Nanoparticle-Enabled Cancer Theranostics: Recent Advances in Diagnosis, Targeted Therapy, and Immunomodulation

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Abstract

Nanoparticles have rapidly become central tools in oncology, enabling higher-resolution cancer diagnosis and more effective, less toxic therapies through precisely engineered physicochemical and biological properties. This article reviews recent advances in nanoparticle-based strategies in cancer biomedicine, emphasizing mechanisms of tumor targeting, image contrast enhancement, controlled drug and gene delivery, and integration with photothermal, photodynamic, and immunotherapies. Key nanoparticle classes (lipid-based, polymeric, inorganic, and biomimetic systems) are discussed in relation to conventional chemotherapy, radiotherapy, biologics, and emerging cell-based and gene-based treatments. We critically examine benefits, including improved efficacy and specificity, as well as limitations such as off-target accumulation, immunogenicity, manufacturing complexity, and translational gaps between preclinical models and clinical practice. A comparative framework highlights how nanoparticle platforms reshape the therapeutic index and diagnostic performance versus non-nano approaches. Finally, we outline future directions toward smart, stimuli-responsive, and immunomodulatory nanotheranostics and the standards needed to realize their clinical potential.

Keywords: nanoparticles, cancer, diagnosis, therapy, drug delivery, imaging, phototherapy, immunotherapy, nanomedicine

Introduction

Nanotechnology has transformed contemporary cancer research by enabling manipulation of materials at the 1–100 nm scale, where size-dependent optical, magnetic, and surface phenomena can be exploited for selective tumor imaging and therapy. Nanoparticles (NPs) can be engineered to exploit the enhanced permeability and retention (EPR) effect, as well as active ligand-mediated targeting, to increase accumulation of therapeutic and diagnostic payloads in tumors while limiting exposure to normal tissues. This has prompted the development of diverse nanomedicines, including liposomal formulations, polymeric micelles, inorganic metal and metal-oxide nanoparticles, dendrimers, and biomimetic nanosystems designed for chemotherapy, gene therapy, phototherapy, and immunotherapy. Recent reviews underscore that nanoparticle-based cancer technologies not only improve drug delivery

but also enable novel strategies such as nanoprobes for early detection, nanobiosensors for liquid biopsy, and multifunctional theranostic platforms that couple imaging with therapy. Despite remarkable preclinical progress, translation into routine clinical oncology remains uneven, and a critical comparison with conventional and other emerging modalities is necessary to define where nanoparticles provide the greatest added value and what challenges must be overcome.

In cancer diagnosis, nanoparticle-based contrast agents and probes improve sensitivity and specificity of imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), and optical imaging by enhancing signal-to-noise ratios and enabling molecularly targeted visualization of tumor-associated biomarkers. Nanobiosensors and circulating nanoprobes are being explored to detect cancer-related nucleic acids, proteins, and metabolites in blood and other biofluids at low concentrations, potentially shifting the diagnostic window toward earlier disease stages. On the therapeutic side, nanoparticle-based drug delivery systems have shown the ability to increase intratumoral drug concentrations, overcome multidrug resistance, and support combination regimens such as chemotherapy plus photothermal therapy or immunotherapy in a single platform. In parallel, “smart” nanoparticles responsive to pH, redox state, enzymes, or external stimuli such as light and magnetic fields are enabling spatiotemporally controlled release and image-guided interventions.

Conventional cancer treatments—including surgery, cytotoxic chemotherapy, and radiotherapy—have achieved important survival benefits but are frequently limited by non-specific toxicity, systemic side effects, and incomplete eradication of microscopic disease. Novel biologic and cellular approaches such as immune checkpoint inhibitors, CAR-T cells, and oncolytic viruses offer higher specificity but face issues of heterogeneous responses, immune-related toxicities, and challenges in delivery to solid tumors. Nanoparticle-based strategies are increasingly integrated with these modalities, either to enhance drug delivery (e.g., nanoformulated chemotherapeutics), improve radiosensitization and phototherapy, or modulate the tumor immune microenvironment to potentiate immunotherapies. Consequently, understanding the mechanistic interplay between nanoparticle properties, tumor biology, and host responses is critical for rational design and clinical translation of next-generation nano-oncology platforms.

Methods

This review synthesizes current evidence on nanoparticle applications in cancer diagnosis and therapy from peer-reviewed articles, focusing on publications from approximately 2020 onward that address mechanistic advances and translational relevance. Priority was given to comprehensive reviews, clinical or late preclinical studies, and mechanistic investigations describing nanoparticle design, targeting

strategies, bio-distribution, therapeutic and diagnostic performance, and safety profiles in oncology. Data were conceptually organized to compare nanoparticle-based approaches with conventional chemotherapy, radiotherapy, biologics, and other emerging modalities in terms of efficacy, specificity, toxicity, delivery route and control, and clinical applicability.

We classified nanoparticle systems broadly as lipid-based, polymeric, inorganic/metal-based, and biomimetic or hybrid constructs, with subcategories for photothermal, photodynamic, and immunomodulatory designs. For the comparative analysis, representative examples of each class and comparator modality were selected based on reported in vivo performance and, where available, clinical trial data. As this is a narrative review, no formal meta-analysis or quantitative pooling of effect sizes was performed; instead, qualitative trends in benefits and limitations were extracted from the literature.

Results

Nanoparticles in cancer diagnosis

Nanoparticle-based diagnostic systems leverage size, surface chemistry, and material composition to improve tumor detection by enhancing contrast or enabling molecularly targeted imaging. Superparamagnetic iron oxide nanoparticles (SPIONs) and other magnetic nanomaterials increase MRI sensitivity by altering T1 or T2 relaxation, allowing better delineation of primary and metastatic lesions. Gold nanoparticles, quantum dots, and upconversion nanoparticles provide strong optical or photoacoustic contrast for high-resolution imaging and intraoperative guidance, sometimes combining fluorescence with CT or MRI contrast in a single platform. Functionalization of nanoparticle surfaces with antibodies, peptides, aptamers, or small molecules enables specific recognition of targets such as HER2, EGFR, PSMA, and integrins, improving tumor-to-background ratios compared with non-targeted contrast agents. In addition, nanoprobes and nanobiosensors are engineered to detect circulating tumor DNA, microRNAs, exosomes, and other biomarkers, which may facilitate earlier diagnosis and minimal residual disease monitoring via liquid biopsy approaches.

Several studies highlight that nanoparticle-based imaging agents can support multimodal imaging, where a single construct is visible in multiple modalities such as MRI/PET/optical, thereby providing complementary anatomical, functional, and molecular information. Metal nanoparticles, especially gold and hafnium oxide, have been explored as CT contrast agents due to their high X-ray attenuation, and some of these platforms also act as radiosensitizers that enhance local dose deposition during radiotherapy. Importantly, diagnostic nanoparticles can be integrated with therapeutic payloads to form theranostic systems that allow simultaneous imaging and therapy, enabling treatment planning, real-time guidance, and post-therapy response assessment

within the same platform. Nonetheless, challenges remain in precisely quantifying accumulation, understanding long-term biodistribution, and ensuring safety of inorganic cores, especially when repeated imaging or high doses are required.

Mechanisms of nanoparticle-mediated cancer therapy

Nanoparticles improve cancer therapy through multiple mechanisms, including enhanced delivery of small-molecule drugs, nucleic acids, proteins, and combinations thereof. Liposomes and polymeric nanoparticles encapsulate chemotherapeutic agents, altering their pharmacokinetics and increasing tumor accumulation via the EPR effect while reducing systemic exposure, which can lower dose-limiting toxicities compared with free drugs. Functionalized metal nanoparticles, such as gold and other inorganic systems, can carry cytotoxics or gene-silencing agents and have been shown to improve targeting, gene knockdown, and controlled drug release via external stimuli such as light or magnetic fields. Polymeric micelles and dendrimers enhance solubility and stability of hydrophobic anticancer drugs and can co-deliver multiple agents, thereby enabling synergistic chemotherapy or chemo–immunotherapy combinations. Importantly, nanoparticles are being used to deliver siRNA, miRNA, mRNA, CRISPR components, and plasmids for gene regulation and genome editing in tumors, addressing delivery barriers that limit many nucleic acid therapeutics.

Photothermal therapy (PTT) and photodynamic therapy (PDT) have been significantly advanced by nanoparticle-based platforms that improve photothermal conversion efficiency, reactive oxygen species (ROS) generation, and tumor-selective accumulation. In PTT, nanoparticles such as gold nanorods, carbon-based materials, and semiconducting polymers absorb near-infrared light and convert it to heat, inducing localized tumor ablation while sparing surrounding tissues. In PDT, nanoparticle carriers deliver photosensitizers that generate ROS upon light activation, and nanostructures help overcome limitations such as poor solubility, off-target phototoxicity, and tumor hypoxia by co-delivering oxygen-generating or hypoxia-relief components. Multifunctional nanoplatforms combining PTT and PDT with chemotherapy or immunomodulators show synergistic antitumor effects and can induce immunogenic cell death, thereby enhancing systemic antitumor immunity. These mechanistic advances are fostering the development of "smart" nanotherapeutics that can respond to tumor microenvironment cues (pH, redox state, enzymes) or external triggers to achieve spatiotemporally precise therapy.

Nanoparticles and cancer immunotherapy

Nanoparticle-based drug delivery systems are increasingly used to enhance cancer immunotherapy, particularly in solid tumors where immunosuppressive microenvironments and physical barriers limit the efficacy of checkpoint inhibitors and adoptive cell therapies. Nanocarriers can deliver immunomodulatory agents such as cytokines, agonistic antibodies, small-molecule inhibitors, and nucleic acids to specific

immune cell populations or tumor sites, thereby amplifying local immune activation while reducing systemic toxicity. For example, nanoparticles have been designed to co-deliver phototherapeutic agents and immune checkpoint inhibitors, enabling phototherapy-induced immunogenic cell death followed by checkpoint blockade to achieve systemic tumor control, including abscopal effects. Other platforms encapsulate toll-like receptor agonists, STING agonists, or vaccine antigens, enhancing antigen presentation and T cell priming while protecting labile components from degradation.

Recent work on "immunotheranostic" nanoparticles combines imaging, immune modulation, and conventional cytotoxic therapy in a single construct, enabling real-time monitoring of immune responses and treatment outcomes. Inorganic nanoparticle-based immunotheranostics, such as those employing metal or metal-organic frameworks, integrate diagnostic imaging capabilities with delivery of immune checkpoint inhibitors, adjuvants, or other immunoregulatory molecules to improve response rates and durability. Moreover, nanoparticles can modulate the tumor microenvironment by reprogramming tumor-associated macrophages, normalizing vasculature, and alleviating hypoxia, thereby creating conditions more favorable for immune effector cell infiltration and function. Although these approaches show promising preclinical efficacy, translating complex immunomodulatory nanoplatforms to the clinic will require careful evaluation of immune safety, long-term biodistribution, and interactions with standard immunotherapies in diverse patient populations.

Safety, toxicity, and translational considerations

While nanoparticle-based cancer therapies offer the potential to reduce off-target toxicities compared with conventional cytotoxic drugs, safety and biocompatibility remain critical concerns for clinical translation. Organic nanocarriers such as liposomes and biodegradable polymers are generally better tolerated, yet they can still induce complement activation, infusion reactions, or liver accumulation, and require optimization of size, surface charge, and PEGylation to minimize adverse effects. Inorganic nanoparticles, including metals and metal oxides, may generate long-term concerns related to persistence, organ accumulation, and oxidative stress, necessitating rigorous evaluation of clearance pathways and chronic toxicity. Furthermore, the EPR effect varies widely between tumor types and patients, and in some human cancers it appears less pronounced than in preclinical models, which may limit the expected targeting advantage of some nanoformulations.

Manufacturing, reproducibility, and regulatory considerations present additional challenges for complex multifunctional nanomedicines. Batch-to-batch variation in size distribution, surface functionalization, and drug loading can significantly influence pharmacokinetics and therapeutic performance, making robust quality control

essential. Regulatory pathways for nanomedicines often require extensive characterization and safety data, and the lack of standardized assays for nanoparticle characterization and biological evaluation can slow development. Economic and practical factors—such as scalability, cost of goods, and compatibility with existing clinical workflows—also impact the adoption of nanoparticle-based diagnostics and therapeutics in oncology. Consequently, early integration of translational considerations into nanoparticle design, along with harmonized standards for characterization and preclinical testing, will be crucial to expand the number of clinically approved nano-oncology products.

Comparative analysis: nanoparticle-based versus conventional and emerging techniques

The following table summarizes key differences between nanoparticle-based methods and representative conventional or emerging modalities across major dimensions relevant to cancer research and clinical translation. Information reflects trends reported in recent reviews and studies comparing nanoformulations with free drugs or other treatment paradigms.

Table 1. Comparative overview of nanoparticle-based and other cancer research/therapy modalities

Modality	Representative examples	Efficacy (tumor control, drug exposure)	Target specificity (tumor vs normal)	Toxicity profile	Delivery and control	Clinical applicability and status
Nanoparticle-based chemotherapy	Liposomal doxorubicin, albumin-bound paclitaxel, polymeric micelles	Often improved intratumoral drug concentration and prolonged exposure versus free drug, with maintained or enhanced response rates in selected cancers	Enhanced passive targeting via EPR and potential active ligand targeting; still subject to inter-patient variability in accumulation	Reduced systemic toxicities such as cardiotoxicity or hypersensitivity compared with conventional formulations, but risk of infusion reactions and class-specific effects persists	Intravenous administration dominates; limited spatiotemporal control beyond pharmacokinetics, though stimuli-responsive systems are emerging	Several agents approved and integrated into standard of care; others in clinical trials for solid tumors and hematologic malignancies
Conventional chemotherapy	Free small-molecule cytotoxics (e.g., cisplatin, paclitaxel)	Broadly effective but often constrained by dose-limiting toxicity, leading to suboptimal tumor	Largely non-specific, targeting rapidly dividing cells in both tumors and healthy tissues such	High systemic toxicity including myelosuppression, neuropathy, and organ damage; narrow	Typically intravenous or oral with limited control over distribution and timing; dosing adjusted	Widely used standard treatment across tumor types; extensive clinical

		exposure in some patients	as bone marrow and gut epithelium	therapeutic index	mainly by body surface area or organ function	experience but constrained by resistance and toxicity
Nanoparticle-based phototherapy (PTT/PDT)	Gold nanorods, semiconducting polymer nanoparticles, photosensitizer-loaded nanocarriers	Effective local tumor ablation and growth control; combination with chemo- or immunotherapy can yield synergistic effects	High spatial specificity due to light targeting plus nanoparticle accumulation; molecular targeting possible via surface ligands	Primarily localized damage with relatively low systemic toxicity; risks include local inflammation, off-target phototoxicity, and thermal injury if misapplied	Requires light delivery (often NIR) to tumor; stimuli-responsive designs enable on-demand activation and controlled release	Several PDT agents approved (mostly non-nano); multiple nano-PTT/PDT platforms in preclinical and early clinical development
Radiotherapy ± radiosensitizing nanoparticles	External beam RT with gold or hafnium-based nanoparticles	Enhanced local dose deposition and tumor cell kill when nanoparticles are present; potential for dose reduction to normal tissues	Physical targeting via beam shaping plus biological modulation by nanoparticle accumulation; degree of selective uptake varies	RT-related toxicities remain but may be mitigated by improved dose conformality; nanoparticle-specific toxicity depends on material and clearance	Precision external control over dose and timing; nanoparticles may allow image-guided, theranostic approaches	Standard RT widely used; nanoparticle radiosensitizers advancing through clinical trials for selected cancers
Nanoparticle-enhanced immunotherapy	NP delivery of checkpoint inhibitors, cytokines, vaccines, adjuvants	Potentially improved response rates and durability by overcoming local immunosuppression and enhancing antigen presentation	High specificity achievable by targeting immune cell subsets or tumor microenvironment components; off-target immune effects still possible	May reduce systemic immune-related adverse events via localized delivery but carries risk of exaggerated local inflammation or cytokine release	Routes include intravenous, intratumoral, or subcutaneous injection; tunable release kinetics and co-delivery of multiple immunomodulators	Predominantly preclinical and early clinical; integrates with approved checkpoint inhibitors and experimental cell therapies
Immune checkpoint inhibitors (non-nano)	Anti-PD-1, anti-PD-L1, anti-CTLA-4 antibodies	High efficacy in subsets of patients with responsive tumor types;	Target-specific but systemic modulation of immune	Immune-related adverse events (colitis, hepatitis, endocrinopathi	Intravenous infusions at fixed intervals; minimal	Widely approved in multiple indications; cornerstone

		many non-responders and acquired resistance	checkpoints leads to widespread immune activation	es) can be severe and require immunosuppression	control over tissue distribution beyond pharmacokinetics	of modern oncology
Nanoparticle-based gene delivery	siRNA, miRNA, mRNA, CRISPR systems in lipid/polymer/inorganic NPs	Promising knockdown or editing of oncogenes and resistance pathways in preclinical models; clinical efficacy still being established	Sequence-specific targeting with potential tumor-selective delivery via ligands; off-target gene modulation and innate immune sensing remain concerns	Toxicity depends on carrier and cargo; risks include immune activation, off-target editing, and organ accumulation	Typically systemic or local injection; can enable controlled, transient expression or silencing with tunable dosing schedules	A few nucleic acid nanomedicines approved outside oncology; multiple cancer-directed candidates in clinical trials
CAR-T and cell-based therapies (non-nano)	Autologous CAR-T cells, TCR-engineered T cells	High efficacy in hematologic malignancies; limited and heterogeneous responses in solid tumors due to trafficking and microenvironment barriers	Highly specific antigen recognition; risk of on-target off-tumor effects if antigens also expressed on normal tissues	Potential for cytokine release syndrome and neurotoxicity; long-term immune modulation with uncertain late effects	Complex ex vivo manufacturing; administration usually intravenous with in vivo expansion difficult to modulate precisely	Approved for several hematologic cancers; active trials in solid tumors and earlier lines of therapy

Discussion

Recent advances underscore that nanoparticles offer a versatile platform to address multiple shortcomings of conventional cancer diagnostics and therapeutics through improved targeting, controlled release, and integration of imaging and therapy. In diagnostics, nanoparticle contrast agents and nanoprobes can significantly enhance sensitivity and specificity of imaging and biomarker detection, potentially enabling earlier disease detection and better response assessment compared with traditional agents. On the therapeutic side, nanoformulated chemotherapeutics, photothermal and photodynamic nanoplatforms, and nanocarrier-based gene and immunotherapies collectively shift the therapeutic index by concentrating activity in tumors and limiting systemic toxicities. However, heterogeneity in the EPR effect, tumor vascularization, and microenvironmental barriers across patients and tumor types complicates the generalization of these benefits, and indicates that patient stratification and personalized design may be necessary to fully realize the potential of nano-oncology.

The integration of nanotechnology with immunotherapy is particularly promising, as it enables local delivery of potent immunomodulators and co-ordination of antigen release with checkpoint blockade, thereby amplifying systemic antitumor immunity while potentially mitigating immune-related adverse events. Nanoparticle-based phototherapies can induce immunogenic cell death and release of tumor antigens, which, when coupled with nano-delivered checkpoint inhibitors or adjuvants, may generate abscopal effects and improved control of metastatic disease. Additionally, nanoparticles can be tailored to reprogram tumor-associated macrophages, normalize vasculature, and alleviate hypoxia, enhancing T cell infiltration and function, which are key hurdles for both checkpoint inhibitors and cell-based therapies in solid tumors. Nonetheless, the complexity of these multi-component systems raises challenges for manufacturing, regulatory approval, and mechanistic interpretation, and calls for standardized frameworks to evaluate immunological safety and efficacy.

Safety and translational challenges remain central concerns that limit the widespread clinical adoption of nanoparticle-based cancer interventions despite a growing body of evidence supporting their benefits. Organic nanocarriers have relatively favorable safety profiles but still require careful tuning to avoid complement activation and off-target organ accumulation, while inorganic nanoparticles pose unique questions regarding long-term retention and potential toxicity. The discrepancy between robust EPR-based targeting in animal models and more variable behavior in human tumors underscores the need for better translational models and non-invasive tools to quantify nanoparticle delivery in patients. Moreover, cost, scalability, and the need for sophisticated imaging or light-delivery infrastructure can limit access in routine clinical practice, particularly in resource-constrained settings. Emerging guidelines advocate for early integration of manufacturability, standardized characterization, and regulatory considerations into nanoparticle design to avoid late-stage failures and accelerate clinical translation.

Looking ahead, the field is moving toward smart, adaptive, and highly integrated “immunotheranostic” nanoparticles that couple real-time sensing of tumor biology with on-demand release of therapeutics and dynamic modulation of the immune microenvironment. Advances in materials science, such as stimuli-responsive polymers, DNA origami, and biomimetic coatings derived from cell membranes or extracellular vesicles, are expected to improve biocompatibility, circulation half-life, and immune evasion while enabling multi-targeted strategies. Coupling nanoparticle platforms with computational modeling, imaging-based patient selection, and bioinformatic analysis of tumor and immune profiles may support precision nano-oncology, where specific designs are matched to individual patients based on predicted delivery and response patterns. Ultimately, rigorous comparative studies against best-available non-nano treatments, combined with attention to patient-centered outcomes

and health system feasibility, will determine where nanoparticle-based approaches become standard-of-care versus niche or adjunctive therapies in clinical oncology.

Conclusion

Nanoparticle-based technologies have reshaped the landscape of cancer research by offering multifunctional platforms that enhance diagnostic accuracy, improve therapeutic index, and enable sophisticated integration of imaging, cytotoxic therapy, and immune modulation. By tuning size, composition, and surface chemistry, nanoparticles can concentrate drugs and imaging agents within tumors, enable spatiotemporally controlled therapies such as photothermal and photodynamic treatments, and support targeted delivery of nucleic acids and immunomodulators. Compared with conventional chemotherapy, radiotherapy, and many biologic approaches, nanoformulations often provide superior tumor selectivity and reduced systemic toxicity, while also facilitating innovative theranostic and immunotheranostic strategies. At the same time, variability in tumor biology, safety concerns—especially for inorganic systems—and manufacturing and regulatory complexities highlight the need for meticulous design, standardized characterization, and robust translational pipelines. As smart, stimuli-responsive, and immune-integrated nanoplatforms progress from bench to bedside, their most impactful role is likely to be within personalized, combination regimens that strategically exploit their strengths in targeting, control, and multimodal functionality to achieve durable cancer control with fewer adverse effects.

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