

Lanthanides in oncology: A narrative review of advances in imaging, therapy, and theranostics

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ABSTRACT

Conventional cancer therapies typically appear constrained by systemic toxicity and developed drug resistance, necessitating the establishment of high-precision diagnostic and therapeutic platforms. This review assesses the transformational potential of the lanthanide series in oncology, specifically their distinct 4f-electronic arrangement and magnetic properties to create versatile biomedical medications. We outline the latest developments in diagnostic modalities, following the transition from classic gadolinium-based magnetic resonance imaging (MRI) contrast agents to deep-tissue near-infrared (NIR-II) luminescent probes and emerging nuclear imaging isotopes, including terbium-152. Therapeutically, the article explores lanthanide-mediated cytotoxicity mechanisms such as oxidative stress induced by reactive oxygen species (ROS) formation. We also address the clinical efficacy of targeted radioligand therapy, particularly Lutetium-177, and the introduction of synergistic photodynamic and photothermal interventions using nanoparticles. The spotlight is placed on integrated "theranostic" systems, in which the isostructural modularity of lanthanides enables the formation of chemically identical matched pairs for simultaneous diagnosis and therapy. Despite this potential, clinical application remains limited by concerns about kinetic stability and long-term tissue retention. We recommend that future investigations prioritize thermodynamically stable, stimuli-responsive substances to overcome toxicity obstacles and establish lanthanides as critical components of next-generation precision oncology.

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Introduction

Cancer is one of the most significant health problems and ranks as the second leading cause of mortality in developed countries (1). In 2022, around 20 million new cancer cases and approximately 9.7 million cancer-related deaths were documented globally. According to estimates, one in every five men and women will develop cancer at some point in their lives, with one in every nine men and one in every 12 women dying from it. The most prevalent malignancies are lung, female breast, and colorectal cancers, while lung, colorectal, and liver cancers are the primary causes of cancer-related deaths. The magnitude of the problem is expected to increase, with new cases possibly exceeding 35 million by 2050, driven mainly by demographic shifts from population aging (2).

To address this concern, researchers have developed and implemented countless therapeutic strategies over the past few decades. The primary cornerstone of these approaches is chemotherapy, radiotherapy, hormonal therapy, and surgery, which are recognized as conventional treatment methods. These therapeutic techniques have demonstrated great success in treating several malignancies. However, for a variety of reasons, there is a significant demand for

alternative and complementary therapies (3).

Conventional cancer treatments, specifically chemotherapy, radiation therapy, and hormonal therapy, face significant limitations due to their inherent lack of specificity. This contributes to substantial systemic toxicity because the treatments affect rapidly growing healthy host tissues alongside malignant cells, commonly requiring dose reductions and significantly decreasing patient quality of life (4). Another significant obstacle is the development of drug resistance, which can be either intrinsic or acquired (5, 6). This phenomenon, often driven by mechanisms such as up-regulation of drug efflux pumps and widespread tumor heterogeneity, allows malignant cells to survive initial therapy, resulting in disease relapse and poor outcomes (7).

In recent years, several studies have been conducted on the potential of implementing new strategies to overcome cancer. One of these techniques that has attracted considerable interest in studies is the use of less commonly used elements from the periodic table. The synthesis of complexes for imaging, the synthesis of carrier nanoparticles (NPs) for drug delivery, radioisotopes, and biosensors represent some of the different applications of these elements.

The lanthanide (Ln) series, also known as rare elements,

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consists of 15 elements from lanthanum (La) to lutetium (Lu) and possesses unique physicochemical characteristics that make it useful in biomedical research and diagnostic procedures (8, 9). Their distinctive electronic configuration, $[\text{Xe}] 4f^{1-14} 5d^0 6s^2$, is essential to their particular chemistry. The shielding of the 4f orbitals by the outer $5s^2$ and $5p^6$ shells results in the predominant and highly stable oxidation state of Ln^{3+} across the series (9, 10).

Compared to traditional organic fluorophores and transition metal complexes, trivalent lanthanides (Ln^{3+}) possess distinct electronic and coordination features that make them superior platforms for precision oncology; shielded 4f-4f transitions in produce narrow emission bands and long luminescence lifetimes (μs to ms), which are advantages of lanthanides over organic fluorophores. This enables time-gated imaging, which suppresses short-lived (ns) tissue autofluorescence and markedly enhances signal-to-noise ratios (11-13). Moreover, unlike transition metals with restricted coordination numbers or lower magnetic moments, ions like feature seven unpaired 4f electrons and high coordination capacity, facilitating optimal inner-sphere water exchange for high longitudinal (T_1) relaxivity (12, 14). The unique ionic state of these elements supports large coordination numbers (usually 6-12) and diverse coordination geometries, enabling complexation with biological ligands (15, 16). Collectively, these features position lanthanides as adaptable substrates for producing next-generation imaging agents, biosensors, and therapeutic radiopharmaceuticals (17).

This review highlights recent and transformative advances in Ln-based compounds for cancer theranostics, primarily encompassing literature published within the last ten years (2015-2025). We attempt to objectively analyze the most recent methods being investigated to overcome the limits of conventional cancer therapy. We examine how these Ln-based architectures—leveraging their unique magnetic, optical, and nuclear characteristics—can be used to accomplish exact cancer diagnosis (e.g., MRI contrast, luminescence imaging) and targeted therapeutic intervention (e.g., radiopharmaceuticals).

Literature search methodology

A systematic search was conducted across Web of Science, PubMed, Scopus, and Embase to identify relevant peer-reviewed studies published between December 2015 and December 2025. The search strategy combined Boolean operators with terms related to lanthanide chemistry and oncology such as: ("lanthanide" OR "rare earth" OR "gadolinium") AND ("oncology" OR "cancer therapy" OR "theranostics" OR "MRI contrast" OR "radiopharmaceutical" OR "photodynamic therapy"). This method was used for all of the lanthanide elements.

Fundamental chemistry of lanthanide–biological interactions

Lanthanide biological behavior is governed by their coordination chemistry and physicochemical properties. Under physiological conditions, lanthanides predominantly exist as trivalent ions (Ln^{3+}), which are strongly Lewis acidic and strongly prefer hard donor atoms, particularly oxygen atoms in carboxylate, phosphate, hydroxyl, and carbonyl groups (18, 19). Consequently, Ln^{3+} ions readily coordinate with biomolecules, including proteins, phospholipids, nucleic acids, and endogenous chelators, forming thermodynamically stable coordination complexes while maintaining relatively rapid ligand-exchange kinetics (18, 20). Across the lanthanide series, the gradual decrease in ionic radius caused by the lanthanide contraction further

modulates coordination geometry, complex stability, hydration energy, and biological interactions (18, 19). These fundamental chemical characteristics underlie many of the biomedical applications discussed throughout this review. For example, the comparable ionic radii but distinct charge density and coordination preferences of Ln^{3+} relative to Ca^{2+} explain their ability to compete for selected calcium-binding sites while yielding different thermodynamic outcomes (18, 21). Likewise, the high affinity of lanthanides for multidentate chelators such as DOTA and DTPA enables the formation of kinetically stable radiopharmaceuticals for nuclear imaging and radionuclide therapy (19, 20), whereas their versatile coordination chemistry facilitates incorporation into nanoparticles, metal–organic frameworks, and multifunctional drug-delivery platforms (19-22). Therefore, understanding the coordination chemistry of lanthanides provides the molecular basis for interpreting both their therapeutic potential and their biological responses.

Lanthanides for cancer diagnosis (imaging and sensing)

MRI contrast agents

MRI is a prominent non-invasive diagnostic method for cancer detection and monitoring and offers considerable spatial resolution (23). The two principal categories of MRI contrast media are T1-weighted agents, which generate bright (longitudinal) contrast, and T2-weighted agents, which yield dark (transverse) contrast (24). Concerning the high magnetic moment and seven unpaired electrons, gadolinium (III) (Gd^{3+}) has historically been the most preferred T1 contrast agent (23, 25). By reducing proton longitudinal relaxation times, they generate strong contrast in T1-weighted images (12). However, its longitudinal relaxivity (r_1) efficiency decreases significantly at ultra-high magnetic fields ($\geq 7\text{T}$) due to field-dependent electron spin relaxation dynamics (12, 26). Macrocyclic or linear polyaminocarboxylate ligands are used in clinically authorized Gd complexes consisting of gadoterate meglumine (Dotarem) and gadopentetate dimeglumine (Magnevist) to chelate Gd^{3+} and lessen its intrinsic toxicity (27). Nevertheless, these agents raise many concerns. One concern is potential gadolinium accumulation in the kidney and the formation of nephrogenic systemic fibrosis (NSF) in individuals with impaired renal function, which requires the development of novel ligands (macrocyclic chelates with higher kinetic inertness) and other approaches to minimize the release of free Gd^{3+} (28). Meanwhile, the limited deposition in, and rapid clearance from, cancerous tissue of clinically available low-molecular-weight Gd^{3+} contrast complexes often limits their use in tumor imaging, resulting in insufficient MRI sensitivity and specificity (29). The necessity for alternative approaches in this field is highlighted by these challenges as well as others like Gadolinium Retention/Deposition Disease (GDD) (30).

To date, several approaches have been investigated that involve the utilization of iron and manganese in MRI (31, 32). Gadolinium NPs and other lanthanide-series elements, including holmium and Dysprosium, which can function as T2 contrast agents, are other possible strategies (33, 34). Possessing high effective magnetic moments ($\mu_{\text{eff}} \approx 10.6 \mu_B$) and ultrafast electronic relaxation ($\tau_s \approx 10^{-13} \text{s}$), Dy^{3+} and Ho^{3+} generate strong local magnetic susceptibility gradients (34). Furthermore, neodymium can function as a T1 contrast agent (35), where despite yielding lower r_1 relaxivity

Table 1. Lanthanide-incorporated agents employed in MRI

Lanthanide	Representative agent/material	Ligand / Matrix	Imaging mode	Clinical/Preclinical notes	Ref.
Gd(III)	Gadoterate (Dotarem), Gadopentetate (Magnevist)	Macrocyclic DOTA-like; linear DTPA variants	T ₁	Widely used; safety concerns → macrocyclic preferred	(36)
Ho(III)	HoF ₃ NPs	PEG 4000 (PEGylation)	T ₂	Preclinical; good water solubility and biocompatibility; demonstrates feasibility of an Ho-based dual-modal contrast agent for cancer imaging.	(33)
Dy(III)	Dysprosium-modified gold NPs (AuNP-Dy)	Au (gold) core NPs, modified with a chelate: Dy-DOTA(amide) ₂ bound at the surface of the AuNPs.	T ₂	Preclinical; demonstrated efficient tumor accumulation and strong T ₂ Contrast; potential as a non-Gd alternative.	(34)
Nd(III)	Silver-Neodymium bimetallic nanoparticles (Ag-Nd) loaded with Paclitaxel	Chitosan	T ₁ (Multimodal) NIR / MRI / CT	Evaluated <i>in vitro</i> on human cervical cancer cells (HeLa) Superparamagnetic with strong T ₁ -weighted MRI longitudinal relaxivity	
Gd(III) based NPs	Gd ₂ O ₃ NPs	Glucosamine (glucose-shell) coating	T ₁	Enhanced uptake in high-metabolism cancer cells; demonstrates functionalized Gd NP targeting metabolic phenotype	(37)
Gd(III) based liposomes	Gadolinium (Dual-Gd) liposome	liposomal lipid bilayer with Gd-chelates (core-encapsulated + surface) + NIR dye + PEGylation (or typical liposome coating)	T ₁	Demonstrated <i>in vivo</i> imaging of intraperitoneal ovarian tumors; illustrates the feasibility of dual-mode liposome-based lanthanide imaging agents.	(38)

Ag: silver; Au: gold; AuNPs: gold nanoparticles; CT: computed tomography; DOTA: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DTPA: diethylenetriaminepentaacetic acid; Dy(III): dysprosium(III); Gd(III): gadolinium(III); Gd₂O₃: gadolinium(III) oxide; HeLa: Henrietta Lacks human cervical cancer cell line; Ho(III): holmium(III); HoF₃: holmium trifluoride; MRI: magnetic resonance imaging; Nd(III): neodymium(III); NIR: near-infrared; NPs: nanoparticles; PEG: poly(ethylene glycol); T₁: longitudinal relaxation time (T₁-weighted); T₂: transverse relaxation time (T₂-weighted)

than Gd³⁺(S=3/2), it uniquely provides narrow near-infrared (NIR-II) luminescence for simultaneous optical and MR imaging (35). Furthermore, selecting an optimal lanthanide platform for diagnostic MRI requires evaluating distinct electronic configurations, relaxation mechanisms, and field-dependent performance. To fully achieve this understanding, conducting more studies on different lanthanide applications as MRI contrast agents is required. A tabular summary of the lanthanide-incorporated agents employed in MRI is provided (Table 1).

Luminescent and optical imaging probes

The distinctive electronic structure of trivalent lanthanides [Xe]4fⁿ provides them with sharp, atomic-like emission patterns and extremely long luminescence lifetimes (μs-ms), properties which are essential to eliminate autofluorescence via time-gated imaging (13, 39). Terbium (Tb³⁺) and Europium (Eu³⁺) complexes have been developed for high-specificity diagnostic use across the visible spectrum. For instance, Lengacher *et*

al. recently created a targeted Eu³⁺ probe using a pycnol-based macrocycle sensitized by a pegylated aryl alkyne, which exhibited enhanced brightness and stability for luminescence-guided resection of solid tumors targeting Prostate-Specific Membrane Antigen (PSMA) (40). In addition to molecular complexes, Gómez-Morales *et al.* established the effectiveness of biomimetic, citrate-coated Eu³⁺-doped apatite NPs that combine continuous luminescence with outstanding cytocompatibility for long-term cell imaging (41). To overcome tissue penetration limitations, studies are increasingly focusing on Near-Infrared (NIR)-emitting lanthanides and Upconversion Nanoparticles (UCNPs). Unlike downconversion processes that absorb single higher-energy photons to produce longer-wavelength emissions (Stokes shift) with relatively high photoluminescence quantum yields, UCNPs sequentially absorb two or more lower-energy NIR photons to generate higher-energy anti-Stokes emissions (42). A schematic figure of comparison between Downconversion and Upconversion is provided as Figure 1.

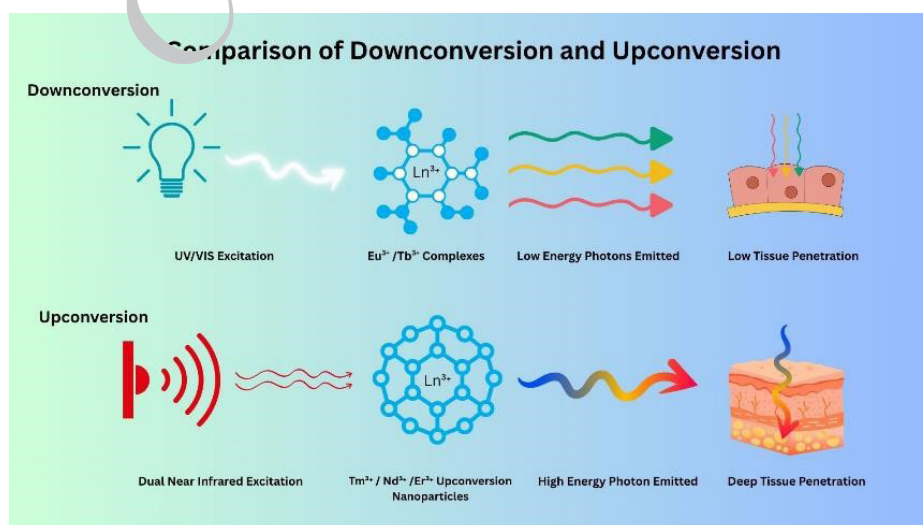


Figure 1. Schematic comparison of lanthanide-based downconversion and upconversion luminescence. Downconversion involves UV/visible excitation followed by the emission of lower-energy photons, typically resulting in limited tissue penetration. In contrast, upconversion nanoparticles are excited by near-infrared light and emit higher-energy photons, enabling deeper tissue penetration and offering advantages for biomedical imaging and therapeutic applications.

Table 2. Lanthanide luminescent probes and Upconversion Nanoparticles (UCNP) systems for cancer imaging

Ln probe/material	Emission region	Typical use	Targeting ligand and target/ functionalization	Ref.
[Eu(III)(pcta-PEPA2)] and [Eu(III)(tacn-pic-PEPA2)]	Visible red (Characteristic peaks at 597 nm and 621 nm)	Luminescence-guided surgery (Intraoperative tumor margin delineation) Post-surgical microscopy (1-photon and 2-photon excitation of fixed tissue)	Targeting ligand: PSMA-targeting peptide (linked via cysteine) Target: PSMA on prostate cancer cells (e.g., PC-3)	(40)
Eu(III)-doped carbonated apatite NPs (Eu-doped cit-cAp)	Visible red (Dominant emission at 616 nm)	<i>In vitro</i> cell imaging (demonstrated cytocompatibility and imaging potential in GTL-16 human gastric carcinoma cells and m17.ASC murine mesenchymal stem cells)	Functionalization: Biomimetic citrate surface coating (via thermal decomplexing synthesis)	(41)
RVLu@ICG	NIR-II	Multimodal theranostics in colorectal cancer: 1. NIR-II Guided Surgery 2. Radiosensitization 3. Immunomodulation	Targeting Ligand: Cyclic RGD peptide (c(RGDfK)) Target: Integrin receptors (e.g., $\alpha_v\beta_3$) are overexpressed on tumor cells and neovasc. structure	(43)
Gd:Nd-RENPs	NIR-II (Dual emission peaks at 1060 nm and 1340 nm)	Intraoperative sentinel lymph nodes mapping Dual-modal imaging (NIR-II fluorescence combined with MRI via Gd ³⁺)	Targeting Mechanism: Passive / Drainage Kinetics: The probe differentiates metastatic nodes from normal ones based on physiological changes rather than specific molecular ligand	(44)
Tm ³⁺ -doped UCNPs	Visible Blue & NIR (Multiphoton emissions: 475 nm [Blue] and 800 nm [NIR] under 1150 nm excitation)	Multiphoton microscopic imaging	Targeting: This study did not use specific targeting ligands; the UCNPs served as general cellular labels to demonstrate the imaging modality	(45)
α -Tm NP (Core/Shell/Shell NPs: Cubic-phase α -NaYF ₄ @NaYF ₄ :Tm@NaYF ₄)	NIR-IIb (Emission peak at 1630 nm)	Bone metastasis imaging	Targeting: The study focuses on passive accumulation and probe structural engineering rather than a specific conjugated ligand	(47)
Er(III)-bacteriochlorin complex	NIR-II (Narrowband emission at 1530 nm; large Stokes shift >750 nm)	Multiplexed bioimaging	Targeting: The study highlights multiplexing (excitation/emission) capabilities. For brain imaging, the probe allows non-invasive tracking due to high resolution and penetration, rather than a specific antibody-based targeting mechanism mentioned in the abstract	(48)

α -NaYF₄: cubic-phase sodium yttrium fluoride; $\alpha_v\beta_3$: $\alpha_v\beta_3$ integrin receptor; c(RGDfK): cyclo(Arg-Gly-Asp-D-Phe-Lys) peptide; cit-cAp: citrate-functionalized carbonated apatite; Er(III): erbium(III); Eu(III): europium(III); Gd: gadolinium; Gd:Nd-RENPs: gadolinium and neodymium co-doped rare-earth nanoparticles; GTL-16: human gastric carcinoma cell line; ICG: indocyanine green; Ln: lanthanide; m17.ASC: murine mesenchymal stem cell line; MRI: magnetic resonance imaging; Nd: neodymium; NIR: near-infrared; NIR-II: second near-infrared window (1000–1700 nm); NIR-IIb: second near-infrared sub-window b (1500–1700 nm); nm: nanometer; NPs: nanoparticles; PC-3: human prostate cancer cell line; pcta: 3,3',9,9'-tetraazatetracyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid; PEPA: phenethylpyridyl-arm ligand derivative; pic, picolinate; PSMA: prostate-specific membrane antigen; RENPs: rare-earth nanoparticles; RGD: arginine-glycine-aspartic acid; tacn: 1,4,7-triazacyclononane; Tm / Tm³⁺: thulium / thulium(III); UCNPs: upconversion nanoparticles

The “second biological window” (NIR-II, 1000–1700 nm) is especially beneficial for reducing scattering; Dang *et al.* exemplified this by developing Lutetium-based nanoprobe that use NIR-II fluorescence to guide the precise surgical removal of colorectal tumors while concurrently modulating the immune microenvironment (43). Duan *et al.* established a Neodymium (Nd³⁺)-doped nanoprobe for intraoperative detection of early lymphatic metastases with high signal-to-background ratios in the NIR-II region (44). In addition to these down-conversion methods, Peng *et al.* characterized Thulium (Tm³⁺)-doped UCNPs, which, upon 980 nm or 808 nm excitation, produce anti-Stokes emissions that are free of background noise, optimizing deep-tissue microscopic imaging (45).

However, the clinical translation of UCNPs requires addressing potential toxicological risks. In most studies to date, no serious toxicity has been observed after *in vitro* administration of lanthanides (46). However, the safety of these compounds in *in vivo* studies is still debated, and further research is needed to assess this issue. Details of the lanthanide probes and their corresponding imaging modalities and targeting mechanisms are listed in Table 2

(Table 2). Collectively, these advances underscore the shift toward lanthanide-based probes that integrate deep-tissue penetration with high-contrast sensing capabilities.

Nuclear imaging techniques

Lanthanide radioisotopes are important to the advancement of nuclear imaging, specifically single-photon emission computed tomography (SPECT) and positron emission tomography (PET), because of their unique coordination chemistry and theranostic characteristics. Terbium-155 (¹⁵⁵Tb) provides ideal low-energy gamma emissions for SPECT; recent isolation procedures using cation-exchange chromatography and mass separation have achieved radionuclidic purities greater than 99%, which are crucial for preclinical phantom studies (49). For radiopharmaceutical preparation, ¹⁵⁵Tb has been successfully coordinated with DOTA-functionalized targeting vectors, with radiolabeling performed under standard lanthanide labeling conditions to produce complexes exhibiting high radiochemical purity and excellent stability in human serum, supporting their suitability for SPECT imaging and preclinical applications (49). Similarly, Terbium-161 (¹⁶¹Tb) is a dual-modal

Table 3. Key lanthanide radioisotopes for diagnostic imaging: physical decay properties, emission profiles, and imaging applications

Isotope	Half-life	Emission	Typical application	Ref.
¹⁵⁵ Tb	5.32 days	Gamma (γ) radiation and X-rays (via Electron Capture decay)	SPECT	(49)
¹⁶¹ Tb	6.90 days	Beta (β ⁻) particles Auger/conversion electrons Gamma (γ) photons	SPECT	(50, 55)
¹⁵² Tb	17.5 hr	Positron (β ⁺) particles	PET/CT	(51)
¹³² La and ¹³⁵ La	4.59 hr 18.91 hr	Positron (β ⁺) particles and Gamma (γ) rays Auger electrons following Electron Capture	PET	(52)
¹⁵³ Sm	1.93 days	Beta (β ⁻) particles significant co-emission of auger-meitner and conversion electrons Gamma (γ) rays	SPECT	(53)

β⁻: beta-minus particle (negatron); β⁺: beta-plus particle (positron); γ: gamma ray/radiation; CT: computed tomography; EC: electron capture; La: lanthanum; PET: positron emission tomography; Sm: samarium; SPECT: single-photon emission computed tomography; Tb: terbium

alternative; recent assessments have demonstrated the stability of albumin tagged with ¹⁶¹Tb (using DOTA and DTPA chelators) for vascular imaging (50). Radiolabeling of DOTA-, DOTA-GA-, and NETA-conjugated albumin under mild aqueous conditions (40 °C) afforded high radiochemical yields (>90%), while DOTA- and NETA-based complexes exhibited excellent *in vitro* and *in vivo* stability with negligible bone accumulation, indicating minimal radiometal dissociation (50). Terbium-152 (¹⁵²Tb) proved clinical success in the PET domain in a first-in-human trial using ¹⁵²Tb-DOTATOC for illustrating neuroendocrine neoplasms with high contrast, surpassing short-lived options for delayed imaging (51). The radiopharmaceutical was prepared by labeling DOTATOC in sodium acetate buffer (pH 4.6) at 95°C for 40 min, producing a preparation suitable for clinical PET/CT imaging and demonstrating the feasibility of ¹⁵²Tb-based radiopharmaceuticals for extended imaging protocols (51). Furthermore, recent research has established the first targeted application of radiolanthanum, identifying Lanthanum-132 (¹³²La) as a viable PET imaging agent that forms a theranostic matched pair with the therapeutic Auger-emitter Lanthanum-135 (¹³⁵La), using PSMA-targeting conjugates based on macropa and DO3Apic chelators (47). Radiochemical investigations demonstrated that macropa achieved higher apparent molar activity under mild labeling conditions, while both chelators exhibited excellent kinetic stability and *in vivo* integrity, supporting targeted PET imaging applications (52). Advancements in high-molar-activity Samarium-153 (¹⁵³Sm) have enabled the synthesis of [¹⁵³Sm] Sm-DOTA-TATE, permitting tailored SPECT imaging previously limited by activity constraints (53). Radiolabeling of [¹⁵³Sm] Sm-DOTA-TATE was achieved in sodium acetate buffer (pH 4.7) at 95°C for 15 min, yielding radiochemical conversion rates >99%. The resulting complex remained highly stable for up to 7 days in PBS and human serum, with radiochemical purity exceeding 99%, supporting its suitability for SPECT imaging and theranostic applications (53). Table 3 summarizes the key characteristics of the proposed isotope complexes.

Beyond radionuclide-based imaging, lanthanides have also enabled high-dimensional single-cell analytical approaches, particularly mass cytometry (CyTOF), in which lanthanide isotope-tagged antibodies allow simultaneous measurement of numerous cellular markers at single-cell resolution. Imaging mass cytometry further extends this approach to spatially resolved analysis of tumor tissues, enabling

highly multiplexed characterization of tumor heterogeneity and the tumor-immune microenvironment (54).

Biosensors for cancer biomarkers

Lanthanide-based biosensors provide molecular assessment of the tumor microenvironment by utilizing unique optical lifetimes and catalytic surface characteristics for high specificity and sensitivity.

Luminescent and ratiometric probes

Time-resolved photoluminescence (TRPL) leverages lanthanide complexes' long-lived emission to filter out short-lived background fluorescence, leading to background-free detection. Xu *et al.* employed Eu³⁺-doped lutetium oxyfluoride nanoprobes to detect prostate-specific antigen (PSA) with high sensitivity (56). Similarly, Gidwani *et al.* used Eu³⁺ NPs to determine cancer-associated glycosylation patterns on CA125, enhancing specificity for ovarian cancer (57). Recent advances in the NIR-II window have applied Nd³⁺ tags to measure circulating tumor cells (58), while novel europium organometallic gels enable ratiometric detection of hepatocellular carcinoma markers (59).

Electrochemical and photoelectrochemical sensors

Electrochemical systems depend on the redox reversibility (e.g., Ce³⁺/Ce⁴⁺) and high surface area of lanthanide NPs for facilitating electron transfer (60). Cerium oxide (CeO₂)-based immunosensors have used this property to acquire superior sensitivity for pancreatic Carbohydrate Antigen 19-9 (CA19-9) (60) and lung Carcinoembryonic Antigen (CEA) antigens (61), along with non-invasive epidermal growth factor receptor (EGFR) screening in physiological fluids (62) and T-cell immunoglobulin and mucin domain 1 (TIM-1) biomarker detection in colorectal tumors (63). La³⁺ doping enhances charge transfer in semiconductor matrices for protein detection (64, 65). Table 4 presents key detection modalities and analytical sensitivities of lanthanide-based diagnostic systems.

Lanthanides for cancer treatment (Therapy)

Cytotoxic agents (chemotherapy alternatives)

The establishment of lanthanide-based cytotoxic medicines has been recognized as a promising strategy for addressing the drawbacks of conventional cancer therapies, including systemic toxicity and drug resistance (66). The reported antitumor effects of lanthanide-based systems may arise from different mechanisms depending on the material design. In some cases, cytotoxicity is mediated directly by the

Table 4. Lanthanide-based biosensing platforms for cancer biomarker detection

Lanthanide	Detection modality	Target biomarker and cancer type	Key performance/ LOD	Ref.
Eu ³⁺ -doped Lu ₂ O ₃ F ₃ nanoprobosc	Optical (TRPL / dissolution-enhanced bioassay)	PSA/ Prostate cancer	LOD: 0.52 pg/ml; Achieved a ~200-fold sensitivity improvement over commercial DELFIA kits	(56)
Eu ³⁺ chelate-doped NPs	Optical (TRPL / nanoparticle immunoassay)	CA125 (specifically the Sialyl-Tn glycoform)/ Epithelial ovarian cancer	Sensitivity: 73.3% at 95% specificity; Successfully distinguished malignant ovarian cancer from benign endometriosis (reduced false positives)	(57)
Nd ³⁺ -cored small molecule tag (AMF-DOTA-Nd)	Optical (NIR-II luminescence) & mass spectrometry (ICP-MS)	PSMA/ prostate cancer	LOD: 0.3 ng/ml; Enabled "Liquid biopsy" by counting circulating tumor cells (CTCs) (134–773 cells) and differentiating cancer from benign hyperplasia	(58)
Eu-based Metal-Organic Gel (Eu-MOG)	Optical (Ratiometric fluorescence)	Cholyglycine (CG)/ hepatocellular carcinoma	LOD: 307 ppb; Exhibits a distinct visual color shift (red to blue) upon binding, enabling "naked-eye" detection with high selectivity against other bile acids	(59)
Bimetallic Ce/Fe oxides in mesoporous carbon (CeO ₂ /FeO _x @mC)	Electrochemical	CA19-9/ pancreatic and colorectal cancer	LOD: 10 µU/ml; Porous carbon matrix prevents NP aggregation, while bimetallic synergy (Ce/Fe) enhances electron transfer for high sensitivity	(60)
CeO ₂ -carbon nanoparticle-chitosan Nanohybrid	Electrochemical (label-free / voltammetry)	CEA/Lung cancer	LOD: 0.037 ng/ml; high sensitivity (22.40 µA cm ⁻² per decade) achieved by combining the redox activity of CeO ₂ with the high conductivity of carbon NPs	(61)
CeO ₂ functionalized graphene oxide	Electrochemical (impedimetric aptasensor)	EGFR/ breast cancer	LOD: 1.87 fg/ml; enabled non-invasive detection in sweat and saliva samples with femtogram-level sensitivity	(62)
Multifunctional CeO ₂ NPs	Electrochemical (nanozyme-based immunoassay)	TIM-1/colorectal cancer	LOD: 9.9 pg/ml; CeO ₂ NPs acted as "nanoenzymes" (mimicking peroxidase activity) and nanocarriers, allowing for robust detection in plasma without competitive inhibition	(63)
La-doped TiO ₂ (La-TiO ₂) sensitized with CdSe	Photoelectrochemical	PSA/ prostate cancer	LOD: 17 fg/ml; La ³⁺ doping reduced electron-hole recombination, doubling the photocatalytic intensity compared with undoped TiO ₂	(64)
L-cysteine capped La hydroxide NPs (La(OH) ₃ NPs)	Electrochemical (immunosensor)	Cytokeratin fragment-21-1 (Cyfra-21-1)/oral cancer	LOD: 0.001 ng/ml; L-cysteine capping provided functional groups (-COOH, -NH ₂) for efficient antibody binding, enabling high sensitivity superior to commercial ELISA kits	(65)

COOH: carboxyl group; -NH₂: amino group; AMF-DOTA-Nd: amino-functionalized magnetic nanodiamond-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-neodymium complex; CA125: cancer antigen 125; CA19-9: carbohydrate antigen 19-9; CdSe: cadmium selenide; CEA: carcinoembryonic antigen; CeO₂: cerium (IV) oxide (nanoceria); CeO₂/FeO_x@mC: cerium oxide and iron oxide embedded in mesoporous carbon; CG: cholyglycine; CTCs: circulating tumor cells; Cyfra-21-1: cytokeratin fragment 21-1; DELFIA: dissolution-enhanced lanthanide fluorescent immunoassay; EGFR: epidermal growth factor receptor; ELISA: enzyme-linked immunosorbent assay; Eu/Eu³⁺: europium /europium(III); Eu-MOG: europium-based metal-organic gel; fg/ml: femtograms per milliliter; ICP-MS: inductively coupled plasma mass spectrometry; La/La³⁺: lanthanum /lanthanum(III); La(OH)₃: lanthanum hydroxide; La-TiO₂: lanthanum-doped titanium dioxide; LOD: limit of detection; Lu₂O₃F₃: lutetium oxyfluoride; Nd³⁺: neodymium(III); ng/ml: nanograms per milliliter; NIR-II: second near-infrared optical window (1000–1700 nm); NPs: nanoparticles; pg/ml: picograms per milliliter; ppb: parts per billion; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; TIM-1: T cell immunoglobulin and mucin domain 1; TiO₂: titanium dioxide; TRPL: time-resolved photoluminescence; µA cm⁻²: microamperes per square centimeter; µU/ml: micro units per milliliter

intrinsic chemical or radiological properties of lanthanide ions or their coordination complexes, whereas in others the lanthanide primarily functions as a structural or imaging component of a nanocarrier, with therapeutic efficacy resulting predominantly from the encapsulated drug, the carrier architecture, or synergistic interactions between these components. Accordingly, the studies discussed below distinguish, where applicable, between direct lanthanide-mediated effects and carrier-mediated therapeutic mechanisms. Despite their diagnostic counterparts, these chemicals are intended to provide direct therapeutic advantages via specific intracellular processes. The "calcium mimicry" effect happens when Ln³⁺ ions, possessing similar ionic radii and complex acid characteristics to Ca²⁺, displace calcium in critical signaling pathways, affecting mitochondrial function and cell cycle progression (67). However, this mimicry is governed by thermodynamic and coordination differences rather than simple ionic size similarity. Although Ln³⁺ ions have ionic radii comparable to Ca²⁺, their higher positive charge confers greater ligand affinity and hydration free energy, and they typically favor higher coordination numbers. Consequently, the ability of Ln³⁺ to replace Ca²⁺ depends on the charge and solvent accessibility of the calcium-binding pocket, with more negatively charged sites exhibiting greater thermodynamic preference for lanthanide binding (67). Furthermore, plenty

of lanthanide coordination complexes and nanomaterials are designed to function as "pro-oxidants" in the tumor microenvironment, producing lethal levels of reactive oxygen species (ROS), triggering apoptosis or necrosis (68). As an example of these compounds and the mechanisms associated with cytotoxicity, recent study on erbium indicates that coordination complexes (69) and oxide NPs (70) may induce lethal oxidative stress, which may contribute to G0/G1 cell cycle arrest and mitochondrial dysfunction. Lanthanides can result in targeted molecular interference in addition to general DNA damage; CeO₂ NPs have been used to specifically break down mutant p53 proteins in pancreatic cancer (71). In addition to this, compounds based on lanthanum—ranging from protein adducts (72) and small molecule complexes (73) to "nanozymes" that can cause pyroptosis (74)—demonstrate considerable cytotoxicity via multiple necrotic and apoptotic routes. Table 5 summarizes the primary cytotoxic pathways induced by these lanthanide compounds, highlighting their therapeutic potential across numerous cancer models. Moreover, a schematic figure of Lanthanides cytotoxic strategies is provided as Figure 2.

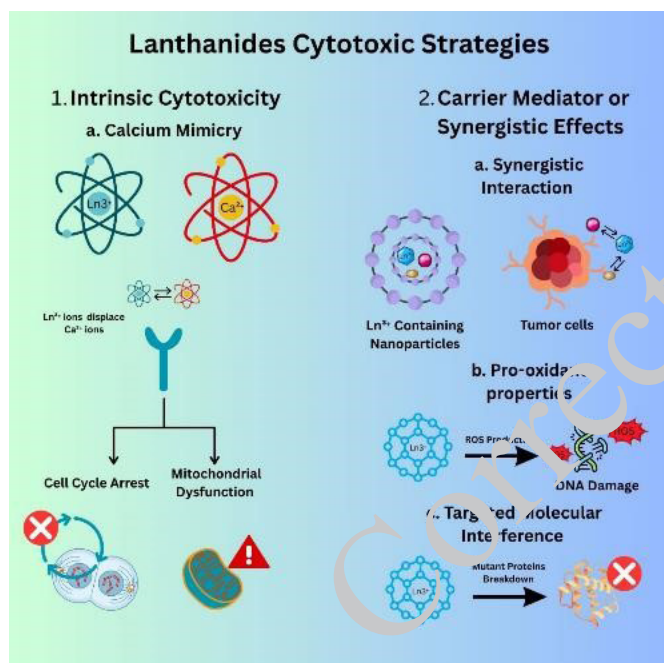
Photodynamic therapy (PDT)

Lanthanide-based systems have redefined photochemical oncology by overcoming tissue-penetration and hypoxia constraints. UCNPs doped with Ytterbium and Erbium

Table 5. Cytotoxic mechanisms of lanthanide compounds in cancer therapy

Lanthanide	Target cancer type	Primary mechanism of cytotoxicity	Key therapeutic outcome	Ref.
Erbium complex (Er(acac)TPP)	Lung adenocarcinoma	Mitochondrial dysfunction: Collapse of mitochondrial membrane potential and activation of Caspase-3	Effective killing of drug/radiation-resistant cells via intrinsic apoptosis	(69)
Er ₂ O ₃ NPs	Hepatic carcinoma (Hep-G2)	ROS Generation: Induction of oxidative stress leading to DNA damage and p53/Bax pathway activation	Triggered G0/G1 cell cycle arrest and significant apoptosis	(70)
CeO ₂ NPs	Pancreatic ductal adenocarcinoma	Protein Degradation: ROS-mediated selective degradation of mutant p53 (mutp53) protein	Inhibited tumor growth by eliminating the gain-of-function mutant p53	(71)
La ³⁺ -α-Lactalbumin	Breast carcinoma (MCF-7)	Oleic acid-independent protein complex enters cells to trigger caspases	Selective induction of apoptosis in cancer cells while sparing healthy cells	(72)
La ³⁺ nitrate (La(NO ₃) ₃) coordinated with an amphiphilic 1,4-diazabicyclo[2.2.2]octane derivative	Cervical, breast carcinoma (HeLa, MCF-7)	Mitochondrial Apoptosis: Interactions causing organelle stress distinct from conventional drugs	High cytotoxicity with a unique resistance profile	(73)
LaCoO ₃ Nanocrystals	Lung cancer (specifically Lung Metastasis)	Pyroptosis Induction: "Nanozyme" activity generating ROS and releasing La ³⁺ to rupture lysosomes	Induced pyroptosis (lytic cell death) and immune activation	(74)

α-Lactalbumin: alpha-lactalbumin protein; acac: acetylacetonate; Bax: Bcl-2-associated X protein; CeO₂: cerium(IV) oxide (nanocerium); DABCO: 1,4-diazabicyclo[2.2.2]octane; DNA: deoxyribonucleic acid; Er/Er(III): erbium/erbium(III); Er(acac)TPP: erbium(III) acetylacetonate tetraphenylporphyrin complex; Er₂O₃: erbium(III) oxide; G0/G1: gap 0 / gap 1 phase of the cell cycle; HeLa: Henrietta lacks human cervical cancer cell line; Hep-G2: human hepatocellular carcinoma cell line; La/La³⁺: lanthanum/lanthanum(III); La(NO₃)₃: lanthanum(III) nitrate; LaCoO₃: lanthanum cobaltite (lanthanum cobalt oxide); MCF-7: Michigan cancer foundation-7 human breast adenocarcinoma cell line; mutp53: mutant tumor protein 53; NPs: nanoparticles; p53: tumor protein 53; ROS: reactive oxygen species; TPP: tetraphenylporphyrin

**Figure 2.** Lanthanide Cytotoxic Strategies

Schematic overview of the primary mechanisms driving lanthanide-mediated cancer cell cytotoxicity, divided into: (1) Intrinsic Cytotoxicity, wherein trivalent lanthanide ions (Ln³⁺) mimic and displace calcium ions (Ca²⁺), leading downstream to cell cycle arrest and mitochondrial dysfunction; and (2) Carrier Mediator or Synergistic Effects, encompassing (a) synergistic interaction between Ln³⁺-containing nanoparticles and tumor cells, (b) pro-oxidant properties leading to ROS production and subsequent deoxyribonucleic acid (DNA) damage, and (c) targeted molecular interference inducing the degradation and breakdown of mutant tumor proteins. Ca²⁺: calcium ion; DNA: deoxyribonucleic acid; Ln³⁺: trivalent lanthanide ion; NPs: nanoparticles; ROS: reactive oxygen species

can trigger photosensitizers with deep-penetrating Near-Infrared light, efficiently bypassing the shallow depth of visible light (75-77). Concurrently, discrete Thulium and Terbium compounds have been developed as direct phototoxic agents or antenna moieties to boost excitation wavelengths (78, 79). CeO₂ nanostructures act as smart catalysts in tumor hypoxia, providing endogenous oxygen that drives the production of ROS required for cell death (80-82). Furthermore, X-ray-induced PDT using lanthanide scintillators is a promising technique for treating deep-seated malignancies that optical lasers cannot penetrate, as it converts X-ray photons into UV-visible light (83-85).

Multimodal synergies: Photodynamic and photothermal therapy (PDT + PTT)

To achieve synergistic tumor ablation, a growing academic consensus supports combining PDT with PTT. PTT-induced hyperthermia promotes sensitizer absorption and vascular permeability, intensifying oxidative stress. Lanthanum hexaboride (LaB₆) nanostructures, which concurrently act as effective heat transducers and ROS producers in the NIR-II window (86), are a prime example of this synergy. Similarly, integrating nanozymes represents a significant advance; cerium-based nanozymes have been developed that combine photothermal conversion with enzymatic activity to relieve hypoxia, thereby preventing the heat-shock resistance that often limits PTT efficacy (87). This 'all-in-one' approach is further exemplified by recent work on composite nanoplateforms that couple lanthanide luminescence with photothermal agents, offering a robust solution that outperforms monotherapies by attacking the

Table 6. Lanthanide-based photodynamic and synergistic photothermal therapeutic systems: Mechanisms and key findings

Category	Lanthanide material system	Mechanism / Principal outcome	Ref.
Pure PDT	Yb – Carbon dot–conjugated UCNP (UCNP@CDs)	Mechanism: Yb-doped UCNPs transfer 980 nm NIR energy via FRET to carbon-dot photosensitizers Outcome: Singlet oxygen generation for PDT	(75)
	2D Yb-TCPP Metal-Organic Frameworks (MOFs)	Mechanism: 2D MOF architecture minimizes photosensitizer aggregation Outcome: Enhanced ROS generation and PDT efficiency	(76)
	Er/Lu – core–shell UCNPs (Er-core/Lu-shell) with silica/PEG/folic acid/TCPP	Mechanism: Folate-mediated targeting combined with red-emitting upconversion activates TCPP photosensitizers in targeted cells Outcome: Selective PDT activity in HeLa cells	(77)
	Tm(III)-Terpyridine complex with light-harvesting antenna	Mechanism: Antenna ligand absorbs 630 nm light and transfers excitation energy to the Tm(III) complex Outcome: Intracellular ROS generation for PDT	(78)
	DO3A-Tb complex conjugated to polycyclic aromatic Hydrocarbons (Tb1-Tb6)	Mechanism: Tb acts as an energy donor to the attached photosensitizers through the antenna effect Outcome: Extended excitation capability and enhanced photosensitizer activation.	(79)
	Hollow Virus-Like CeO ₂ (HvCeO ₂) loaded with chlorin e6 derivative (LS-HB) and antibody (NRP1 mAb)	Mechanism: Hollow CeO ₂ structure exhibits catalase-like activity and converts H ₂ O ₂ to O ₂ . Outcome: Reduced tumor hypoxia and enhanced PDT efficacy	(80)
	CeOx NPs linked to pyropheophorbide-a (PPa) via MMP-2 peptide (EGPLGVRGK)	Mechanism: MMP-2-mediated cleavage activates the photosensitizer, while CeOx catalase-like activity converts endogenous H ₂ O ₂ to O ₂ Outcome: Tumor-responsive PDT activation and improved oxygen availability under hypoxic conditions	(81)
	Manganese-doped CeO ₂ nanocomposite (Mn _x Ce _{1-x} O ₂)	Mechanism: Mn doping modulates the Ce ³⁺ /Ce ⁴⁺ ratio and redox activity Outcome: Enhanced ROS generation for PDT together with antibacterial activity	(82)
	CeF ₃ NPs functionalized with flavin mononucleotide	Mechanism: CeF ₃ acts as a nanoscintillator, converting penetrating X-rays into UV light that activates FMN through energy transfer Outcome: X-ray-induced ROS generation for PDT	(83)
	Tb – AGuIX@Tb-P1 NPs	Mechanism: Tb absorbs X-ray photons and transfers the energy to porphyrin (P1) through resonance energy transfer Outcome: Singlet oxygen generation for X-ray-induced PDT	(84)
PDT+PTT	Terbium-Rose Bengal coordination nanocrystals (T-RBNs)	Mechanism: Crystalline Tb–Rose Bengal coordination minimizes energy dissipation during X-ray excitation Outcome: Efficient ROS generation under low-dose X-ray irradiation (0.5 Gy)	(85)
	LaB ₆ NPs	Mechanism: LaB ₆ facilitates ROS generation through its low work function and converts NIR light into heat through plasmonic resonance Outcome: Synergistic photodynamic and photothermal effects	(86)
	Regenerable CeO ₂ nanozymes + indocyanine green (ICG) in hyaluronic acid nanovesicles	Mechanism: CeO ₂ acts as a regenerable catalase mimic, converting H ₂ O ₂ to O ₂ and supporting ICG-mediated phototherapy Outcome: Enhanced synergistic PDT/PTT efficacy under hypoxic conditions	(87)
	Prussian blue functionalized erbium-doped hydroxyapatite (PE-Er-HAp)	Mechanism: Prussian Blue provides photothermal conversion, while erbium-doped hydroxyapatite provides the lanthanide-based structural and imaging component. Outcome: Simultaneous heat- and ROS-mediated tumor cell death under 808 nm laser irradiation	(88)
	Cancer-thylakoid hybrid membrane camouflaged TiO ₂ NPs	Mechanism: Thylakoid membrane provides photosensitizing and catalase-like activity, while the TiO ₂ core contributes to photothermal effects. Outcome: Synergistic PDT/PTT-mediated tumor cell killing	(89)

2D: two-dimensional; AGuIX: Activation and guidance by irradiation X-ray (polysiloxane-based nanoparticle platform); CDs: carbon dots; CeF₃: cerium(III) fluoride; CeO₂/CeOx: cerium oxide/non-stoichiometric cerium oxide (nanoceria); DO3A: 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid; EGPLGVRGK: glutamic acid–glycine–proline–leucine–glycine–valine–arginine–glycine–lysine peptide substrate; Er: erbium; FMN: flavin mononucleotide; FRET: Förster resonance energy transfer; Gy: gray (unit of absorbed radiation dose); H₂O₂: hydrogen peroxide; HAp: hydroxyapatite; HeLa: Henrietta lacks human cervical cancer cell line; ICG: indocyanine green; LaB₆: lanthanum hexaboride; Lu: lutetium; mAb: monoclonal antibody; MMP-2: matrix metalloproteinase-2; Mn: manganese; MOFs: metal-organic frameworks; NIR: near-infrared; NRP1: neuropilin-1; NPs: nanoparticles; O₂: molecular oxygen; P1: porphyrin-1; PB: Prussian blue; PDT: photodynamic therapy; PEG: polyethylene glycol; PPa: pyropheophorbide-a; PTT: photothermal therapy; Refs: references; ROS: reactive oxygen species; T-RBNs: terbium–Rose Bengal coordination nanocrystals; Tb: terbium; TCPP: tetrakis(4-carboxyphenyl)porphyrin; Tm/Tm(III): thulium/thulium(III); Tm₂O₃: thulium(III) oxide; UCNP/UCNPs: upconversion nanoparticle(s); UV: ultraviolet; Yb: ytterbium

tumor on both thermal and oxidative fronts (88, 89). Table 6 provides a detailed comparison of lanthanides used in PDT and PDT+PTT, along with their mechanisms.

Radiotherapy, radioimmunotherapy, and radiosensitization

Lanthanide-based radiotherapy employs cytotoxic beta and Auger emissions to precisely strike malignant cells. The pivotal VISION trial (90, 91) evidenced the significant efficacy of lutetium-177 (¹⁷⁷Lu) in treating neuroendocrine tumors via ¹⁷⁷Lu-DOTATATE (92) and prostate cancer via ¹⁷⁷Lu-PSMA-617. Beyond small-molecule ligands, Radioimmunotherapy (RIT) leverages ¹⁷⁷Lu-conjugated monoclonal antibodies to target distinct surface antigens. For instance, ¹⁷⁷Lu-labeled girentuximab has shown potential in stabilizing progressive metastatic clear cell renal cell carcinoma (93), while antibody-conjugated ¹⁷⁷Lu

modulates the osteosarcoma microenvironment (94). Moreover, ¹⁷⁷Lu-TLX591 (an anti-PSMA antibody) offers an alternative pharmacokinetic profile to small peptides (95).

Lanthanide-based microspheres have advanced locoregional therapy. Traditionally employed for bone palliation (96), samarium-153 (¹⁵³Sm) has been designed into stable, neutron-activatable constructions for high-dose hepatic radioembolization (97, 98). Similarly, by combining therapeutic beta emission with paramagnetic characteristics for MR dosimetry, Holmium-166 (¹⁶⁶Ho) enables image-guided Selective Internal Radiation Therapy (SIRT), which has proven beneficial for treating soft tissue sarcomas and liver metastases (99–101). Future directions involve ¹⁶¹Tb and Erbium-169 (¹⁶⁹Er), which target micrometastases with exceptional precision by using Auger electrons and low-

energy beta emissions (102, 103). Quantitative dosimetric evaluations have demonstrated the advantage of ^{161}Tb over ^{177}Lu at the cellular and tumor levels. Monte Carlo simulations estimated that ^{161}Tb deposited 22.9 versus 5.4 keV/decay for ^{177}Lu in isolated cells and 33.2 versus 10.3 keV/decay in confluent cell layers, corresponding to approximately 4.2-fold and 3.2-fold higher energy deposition, respectively. Furthermore, *in vivo* dosimetry calculations showed higher tumor absorbed doses for ^{161}Tb -PSMA-617 compared with ^{177}Lu -PSMA-617 (5.34 vs. 3.90 Gy/MBq), primarily due to the additional conversion and Auger electron emissions of ^{161}Tb (102). In contrast, although ^{169}Er has favorable physical characteristics for highly localized irradiation due to its low-energy β^- emissions and short tissue penetration range, quantitative dosimetric studies directly comparing ^{169}Er with ^{177}Lu or ^{161}Tb were not available at the time of writing this review. While these strategies rely on the intrinsic decay of unstable isotopes

to deliver therapeutic doses, non-radioactive lanthanides play an equally vital complementary role by enhancing the efficacy of external beam radiotherapy through their physical interaction with X-rays.

Compounds such as gadolinium NPs substantially increase the X-ray absorption cross-section of cancers by leveraging the high atomic number (Z) of lanthanides, generating Auger electrons for localized dose enhancement and lethal photoelectrons (104). Recent studies suggest this sensitivity extends beyond physical damage and may further improve targeted radionuclide therapy (105) and modulate autophagy (106). Cerium-based nanomaterials, in particular, use redox chemistry ($\text{Ce}^{3+}/\text{Ce}^{4+}$) to produce ROS and initiate apoptotic pathways (107), providing selective toxicity that preserves healthy tissue (108). Additionally, lanthanum compounds have expanded into binary proton therapy sensitization (109) and are successfully overcoming hypoxia-induced radioresistance (110). Table 7 summarizes

Table 7. Comparative landscape of lanthanide-enhanced radiotherapies and their biological effects across cancer models

Radioisotope & agent	Therapy category	Target/ cancer type	Key findings	Ref.
^{177}Lu -PSMA-617	Targeted radioligand therapy	mCRPC (PSMA-positive metastatic castration-resistant prostate cancer)	Phase 3 VISION trial: Established ^{177}Lu -PSMA-617 as standard of care, showing clear survival benefits	(90)
^{177}Lu -DOTATATE	Systemic PRRT (peptide receptor radionuclide therapy)	Gastrointestinal neuroendocrine tumors, somatostatin receptor-positive	Real-world retrospective study: Disease control rate: High efficacy with a 76.7% rate (partial response + stable disease)	(92)
^{177}Lu -Girentuximab	Radioimmunotherapy	Metastatic clear cell renal cell carcinoma Target: Carbonic anhydrase IX	Phase 2 clinical trial: Demonstrated proof-of-concept for stabilizing progressive disease, but dose-limiting hematological toxicity restricts repeated dosing	(93)
^{177}Lu -IF3 mAb	Radioimmunotherapy	Osteosarcoma Target: IGF2R (Insulin-like growth factor 2 receptor)	Preclinical TME modulation study: Effectively reduced IGF2R-positive tumor cells and osteosarcoma stem cell populations	(94)
^{177}Lu -TLX591	Radioimmunotherapy	mCRPC (PSMA-positive)	Real-world retrospective study: Achieved PSA decline in 38.9% of patients, with stable disease in 54.5% on imaging	(95)
^{153}Sm -EDTMP	Systemic radiotherapy	mCRPC with bone metastasis	Phase 2 randomized combination Trial: The study did not meet its primary endpoint of improving the proportion of patients progression-free at 4 months	(96)
^{153}Sm -Carbonate-PMA	Locoregional Radioembolization	Hepatic malignancies (e.g., hepatocellular carcinoma)	Neutron-Activation Study: Stability: Achieved excellent radionuclide retention (>98% over 120 hr), preventing systemic isotope leaching Specific activity: Produced high specific activity (4.40 GBq/g) suitable for therapy after 18 hr of neutron activation	(97)
^{153}Sm -AcAc-PLLA	Locoregional Radioembolization	Hepatic malignancies	Biodegradable microsphere development	(98)
^{166}Ho -Microspheres	Locoregional SIRT/ Radioembolization	Liver malignancies (hepatocellular carcinoma, cholangiocarcinoma, neuroendocrine tumors, and metastatic colorectal cancer)	Real-world multicenter registry: Validates ^{166}Ho -SIRT as a viable, safe, and effective option for both primary and secondary liver cancers outside of controlled trial settings	(99)
^{166}Ho -Hydroxyapatite	Locoregional SIRT	Liver malignancies	Preclinical dosimetry study	(100)
^{166}Ho -Microspheres	Microbrachytherapy (Intratumoral injection / neoadjuvant)	Soft tissue sarcomas (canine/veterinary model)	Prospective safety & efficacy study	(101)
^{161}Tb -PSMA-617	Systemic radioligand therapy	PSMA-positive mCRPC models	Preclinical comparative study: Demonstrated significantly superior cytotoxicity and survival benefit in mice compared to equal activities of ^{177}Lu -PSMA-617	(102)
^{169}Er -Citrate	Targeted radionuclide therapy	General oncology / prostate cancer (Tested in PC-3 and SK-OV-3 cell lines)	Production & feasibility study: <i>In vitro</i> assays confirmed a significant, dose-dependent reduction in tumor cell viability, validating its potential for future conjugation to targeting vectors (e.g., PSMA-617)	(103)
Gd-loaded Mesoporous Silica NPs (Gd-MSN)	Auger therapy (monochromatic X-ray)	Tumor spheroids (3D Model)	<i>In vitro</i> mechanistic study (3D spheroids)	(104)
Ultra-small gadolinium oxide nanocrystals (GONs)	X-ray radiosensitization	Non-small-cell Lung cancer	<i>In vitro</i> mechanistic study: Radiosensitization was driven by the activation of cytosolic autophagy and ROS production rather than apoptosis alone; it achieved a sensitizer enhancement ratio (SER) of ~19–26%	(106)
^{177}Lu -DOTA-trastuzumab + Gd-NPs (AGuIX)	Targeted radionuclide therapy (TRT)	Ovarian cancer (peritoneal carcinomatosis, HER2+)	preclinical <i>in vivo</i> combination study: Gd-NPs potentiated the efficacy of internal ^{177}Lu radiation	(105)

Continued Table 7.

PQQ-modified CeO ₂ NPs (CeO ₂ @PQQ)	X-ray radiosensitization	Adenocarcinoma (Murine EMT6/P)	Preclinical comparative study: Demonstrated selective cytotoxicity	(107)
Cerium fluoride NPs (CeF ₃)	X-ray modulation (sensitization & protection)	Breast cancer (MCF-7)	<i>In vitro</i> comparative selectivity study: Protected normal mesenchymal stem cells from radiation injury while selectively sensitizing MCF-7 cancer cells by inducing mitochondrial hyperpolarization	(108)
LaB ₆ -polyacrylic acid	Binary proton therapy	Breast cancer (EMT6/P, BT-474)	Preclinical <i>in vivo</i> efficacy study: Established LaB ₆ NPs as effective sensitizers for proton beam irradiation, showing significant tumor growth inhibition and biocompatibility <i>in vivo</i>	(109)
Lanthanum oxide (La ₂ O ₃)+cyanobacteria	Radiotherapy (hypoxia-targeted)	Rectal cancer	Preclinical <i>in vivo</i> therapeutic study: Developed a bioplatfrom where cyanobacteria produced oxygen to reverse hypoxia, while La ₂ O ₃ amplified radiation-induced ROS, triggering pyroptosis via the NLRP3 pathway	(110)

¹⁵³Sm: samarium-153; ¹⁵⁵Tb/¹⁶¹Tb: terbium-155/terbium-161; ¹⁶⁶Ho: holmium-166; ¹⁶⁹Er: erbium-169; ¹⁷⁷Lu: lutetium-177; 3D: three-dimensional; AcAc: acetylacetone; AGuIX: activation and guidance by irradiation X-ray (polysiloxane-based nanoparticle platform); BT-474: human breast ductal carcinoma cell line; CA IX: carbonic anhydrase IX; CeF₃: cerium(III) fluoride; CeO₂: cerium(IV) oxide (nanoceria); DOTA: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DOTATATE: DOTA-(Tyr³)-octreotate; EDTMP: ethylenediaminetetramethylenephosphonic acid; EMT6/P: murine mammary adenocarcinoma cell line; GBq/g: gigabecquerels per gram; Gd: gadolinium; GONs: gadolinium oxide nanocrystals; h, hours; HCC: hepatocellular carcinoma; HER2+: human epidermal growth factor receptor 2-positive; ICC: intrahepatic cholangiocarcinoma; IF3: insulin-like growth factor 2 receptor-targeting monoclonal antibody clone IF3; IGF2R: insulin-like growth factor 2 receptor; La₂O₃: lanthanum(III) oxide; LaB₆: lanthanum hexaboride; mAb: monoclonal antibody; MCF-7: michigan cancer foundation-7 human breast adenocarcinoma cell line; mCRC: metastatic colorectal cancer; mCRPC: metastatic castration-resistant prostate cancer; MSN: mesoporous silica nanoparticles; NET: neuroendocrine tumor; NLRP3: NLR family pyrin domain containing 3; NPs: nanoparticles; O₂: molecular oxygen; PC-3: human prostate cancer cell line; PLLA: poly(L-lactic acid); PMA: poly(methyl acrylate); PQQ: pyrroloquinoline quinone; PRRT: peptide receptor radionuclide therapy; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; PSMA-617: prostate-specific membrane antigen ligand 617; Refs: references; ROS: reactive oxygen species; SER: sensitizer enhancement ratio; SIRT: selective internal radiation therapy; SK-OV-3: human ovarian cancer cell line; TLX591: PSMA-targeted monoclonal antibody radioimmunoconjugate (rosmantuzumab); TME: tumor microenvironment; TRT: targeted radionuclide therapy

current clinical, translational, and preclinical applications of lanthanide- and radioisotope-based cancer therapeutics, including their targets, cancer types, and key outcomes.

Targeted drug delivery systems

Lanthanide-based nanostructures serve as flexible scaffolds for targeted oncology, aiming to minimize systemic toxicity through highly selective targeting mechanisms. In this context, targeted delivery and responsive delivery represent complementary but distinct approaches: targeted systems rely on specific biological recognition or preferential accumulation at tumor sites, whereas responsive systems are engineered to alter their drug-release behavior in response to endogenous or externally applied stimuli within the tumor microenvironment. A dominant strategy in this domain involves functionalizing lanthanide nanocarrier with ligands that recognize receptors overexpressed on tumor surfaces. For instance, researchers have exploited folate receptor overexpression in various cancer cell lines using folate-conjugated europium-doped yttrium vanadate (Eu³⁺:YVO₄) NPs to deliver cisplatin (111), and lanthanum strontium manganese oxide (LSMO) NPs to deliver doxorubicin (112), both showing enhanced cellular uptake and reduced systemic toxicity. Similarly, hybrid carriers such as ytterbium ferrite-loaded PLGA NPs have used β-cyclodextrin and folic acid to deliver camptothecin in breast cancer models (113). Moreover, Peptide-mediated strategies utilize specific ligands to enhance the penetration of CeO₂ NPs into difficult-to-treat tumors. Specifically, RGD (Arg-Gly-Asp) peptides are employed to target α_vβ₃ integrins for the delivery of doxorubicin to glioblastoma (114), while tumor-homing iRGD peptides facilitate the precision delivery of microRNA to esophageal carcinoma (115). These examples represent ligand-mediated targeting approaches, in which therapeutic localization is achieved through molecular recognition rather than stimulus-dependent activation. Complementing these surface modifications are “smart” responsive systems: pH-sensitive MOFs and coated phosphates take advantage of the acidic

tumor microenvironment for triggered payload release (116, 117), whereas intrinsic material properties, involving the osteotropism of cerium-substituted hydroxyapatite, facilitate tissue-specific accumulation in bone malignancies (118). Unlike targeted systems, these responsive platforms are designed to exploit pathological differences between tumor and normal tissues to control drug release or therapeutic activity after delivery. An additional challenge in the clinical translation of these nanocarriers is premature drug release during systemic circulation, which may reduce tumor-specific drug accumulation and increase off-target toxicity. Accordingly, researchers increasingly design responsive lanthanide-based platforms to improve cargo stability under physiological conditions while enabling controlled drug release only after exposure to tumor-specific stimuli, such as acidic pH or other pathological microenvironmental cues. Together, these structures enhance the therapeutic index by ensuring site-specific drug deposition through selective targeting, stimulus-responsive activation, or a combination of both strategies. Table 8 presents a consolidated overview of the different lanthanide systems employed for targeted and stimuli-responsive drug delivery.

Combination therapy and chemosensitization:

Beyond their use as structural components in drug delivery systems, lanthanides have emerged as effective chemosensitizers that can enhance the therapeutic index of conventional cytotoxic medications when administered as co-therapies. This synergistic strategy aims to overcome multidrug resistance (MDR) and reduce the required dose of systemic chemotherapeutics, thereby reducing off-target toxicity. Simple salts, such as lanthanum chloride (LaCl₃), have been demonstrated in experiments to reverse cisplatin resistance in ovarian cancer by suppressing the PI3K/Akt signaling pathway and inhibiting RAD51-mediated DNA repair (120-122). Furthermore, lanthanum coordination complexes (e.g., KP772) have effectively addressed MDR in leukemia by up-regulating pro-apoptotic factors and restoring doxorubicin therapeutic

Table 8. Mechanistic overview of lanthanide systems for tumor-targeted therapeutics

Lanthanide system	Payload (Drug)	Targeting/release mechanism	Application / Target	Ref.
Europium-doped yttrium vanadate (Eu ³⁺ :YVO ₄)	Cisplatin	Active: Folic acid ligand	Reduced systemic toxicity Murine melanoma (B16F10) Male C57BL/6 mice	(111)
LSMO	Doxorubicin	Active: Folic acid ligand	Breast cancer (MDA-MB231)	(112)
Ytterbium ferrite-loaded PLGA NPs	Camptothecin	Active: Folic acid ligand	Breast cancer (MCF-7)	(113)
CeO ₂	Doxorubicin	Active: RGD peptide (Integrin targeting)	Glioblastoma (GL261 and U87-MG)	(114)
CeO ₂ / Graphdiyne	microRNA (miR-181a)	Active: iRGD Peptide (Tumor homing)	Esophageal carcinoma (KYSE30, KYSE180)	(115)
La/Tm-MOF@SiO ₂	Doxorubicin	Responsive: pH-triggered release	Liver cancer (HepG2)	(116)
Lanthanum Phosphate (LaPO ₄)	siRNA (anti-EGFR)	Responsive: pH / Chitosan mucoadhesion	Colorectal cancer (HT-29)	(117)
Ce-substituted Hydroxyapatite	Doxorubicin	Active: Osteotropism (Bone-seeking)	Osteosarcoma (MG-63)	(118)
Gadolinium Oxide (Gd ₂ O ₃)	Curcumin	Passive: Bovine serum albumin coating	Nasal squamous cell carcinoma (CNE-1)	(119)

B16F10: murine melanoma cell line; BSA: bovine serum albumin; Ce: cerium; CeO₂: cerium(IV) oxide (nanoceria); CNE-1: human nasopharyngeal/nasal squamous cell carcinoma cell line; EGFR: epidermal growth factor receptor; Eu³⁺:YVO₄, europium(III)-doped yttrium vanadate; Gd₂O₃: gadolinium(III) oxide; GL261: murine glioblastoma cell line; HepG2: human hepatocellular carcinoma cell line; HT-29: human colorectal adenocarcinoma cell line; iRGD: internalizing arginine-glycine-aspartic acid peptide; KYSE30/ KYSE180: human esophageal squamous cell carcinoma cell lines; La: lanthanum; La/Tm-MOF@SiO₂: lanthanum and thulium metal-organic framework core-shell nanoparticles coated with silica; LaPO₄: lanthanum phosphate; LSMO: lanthanum strontium manganite (La_{1-x}Sr_xMnO₃); MCF-7: michigan cancer foundation-7 human breast adenocarcinoma cell line; MDA-MB-231: human breast adenocarcinoma cell line; MG-63: human osteosarcoma cell line; miR-181a: microRNA-181a; MOF: metal-organic framework; NPs: nanoparticles; pH: potential of hydrogen; PLGA: poly(lactic-co-glycolic acid); Refs: references; RGD: arginine-glycine-aspartic acid peptide; SiO₂: silicon dioxide (silica); siRNA: small interfering ribonucleic acid; Tm: thulium; U87-MG: human glioblastoma multiforme cell line

activity (123). Additionally, lanthanide-based NPs show synergistic cytotoxicity; cerium and La₂O₃ NPs have been shown to enhance the efficacy of paclitaxel, 5-fluorouracil, and temozolomide-radiotherapy regimens, reducing the required therapeutic dose (124-126). Table 9 summarizes the synergistic effects of lanthanide agents with conventional anticancer therapies.

Lanthanide-based theranostics (integrated systems)

Precision oncology has shifted with the convergence of therapeutic intervention and diagnostic imaging into unified “theranostic” platforms, driven largely by the lanthanide series’ adaptable nuclear and electronic properties. These components enable the development of “all-in-one” systems in which a single ionic species functions as both a therapeutic effector and a contrast agent through paramagnetism or luminescence. Gd³⁺ and Nd³⁺ imaging capabilities have recently been successfully coupled with field-induced therapies, such as PTT and photocatalysis; for instance, Nd³⁺ doped graphene quantum dots utilize deep-tissue NIR-II fluorescence to track siRNA gene therapy (127), vacancy-engineered Bismuth ferrite (BiFeO₃) doped with La³⁺ releases tumor-killing ROS under ultrasonic stress while enhancing MRI/CT contrast (128), and Eu³⁺ MOFs sensitize tumors to microwave dynamic therapy while reporting drug release

via luminescence (129). At the same time, Gd³⁺-based “nanomaterials” and polymer conjugates enable MRI-directed thermal ablation (24, 130, 131).

Beyond these external field-responsive systems, lanthanides’ intrinsic nuclear properties enable seamless incorporation into radiotheranostics and neutron capture therapies. ¹⁵⁷Eu is a distinct theranostic agent that emits photons for SPECT imaging as well as lethal Auger electrons or particles for targeted cell damage (132). Subsequently, the high thermal neutron capture cross-section of ¹⁵⁷Gd is being utilized in dual-modal compounds like Gd₁₀B₆ NPs and PSMA-targeted ligands, which optimize localized DNA damage via Auger cascades under strict MRI guidance (133-135), thereby demonstrating the potential of lanthanides to bridge the gap between diagnosis and precision treatment. Table 10 summarizes multimodal lanthanide systems used for cancer diagnosis and therapy.

Challenges and future perspectives

Despite lanthanides’ phenomenal versatility for oncological applications, their path from bench to bedside is now hampered by considerable obstacles in safety aspects and pharmacological optimization. The biological fate of lanthanide-based agents after systemic administration remains an important consideration, as their biodistribution,

Table 9. Synergistic anti-cancer effects of lanthanide agents with conventional therapies

Lanthanide agent	Combined therapy	Target cancer model	Key mechanism/ Finding	Ref.
LaCl ₃	Cisplatin	Ovarian cancer (Cisplatin-resistant SKOV3/DDP)	Inactivates PI3K/Akt signaling; down-regulates RAD51 to inhibit DNA repair and reverse resistance	(120, 121)
LaCl ₃	Cisplatin	Ovarian cancer xenografts (mice) (COC1 and COC1/DDP cells)	<i>In vivo</i> confirmation of synergy; significant tumor growth inhibition compared to monotherapy	(122)
Lanthanum Complex (KP772)	Doxorubicin; Vincristine	Leukemia & lymphoma (MDR lines)	Overcomes P-gp-mediated resistance by up-regulating the pro-apoptotic protein Harakiri (HRK)	(123)
CeONPs	Paclitaxel	Breast cancer (MCF-7)	Synergistically inhibits cell migration and adhesion, while enhancing cytotoxic efficacy	(124)
Gum-Stabilized CeONPs	5-Fluorouracil	Colon cancer (HT-29)	Significantly lowers the IC ₅₀ of 5-Fluorouracil, allowing for effective treatment at reduced drug dosages	(125)
La ₂ O ₃ NPs	Temozolomide+Radiation	Glioblastoma (U87)	Radio-chemo-sensitization; induces autophagy and apoptosis more effectively than single modalities	(126)

5-Fluorouracil: 5-FU pyrimidine analog chemotherapeutic; Akt: protein kinase B; CeO₂ NPs: cerium(IV) oxide nanoparticles (nanoceria); COC1/COC1/DDP: human ovarian carcinoma cell line/cisplatin-resistant variant; DDP: diamminedichloroplatinum(II) (cisplatin); DNA: deoxyribonucleic acid; HRK: harakiri pro-apoptotic protein; HT-29: human colorectal adenocarcinoma cell line; IC₅₀: half-maximal inhibitory concentration; KP772: lanthanum(III) tris(1,10-phenanthroline) trichloride complex; La₂O₃ NPs: lanthanum(III) oxide nanoparticles; LaCl₃: lanthanum(III) chloride; MCF-7: michigan cancer foundation-7 human breast adenocarcinoma cell line; MDR: multidrug-resistant/ multidrug resistance; NPs: nanoparticles; P-gp: P-glycoprotein (ATP-binding cassette sub-family B member 1); PI3K: phosphoinositide 3-kinase; RAD51: RAD51 recombinase protein; Refs: references; SKOV3/SKOV3/DDP: human ovarian adenocarcinoma cell line/cisplatin-resistant variant; U87: human glioblastoma multiforme cell line (U87-MG)

Table 10. Lanthanide-based theranostic systems: Imaging modalities, therapeutic mechanisms, and key outcomes

Lanthanide-based platform	Modalities (Diagnosis / Therapy)	Mechanism & key outcome	Ref.
Nd-doped graphene quantum dots	NIR-II fluorescence/Gene therapy	Real-time tracking of siRNA delivery to KRAS/EGFR mutant cells; deep tissue imaging	(127)
La-doped BiFeO ₃	MRI (T ₂), CT/Piezocatalysis	Ultrasound triggers ROS generation and pyroptosis; La-doping enhances catalytic efficiency	(128)
Eu-MOF nanocomposite	Fluorescence / Microwave thermo-chemotherapy	MOF structure sensitizes cells to microwave heating; fluorescence tracks drug release	(129)
Gd ₂ O ₃ /Au nanomatryoshkas	MRI (T ₁)/PTT	Plasmonic gold shell generates heat while the Gd-oxide core provides stable MRI contrast	(24)
Gd-doped carbon dots	MRI, Fluorescence/PTT	Multimodal imaging ensures precise laser targeting for photothermal ablation	(130)
Gd-chelated polymer	Photoacoustic imaging, MRI, NIR-II/PTT	Tri-modal imaging (Photoacoustic/MRI/Fluorescence) guides photothermal therapy	(131)
¹⁶¹ Tb-radioconjugates	SPECT/Auger electron	Mitochondria-targeting maximizes the lethal effect of short-range auger electrons	(132)
Gd ₁₀ B ₆ NPs	MRI, CT/GdNCT (Gadolinium neutron capture therapy)+BNCT (Boron neutron capture therapy)	Dual neutron capture therapy (Boron + Gadolinium) maximizes localized thermal energy release	(133)
¹⁵⁷ Gd-DOTA-PSMA	MRI/GdNCT	Novel PSMA-targeted agent for MRI-guided neutron capture therapy in prostate cancer	(134)
Gd ₂ O ₃ nanocrystals	MRI (Potential)/Radiosensitization	Enhances the relative biological effectiveness of carbon ion radiotherapy	(135)

¹⁵⁷Gd: gadolinium-157; ¹⁶¹Tb: terbium-161; Au: gold; BiFeO₃: bismuth ferrite (bismuth iron oxide); BNCT: boron neutron capture therapy; CT: computed tomography; DOTA: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; EGFR: epidermal growth factor receptor; Eu: europium; Eu-MOF: europium-based metal-organic framework; Gd: gadolinium; Gd₁₀B₆: gadolinium hexaboride; Gd₂O₃: gadolinium(III) oxide; GdNCT: gadolinium neutron capture therapy; KRAS: Kirsten rat sarcoma virus oncogene homolog; La: lanthanum; MOF: metal-organic framework; MRI: magnetic resonance imaging; Nd: neodymium; NIR-II: second near-infrared optical window (1000–1700 nm); NPs: nanoparticles; PSMA: prostate-specific membrane antigen; PTT: photothermal therapy; Refs: references; ROS: reactive oxygen species; siRNA: small interfering ribonucleic acid; SPECT: single-photon emission computed tomography; T₁/T₂: longitudinal relaxation time (T₁-weighted); T₂/T₂: transverse relaxation time (T₂-weighted); Tb: terbium

clearance, and long-term safety depend heavily on chemical speciation, including free Ln³⁺ ions, coordination complexes, and nanoparticulate formulations. Stable coordination complexes generally show more predictable pharmacokinetic profiles, whereas dissociation may release free lanthanide ions that preferentially accumulate in mineralized tissues because of their strong affinity for phosphate-containing matrices and hydroxyapatite. In contrast, the mononuclear phagocyte system predominantly recognizes lanthanide-based nanoparticles, resulting in preferential uptake and retention in the liver and spleen, where prolonged residence may increase the risk of chronic toxicity and inflammatory responses. Experimental studies have also shown that intravenously administered lanthanides are rapidly cleared from circulation but redistribute primarily to the liver, bone, and spleen, which together account for most of the retained lanthanide burden. Consequently, optimizing coordination stability, nanoparticle physicochemical properties, and biodegradability, along with comprehensive long-term pharmacokinetic and biodistribution studies, remains essential to ensure the safety and successful clinical translation of lanthanide-based theranostic platforms (18, 22, 136, 137).

The release of free lanthanide ions *in vivo*, in particular the long-term tissue retention of Gadolinium, is a significant concern. To prevent transmetalation or dissociation in physiological fluids, coordination complexes with superior thermodynamic stability and kinetic inertness must be developed (138). Additionally, the clinical utility of lanthanide-based nanomaterials depends on strict control of synthetic parameters such as size, shape, and surface chemistry to ensure biocompatibility, biodegradability, and minimal non-specific uptake by the reticuloendothelial system. Another important safety consideration is how lanthanide-based nanomaterials interact with the innate immune system. As demonstrated for engineered nanoparticles, complement activation is strongly influenced by surface morphology, surface chemistry, surface charge, and protein corona formation, which can modulate inflammatory responses and ultimately affect the circulation time and biological performance of nanomedicines. Consequently, rational surface engineering and appropriate surface coatings should be considered when designing

lanthanide-based nanoplatforms to minimize undesirable immune activation while maintaining therapeutic efficacy (139, 140). Further studies should prioritize developing “smart,” stimuli-responsive probes and carriers that can be selectively activated by distinctive tumor microenvironment characteristics, such as acidic pH or specific enzyme activity, thereby raising the therapeutic index. Beyond patient safety, the environmental implications of lanthanide-based technologies should also be considered as their biomedical and industrial applications continue to expand. Increasing production and clinical use of lanthanide-containing materials may release them into aquatic and terrestrial environments during manufacturing, use, or disposal. Although current environmental concentrations are generally considered low, the persistence of lanthanides and lanthanide-based nanoparticles, evidence of bioaccumulation in certain aquatic organisms, and limited understanding of their long-term environmental transformations highlight the need for comprehensive ecological risk assessment. Future investigations should therefore evaluate the environmental fate, bioavailability, chronic ecotoxicity, and life-cycle impacts of lanthanide-based nanomaterials under environmentally relevant conditions, while promoting sustainable design and disposal strategies for next-generation theranostic platforms (141, 142). Ultimately, more complete mechanistic insight into lanthanide-bio interactions, along with enhanced structure-activity relationship research, is needed to pave the way for next-generation clinical trials and the successful establishment of lanthanides as safe, efficient theranostic agents.

Conclusion

Incorporating lanthanide chemistry into oncology represents a crucial transition from monomodal diagnostics to precision theranostics. As explored in this review, the distinct 4f-electronic features of the lanthanide series—ranging from the high magnetic moment of Gd³⁺ to the sharp luminescence of Eu³⁺ and the radiotherapeutic decay of ¹⁷⁷Lu—have enabled the fabrication of systems that map tumor architecture and deliver targeted cytotoxicity. However, the trajectory of the present study is no longer

defined simply by the discovery of new physical qualities, but also by an in-depth comprehension of their biological outcome; addressing challenges of kinetic stability and systemic toxicity is now necessary for clinical application. Critically, this analysis assumes that the ultimate advantage of lanthanides is their unique “isostructural modularity.” Because ionic radii contract gradually across the series, therapeutic and diagnostic ions could be swapped within the same chelating scaffold with negligible impact on pharmacokinetics. The capacity to create chemically identical “matched pairs” provides a streamlined regulatory pathway and a level of personalized dosimetry that other material classes cannot match, establishing lanthanides not only as supplemental agents but as the fundamental foundations of next-generation precision oncology.

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Authors' Contributions

M E designed the study, collected and processed the data, and prepared the initial draft of the manuscript, including visualizations. A M and E S critically revised and edited the article, provided final approval of the version to be published, supervised the work, and secured funding.

Conflicts of Interest

None.

Declaration

We have not used any AI tools or technologies to prepare this manuscript.

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Corrected Proof