]. Therefore, dosimetry transforms theranostics from a one-size-fits-all treatment into a dynamic, adaptable platform, where each cycle can be informed by the biokinetic data of the previous one, pushing the boundaries of precision medicine in oncology.

In summary, patient selection and dosimetry are the critical gatekeepers that ensure the safe and effective application of radioligand therapy. Pre-therapeutic imaging establishes theranostic eligibility by confirming target expression, while personalized dosimetry calculates the radiation dose to both tumors and critical organs to optimize the therapeutic index. This rigorous, patient-specific framework is fundamental to maximizing clinical efficacy while proactively managing toxicity, thereby solidifying the role of theranostics in precision oncology.

Mechanism of Cytotoxicity: How Precisely-delivered Radiation Kills Cancer

While the 'lock and key' mechanism ensures the precise delivery of the radiopharmaceutical to the cancer cell, the ensuing cytotoxic event is a complex interplay of physics and biology. Once the radioligand is bound to its target on the cell surface and internalized, the radioactive payload begins its work, initiating a cascade of damage that ultimately leads to the death of the malignant cell [74]. This process leverages the fundamental properties of ionizing radiation to disrupt the most critical component of the cell: its DNA. The primary mechanism of cell kill is the direct damage inflicted upon the DNA double helix by the emitted particles. Radionuclides like Lu-177 emit beta particles (high-energy electrons), while Ac-225 emits alpha particles (helium nuclei) [75, 76]. Both types of particles have sufficient energy to eject electrons from the atoms they encounter, a process known as ionization. When this ionization event occurs directly within the DNA molecule, it can cause single-strand or, more critically, double-strand breaks, which are highly lethal lesions for the cell.

The biological response to this radiation-induced damage is a race against time. The cancer cell's repair machinery, including enzymes like PARP, is activated in an attempt to mend the DNA breaks. However, the sheer density of ionizations, particularly from high-linear energy transfer radiation like alpha particles, often produce complex,

clustered DNA damage that is irreparable [77, 78]. When the damage overwhelms the cell's repair capacity, it triggers programmed cell death, or apoptosis, leading to the controlled elimination of the tumor cell. Beyond direct damage, a significant portion of the cytotoxic effect is mediated indirectly through the radiolysis of water within the cell [79]. As the radioactive particles travel through the cytoplasm and nucleus, they interact with water molecules, which constitute about 70% of the cell's content. This interaction splits water molecules, generating highly reactive free radicals, such as hydroxyl radicals [80]. These uncharged molecules can diffuse short distances and attack the DNA, causing oxidative damage and amplifying the number of DNA strand breaks beyond those caused by direct ionization alone.

A critical advantage of radioligand therapy, especially with beta-emitting isotopes like Lu-177, is the 'crossfire effect.' Beta particles have a relatively long path length in tissue, traveling several millimeters. This means that the radiation emitted from a radionuclide bound to one cell can reach and damage adjacent tumor cells, even if those neighboring cells do not express the target antigen or are in a poorly perfused area of the tumor [81, 82]. The crossfire effect is a powerful tool for overcoming the challenge of tumor heterogeneity. Solid tumors are often composed of a mix of cells with varying levels of target expression. A purely targeted toxin would only kill the cells with high target density. In contrast, a beta-emitting radiopharmaceutical can deliver a lethal dose to a cluster of cells, effectively eradicating both target-positive and proximate target-negative cells, thereby mitigating one pathway of treatment resistance and producing more consistent tumor shrinkage [83, 84].

The cytotoxicity of alpha emitters like Ac-225 follows a different, more localized pattern. Alpha particles are much larger and carry substantially higher energy over an extremely short, densely ionizing track [76]. Their high linear energy transfer causes severe, clustered DNA damage that is almost always irreparable. The short path length (50 to 100 micrometers) confines this destructive power to a radius of a few cell diameters, creating a 'sniper' effect with minimal collateral damage to surrounding healthy architecture. This makes alpha emitters particularly potent against small tumor clusters, micrometastases, and single disseminated cancer cells [85]. Furthermore, because the damage is so complex and difficult to repair, alpha therapy can be effective against tumors that have developed resistance to beta radiation or conventional chemotherapy. The biological effectiveness of alpha particles per unit of absorbed dose is significantly higher, meaning they require fewer radioactive decays to achieve the same cytotoxic outcome as beta particles.

The ultimate fate of the cancer cell is determined by the cumulative DNA damage from both direct and indirect effects. Persistent double-strand breaks activate critical tumor suppressor proteins, most notably p53, which initiate cell cycle arrest to allow for repair [86]. If repair fails, p53 triggers apoptotic pathways, leading to the systematic dismantling and phagocytosis of the cell. In some cases, particularly with intense radiation exposure, cells may undergo necrosis, a more inflammatory form of cell death, or enter a state of permanent growth arrest known as senescence [87]. The localized nature of this cytotoxicity is what defines the therapeutic window of radioligand therapy. Because the radiation source is concentrated within and around the tumor, the dose to the cancer cells is maximized while the exposure to distant, healthy tissues is minimized. This contrasts with external beam radiotherapy, which must pass through healthy tissue to reach the tumor, and systemic chemotherapy, which distributes its effect throughout the entire body.

It is important to note that radiation also affects the tumor microenvironment. Endothelial cells lining the tumor's blood vessels can also be damaged, potentially compromising blood flow and contributing to tumor necrosis [88]. Furthermore, the immunogenic cell death triggered by radiation can release tumor-specific antigens and danger signals, potentially stimulating an adaptive immune response. This provides a scientific rationale for combining radioligand therapy with immunotherapy agents to enhance systemic anti-tumor immunity.

In summary, the mechanism of cytotoxicity in radioligand therapy is a multi-faceted process that begins with precise molecular targeting and culminates in the lethal irradiation of the tumor mass. Through direct DNA damage, indirect radical formation, and the powerful crossfire effect, this approach effectively kills cancer cells and overcomes heterogeneity. The distinct physical properties of beta and alpha emitters offer complementary tools, enabling clinicians to tailor the type and range of the cytotoxic attack to the specific clinical scenario.

Clinical Trials

The VISION trial (NCT03511664), an international, open-label, phase 3 study, investigated the efficacy and safety of 177Lu–PSMA-617 in patients with metastatic castration-resistant prostate cancer (Figure 2) [89]. The study demonstrated significant improvements in both PFS and overall survival when 177Lu-PSMA-617 was added to standard care. Out of 1179 screened patients, 1003 (85.1%) underwent 68Ga-PSMA-11 PET-CT scanning. Among these, 954 (95.1%) had at least one PSMA-positive metastatic lesion, while 87 (8.7%) had at least one exclusionary PSMA-negative metastatic lesion. A total of 831 patients met the eligibility criteria and were randomized between June 2018 and October 2019. Patients were assigned in a 2:1 ratio to either receive 177Lu-PSMA-617 plus protocol-permitted standard care (551 patients) or standard care alone (280 patients). The baseline characteristics of the patients were well-balanced between the treatment groups. The median follow-up period for the study was 20.9 months. The addition of 177Lu-PSMA-617 to standard care significantly prolonged imaging-based PFS. The median PFS was 8.7 months in the 177Lu-PSMA-617 group compared to 3.4 months in the standard care group (hazard ratio for progression or death, 0.40; 95% confidence interval (CI) 0.29 to 0.57; $p < 0.001$). A significant improvement in overall survival was observed with 177Lu-PSMA-617. The median OS was 15.3 months in the 177Lu-PSMA-617 group versus 11.3 months in the standard care group (hazard ratio for death, 0.62; 95% CI 0.52 to 0.74; $p < 0.001$). The median time to the first symptomatic skeletal event or death was 11.5 months in the 177Lu-PSMA-617 group, significantly longer than the 6.8 months in the control group (hazard ratio, 0.50; 95% CI 0.40 to 0.62; $p < 0.001$). All key secondary endpoints, including objective response and disease control, significantly favored the 177Lu-PSMA-617 group. Among patients with measurable target lesions, 9.2% in the 177Lu-PSMA-617 group achieved a complete response, and 41.8% achieved a partial response, compared to 0% and 3% respectively in the control group. Patients receiving 177Lu-PSMA-617 showed higher proportions of confirmed decreases in prostate-specific antigen levels of at least 50% and 80% from baseline. The time to deterioration in health-related quality of life (FACT-P total score) and pain intensity (BPI-SF score) also favored the 177Lu-PSMA-617 group. The incidence of adverse events of grade 3 or higher was higher in the 177Lu-PSMA-617 group (52.7%) compared to the standard care group (38.0%). The most common adverse events in the 177Lu-PSMA-617 group were fatigue (43.1%), dry mouth (38.8%), nausea (35.3%), and anemia (31.8%). These were predominantly grade

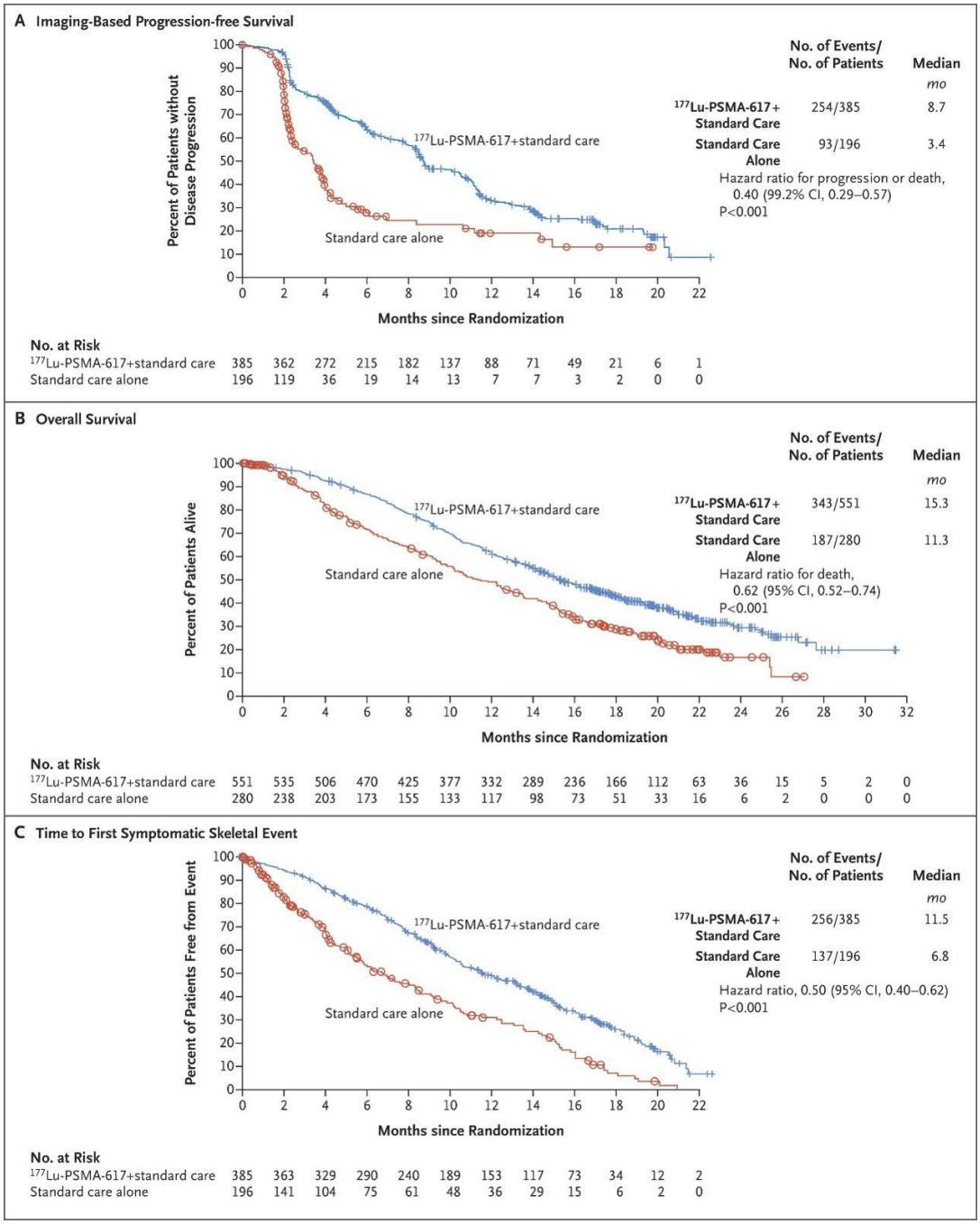

Figure 2: Analysis presents the primary and key secondary outcomes of a clinical trial comparing ^{177}Lu-PSMA-617 plus standard care against standard care alone. **(A)** shows that among 581 post-education patients, the combination therapy significantly improved imaging-based progression-free survival (the time until disease progression or death, as confirmed by central review). **(B)** shows that among all 831 randomized patients, the combination therapy also improved overall survival. **(C)** shows the time to a first symptomatic skeletal event (or death) in the same 581-patient group from panel A. Censored data points are marked with plus signs (treatment group) and circles (control group) [89].

1 or 2 events. Despite the higher incidence of adverse events, the quality of life was not adversely affected. The treatment was associated with a low incidence of adverse events leading to dose reduction, interruption, or discontinuation. In summary, the VISION trial concluded that radioligand therapy with 177Lu-PSMA-617, when added to standard care, significantly prolonged imaging-based PFS and overall survival in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer, with manageable toxicity.

The TheraP trial (NCT03392428), a multicentre, unblinded, randomised phase 2 study, compared the efficacy and safety of [177Lu]Lu-PSMA-617 with cabazitaxel in men with metastatic castration-resistant prostate cancer [90]. The study found that [177Lu]Lu-PSMA-617 demonstrated superior prostate-specific antigen response rates and a more favorable safety profile compared to cabazitaxel (Figure 3). Between February 6, 2018, and September 3, 2019, 291 men were screened, with 200 deemed eligible based on PET imaging. Of these, 91 men were ineligible, primarily due to low [68Ga]Ga-PSMA-11 uptake (29 men) or discordant 2-[^{18}F]FDG-avid disease (51 men). 200

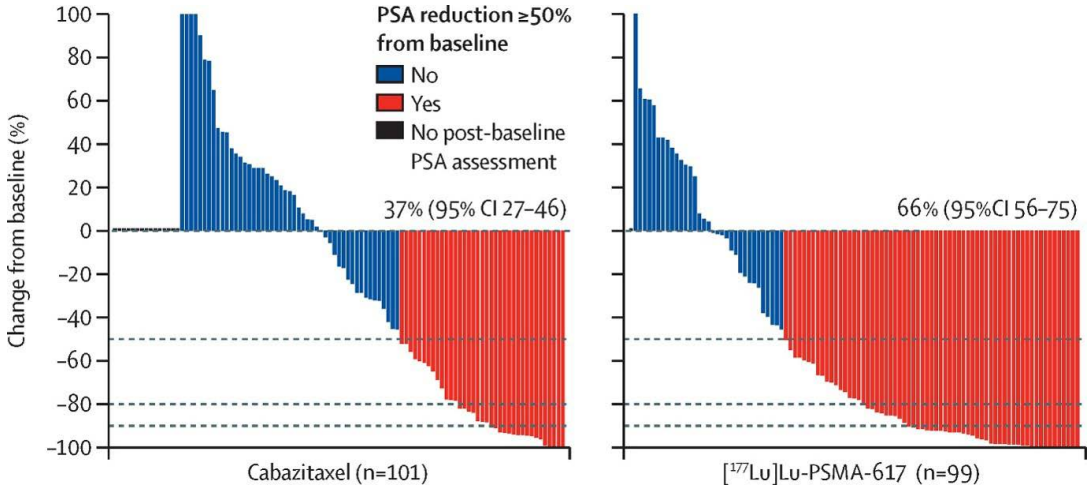

Figure 3: Prostate-specific antigen response [90].

men were randomly assigned, with 101 to the cabazitaxel group and 99 to the [177Lu]Lu-PSMA-617 group. Baseline characteristics were similar between the two groups. A prostate-specific antigen reduction of 50% or more from baseline was significantly more frequent in the [177Lu]Lu-PSMA-617 group (65%; 66% by intention to treat) compared to the cabazitaxel group (37%; 37% by intention to treat). This represented a 29% difference (95% CI 16 to 42; $p < 0.0001$). In a pre-specified sensitivity analysis by treatment received, 66% of 98 men receiving [177Lu]Lu-PSMA-617 achieved a prostate-specific antigen reduction of 50% or more, versus 44% of 85 men receiving cabazitaxel (difference 23% [9 – 37]; $p = 0.0016$). [177Lu]Lu-PSMA-617 significantly delayed progression compared with cabazitaxel (HR 0.63 (95% CI 0.46 – 0.86; $p = 0.0028$)). Similar benefits were observed for radiographic progression (HR 0.64 (0.46 – 0.88)) and prostate-specific antigen PFS (HR 0.60 (0.44 - 0.83)). PFS at 12 months was 19% in the [177Lu]Lu-PSMA-617 group compared to 3% in the cabazitaxel group. The median PFS was 5.1 months for both [177Lu]Lu-PSMA-617 and cabazitaxel groups. Grade 3-4 adverse events occurred in 32% (33% of 98 men) of the [177Lu]Lu-PSMA-617 group, compared to 53% (53% of 85 men) in the cabazitaxel group. Thrombocytopenia (11% vs 0%) was more common with [177Lu]Lu-PSMA-617, while neutropenia (4% vs 13%) and febrile neutropenia (0% vs 8%) were less common with [177Lu]Lu-PSMA-617. Diarrhea (18% vs 52%), dry mouth (60% vs 21%), and dysgeusia (12% vs 27%) were also notable differences. Only 1% of men in the [177Lu]Lu-PSMA-617 group discontinued treatment due to toxicity, compared to 4% in the cabazitaxel group. [177Lu]Lu-PSMA-617 led to clinically meaningful improvements in quality of life and symptoms, including reduced diarrhea, fatigue, and insomnia, and improved social functioning, compared to cabazitaxel. Among men with a baseline PPI score of 2 or more, a pain response occurred in 60% of the [177Lu]Lu-PSMA-617 group versus 43% for cabazitaxel (RR 1.4 [95% CI 0.9 - 2.2]; $p = 0.10$). PPI-progression-free survival also favored the [177Lu]Lu-PSMA-617 group (HR 0.72 (95% CI 0.53 – 0.97); $p = 0.033$). In summary, the TheraP trial concluded that [177Lu]Lu-PSMA-617 provides a more active and safer treatment option for men with metastatic castration-resistant prostate cancer who have progressed after docetaxel, leading to higher prostate-specific antigen response rates, delayed progression, fewer severe adverse events, and improved patient-reported outcomes compared to cabazitaxel. This suggests [177Lu]Lu-PSMA-617 is an effective alternative therapy for this patient population.

A study by Aggarwal et al. [91] (NCT03805594) investigated the combination of 177Lu-PSMA-617 (Lu) and pembrolizumab in metastatic castration-resistant prostate cancer patients. The key findings indicate the therapy's tolerability and its potential for durable responses in a subset of patients. The combination therapy of 177Lu-PSMA-617 as a priming dose followed by pembrolizumab was generally well tolerated by patients. This suggests a favorable safety profile for this novel treatment approach. A subset of patients with mCRPC, even those without high mutational burden or microsatellite instability, demonstrated durable responses to the treatment. This outcome points towards a possible immunogenic priming effect induced by radioligand therapy. In summary, the phase 1b study suggests that combining 177Lu-PSMA-617 with pembrolizumab is well-tolerated and can lead to sustained responses in some metastatic castration-resistant prostate cancer patients, potentially through an immunogenic priming mechanism, even in cases typically less responsive to immune checkpoint inhibitors.

The Safety Profile: Managing On-target and Off-target Effects

While radioligand therapy offers a targeted approach, it is not without adverse effects, which are broadly categorized as on-target or off-target. A clear understanding of this distinction is crucial for anticipating, managing, and mitigating toxicity, thereby ensuring patients' safety and maintaining their quality of life throughout the treatment course. Proactive management is a cornerstone of successful theranostic programs.

On-target, off-tumor effects

A unique category of side effects arises from 'on-target, off-tumor' binding. This occurs when the molecular target (e.g., PSMA or somatostatin receptor) is physiologically expressed at low levels on certain healthy tissues [92]. Although tumor cells exhibit significantly higher expression, the cumulative radiation dose from the therapeutic agent to these normal tissues can lead to class-specific toxicities [93]. These effects are often predictable and manageable but are an inherent consequence of the therapy's mechanism of action.

In PSMA-targeted radioligand therapy, a common on-target, off-tumor effect is xerostomia (dry mouth) and dysgeusia (altered taste). This results from the specific uptake of PSMA-targeting agents in the

salivary and lacrimal glands. The radiation-induced damage to the serous acinar cells reduces saliva production, a side effect that can be bothersome for patients but is rarely severe [94]. Management typically involves supportive care with saliva substitutes, sugar-free gum, and meticulous oral hygiene to prevent complications. For somatostatin receptor-targeted therapies (e.g., with Lu-177-DOTATATE), on-target effects are often related to the hormone-modulating properties of the targeting vector [95]. Patients may experience transient nausea, vomiting, or fluctuations in blood glucose levels due to the peptide's interaction with somatostatin receptors in the gastrointestinal tract and pancreas. These symptoms are usually mild to moderate and self-limiting, often manageable with antiemetic premedication and careful monitoring, especially in diabetic patients.

Off-target, on-organ effects

Off-target effects are not related to the specific target binding but result from the general biodistribution and clearance pathways of the radiopharmaceutical. The two primary dose-limiting organs are the kidneys and the bone marrow. These organs receive radiation exposure not because they express the target, but because they are involved in metabolizing and clearing the agent from the body, leading to nonspecific irradiation.

Hematological toxicity, particularly thrombocytopenia (low platelet count) and neutropenia (low neutrophil count), are the most common off-target effects. This occurs due to the cross-irradiation of the bone marrow from the radiopharmaceutical circulating in the blood pool and, to a lesser extent, from the uptake in bone metastases or the skeletal system [96]. Myelosuppression is typically transient and recovers between treatment cycles, but it requires careful monitoring through regular complete blood counts to guide dose timing and prevent serious complications like bleeding or infection. Renal toxicity is another critical off-target concern. Small peptide-based radiopharmaceuticals are primarily cleared through the kidneys and are partially reabsorbed in the proximal tubules, leading to retention and significant irradiation of the renal parenchyma [97]. Without protective measures, this can lead to a gradual decline in renal function over the long term. The risk is heightened in patients with pre-existing hypertension, diabetes, or renal impairment, making baseline assessment and ongoing monitoring of renal function essential.

Strategies for mitigating toxicity

A multi-faceted approach is employed to mitigate these toxicities and protect patients. For renal protection, the standard of care is the co-infusion of a competitive inhibitor of tubular reabsorption, most commonly a solution of positively charged amino acids (lysine and arginine) [98]. This amino acid infusion saturates the reabsorption mechanisms in the kidney tubules, effectively 'blocking' the radiopharmaceutical from being retained and thereby significantly reducing the radiation dose delivered to the kidneys. To manage hematological toxicity, the primary strategy is vigilant monitoring and personalized dose adjustment. Dosimetry calculations can predict bone marrow exposure, allowing for activity modification in subsequent cycles if necessary. Treatment cycles are typically spaced 6 to 8 weeks apart to allow for bone marrow recovery. In cases of persistent or severe cytopenia, growth factor support (e.g., G-CSF for neutropenia) may be utilized, and the use of more myelosuppressive agents like Ac-225 requires even closer surveillance [99].

For on-target effects like xerostomia, ongoing research is exploring specific mitigation strategies. These include the use of glandular cooling with ice packs during infusion, pilocarpine to stimulate saliva flow, or the administration of blocking agents that temporarily occupy the PSMA receptors in the salivary glands without delivering a therapeutic dose [100]. While supportive care remains the mainstay, these investigational approaches aim to improve patient comfort and treatment tolerability. The management of the safety profile is a dynamic and continuous process that extends across the entire treatment journey. It begins with careful patient selection, considering comorbidities that may predispose to toxicity, and continues through each cycle with pre-medications, protective infusions, and diligent post-treatment monitoring. This comprehensive framework allows clinicians to harness the potent anti-tumor effects of radioligand therapy while maintaining a manageable and predictable safety profile [101].

In summary, the adverse events associated with radioligand therapy are a direct consequence of its pharmacokinetics and mechanism of action. By clearly differentiating between on-target/off-tumor and off-target/on-organ effects, clinicians can implement evidence-based prophylactic and supportive measures. The successful application of renal protection protocols and personalized hematological management has been instrumental in establishing radioligand therapy as a well-tolerated and viable treatment option for a growing number of cancer patients.

Comparative Positioning in the Oncology Landscape

Radioligand therapy has carved out a distinct and expanding niche within the oncology armamentarium. Its value is best understood through a comparative analysis with other established treatment modalities, highlighting its unique mechanism of action, its strengths and limitations, and its evolving role in the treatment sequence from late stage to potentially curative settings.

Contrast with systemic therapies

Compared to traditional chemotherapy, which acts on all rapidly dividing cells and causes widespread cytotoxic effects, radioligand therapy offers a superior therapeutic index through its molecular precision. Chemotherapy's dose-limiting toxicities, such as severe neutropenia, neuropathies, and mucositis, stem from its non-specific mechanism [102]. In contrast, radioligand therapy's toxicity profile is more predictable and organ-specific (renal and hematological), and it largely spares tissues that do not express the target, resulting in a different and often more manageable side effect profile for patients [103].

When positioned against other targeted therapies, such as small molecule inhibitors or monoclonal antibodies, a key distinction emerges: the mechanism of cell kills. Most targeted therapies interfere with specific signaling pathways (e.g., kinase inhibition) to which cancer cells can develop resistance through alternative pathways or mutations [104]. Radioligand therapy, however, utilizes a physical cytotoxic agent—radiation—that directly damages DNA [74]. This fundamental difference means that radioligand therapy can be effective in tumors that have become resistant to pathway-targeted agents, as it does not rely on the continued integrity of a specific signaling cascade for its effect.

Immunotherapy, particularly immune checkpoint inhibitors, has revolutionized oncology by unleashing the host's immune system against cancer. However, its efficacy is highly dependent on the tumor's immunogenic microenvironment, and many 'cold' tumors do not respond. Radioligand therapy's mechanism is independent of the host's

immune status [105]. Intriguingly, emerging evidence suggests that the radiation from radioligand therapy can transform immunologically 'cold' tumors into 'hot' ones by inducing immunogenic cell death, releasing tumor antigens, and promoting T-cell infiltration. This provides a strong rationale for combining radioligand therapy with immunotherapy to overcome resistance and achieve synergistic effects.

Comparison with other radiation modalities

External beam radiation therapy delivers high-dose, focused radiation from outside the body, typically with exquisite precision to a localized tumor. Its primary limitation is that it is a local treatment, unsuitable for widespread metastatic disease due to the toxicity of irradiating large volumes of healthy tissue. Radioligand therapy, in contrast, is a systemic radiation modality [106]. It simultaneously delivers therapeutic radiation to all metastatic sites throughout the body, provided they express the target, making it uniquely suited for treating disseminated cancer.

Brachytherapy involves placing radioactive sources directly inside or next to a tumor, achieving a very high local dose with a rapid dose fall-off to spare surrounding organs. Like external beam radiation therapy, it is a localized technique. Radioligand therapy can be thought of as a 'systemic brachytherapy,' where the radiopharmaceutical automatically seeks out and internalizes within tumor cells, effectively delivering radiation from within [107]. While brachytherapy requires invasive procedures for source placement, radioligand therapy is administered through a simple intravenous infusion.

A critical advantage of external beam radiation therapy and brachytherapy is the ability to plan and confirm the dose distribution with high accuracy before treatment. For radioligand therapy, the dose distribution is dynamic and depends on the biokinetics of the pharmaceutical, making pre-therapeutic imaging and dosimetry vital for predicting and optimizing delivery [108]. The 'crossfire effect' of beta-emitting radioligand therapy is another differentiator, allowing it to irradiate heterogeneous tumors and micrometastases in a way that the direct beam of external beam radiation therapy cannot.

Evolving role: From later-line to earlier-line therapy

The initial regulatory approvals for radioligand therapy agents like Lu-177-DOTATATE and Lu-177-PSMA-617 were in later-line settings for metastatic, treatment-refractory patients. In this role, radioligand therapy has demonstrated significant efficacy in improving progression-free survival and quality of life where other options are limited [109]. Its establishment as a standard of care in these advanced stages has been based on its ability to provide meaningful clinical benefit with a tolerable safety profile in a heavily pre-treated population. The logical and critical evolution for radioligand therapy is its movement into earlier lines of treatment [110]. The successes in late-stage disease have prompted large-scale phase III trials investigating radioligand therapy in the first line and adjuvant settings. The rationale is powerful: deploying a highly targeted, potent therapy when tumor burden is lower and the patient's performance status and organ function are better could lead to deeper responses, longer disease control, and potentially even cures in some cases.

This shift is already underway. For example, studies are evaluating Lu-177-PSMA-617 in combination with standard first-line therapies for metastatic prostate cancer. In neuroendocrine tumors, radioligand therapy is being explored as a first-line option and even in the neoadjuvant setting to downstage tumors before surgery [111]. This transition from a salvage therapy to an integral component of initial treatment represents the maturation of the field and its acceptance as a pillar of modern oncology. The integration of radioligand therapy into the broader treatment paradigm will likely be as a complementary, rather than a replacement, modality [112]. Future treatment sequences may involve debulking with chemotherapy or targeted therapy, followed by radioligand therapy to eradicate residual disease, or combinations of radioligand therapy with other modalities from the outset [113]. Its unique systemic, crossfire-enabled, and physically cytotoxic mechanism makes it an ideal partner in multimodal treatment strategies designed to address the complex challenges of tumor heterogeneity and resistance.

In summary, radioligand therapy occupies a unique and synergistic position in oncology. It offers the systemic reach of chemotherapy with a more targeted toxicity profile, the mechanistic independence from signaling pathway resistance seen with targeted therapies, and the potential to prime an immune response. It extends the curative intent of radiation oncology to the metastatic setting. As clinical evidence continues to accumulate, radioligand therapy is poised to move from a specialized late-line option to a foundational treatment, redefining standards of care across a spectrum of malignancies.

Conclusion

The future of theranostics will be defined by strategic expansion and deeper integration. The immediate horizon involves validating its efficacy in earlier lines of therapy through large-scale clinical trials, a logical progression from its established role in late-stage disease. Concurrently, the theranostic landscape will broaden beyond PSMA and somatostatin receptors, with targets such as fibroblast activation protein, TROP-2, and nectin-4 showing significant promise for extending this platform to a wider array of carcinomas, including pancreatic, breast, and lung cancer. This expansion will be fueled by comprehensive molecular profiling, enabling the identification of new, actionable targets and facilitating truly personalized treatment matching. Furthermore, the next evolutionary leap will come from sophisticated combination regimens and technological innovation. The rational combination of radioligand therapy with immunotherapy, DNA damage repair inhibitors, and other targeted agents holds immense potential to overcome tumor resistance and exploit synergistic anti-tumor effects, including the abscopal effect. Technologically, advances in nanocarriers for improved tumor delivery and the development of novel radionuclides with optimized decay profiles will enhance therapeutic efficacy and safety. As these elements converge, theranostics will evolve from a specialized modality into a foundational pillar of multimodal oncology, fundamentally transforming cancer into a more manageable and precisely targetable disease.

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None.

Conflict of Interest

None.

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