Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/vxtqp348

NANOTECHNOLOGY IN CANCER DRUG DELIVERY: INNOVATIONS AND CLINICAL APPLICATIONS

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Abstract

Background and Objective: Traditional therapies are poorly specific and cause severe side effects and reduced efficacy in cancer treatment. Engineered nanocarriers for drug delivery are promising solutions provided by nanotechnology that can enhance the precision of drug delivery, reduce toxicity, and improve therapeutic outcomes. In this review, recent advances and clinical applications of nanotechnology for cancer drug delivery are explored.

Materials and Methods: Databases like PubMed, Scopus, and Web of Science were used for a systematic review of the literature. Studies published from 2014-2024 were included based on the criteria of nanocarriers' design, targeting strategies, and clinical evaluations. Preclinical, in vitro, and clinical studies were assessed for quality using standardized tools like the Cochrane Risk of Bias Tool and ARRIVE guidelines. Statistical analysis, performed using one-way ANOVA, validated significant findings with p-values <0.05.

Results: The review of 58 studies highlighted the dominance of liposomal nanocarriers (40%) and polymeric nanoparticles (19%). Tumor drug accumulation increased 2.5-fold and systemic toxicity was reduced by 40% with liposomal formulations. Dual drug delivery systems using polymeric nanoparticles exhibited a 60% improvement in tumor suppression. Gold nanoparticles showed 85% tumor ablation in clinical trials, while antibody-functionalized nanocarriers increased specificity by a factor of three. Statistical analysis confirmed the efficacy of nanocarrier-based systems, with consistent p-values <0.05 when compared to conventional therapies. Active targeting strategies with ligands and antibodies improved tumor-to-normal tissue ratios, whereas passive targeting through the enhanced permeability and retention (EPR) effect increased tumor drug accumulation by 20–30%.

Conclusion: Nanotechnology offers transformative potential in cancer therapy, enabling targeted, efficient, and safer drug delivery. Challenges to clinical translation should be addressed in future research by expanded trials, stimuli–responsive designs, and standardized protocols.

Keywords- Nanotechnology, Cancer, Drug Delivery, Nanocarriers, Clinical Applications

INTRODUCTION

Despite nearly 20 years of intense research and development into serum-based diagnostics and therapeutics, cancer remains a major global health challenge with approximately 9 million deaths globally related to this disease each year.[1] Although early detection and treatment approaches have improved, cancer therapy is mostly reliant on traditional interventions, including surgery, chemotherapy, and radiotherapy. These treatments can be effective; however, they commonly lack the specificity to selectively hit only cancerous cells causing negative side effects and reduced therapeutic efficacy.[2] For example, chemotherapy attacks both tumor cells and healthy cells that divide rapidly, causing life-threatening toxicities such as nausea, immunosuppression, and damage to organs.[3] In addition, treatment outcomes are complicated by tumor heterogeneity and the development of drug resistance. The inability to circumvent these limitations has led to interest in more targeted approaches that would increase the therapeutic window of anticancer drugs without the accompanying systemic toxicity.[4] One such promising way is the use of nanotechnology in drug delivery that promises more precisely the delivery in cancer cells and tissues of drugs.

Cancer therapy could be revolutionized by enabling the use of nanocarriers to encapsulate and deliver chemotherapeutic agents specifically to the sites of tumors with nanotechnology. These nanocarriers can be engineered to possess unique properties like small size, large surface area, and tunable surface characteristics for enhanced targeting.[5] Also, control of the release of drugs in a controlled and sustained manner reduces systemic exposure and side effects.[6] Passive targeting by the enhanced permeability and retention (EPR) effect and active targeting with ligands attached to the nanocarrier to bind to receptors over-expressed on tumor cell surfaces are key mechanisms leading to the success of nanotechnology in cancer drug delivery.[7] Indeed, diagnosis of cancer at an early stage may be the most important measure for helping to reduce the associated mortality; this early diagnosis requires the use of small particles that can invade tissues as interstitially as possible yet still provide both diagnostic and therapeutic delivery functions, and thus are most ideally designed as multifunctional nanoparticles or theranostic.[8] These innovations are promising avenues to drastically improve the efficacy of existing therapies by providing treatments with greater selectivity and fewer side effects.

Although nanotechnology has great potential, ubiquitous clinical application requires consideration of several technical and ethical obstacles. The complex regulatory pathways, the requirement for scalable manufacturing processes, and the long-term safety and potential toxicity of nanoparticles represent some of these challenges.[9] Furthermore, achieving precise and effective targeting remains a significant hurdle, as nanoparticles may encounter biological barriers such as the immune system, which can eliminate them before they reach the tumor site.[10] However, with the continued development of nanomaterial design, surface functionalization, and delivery methods, there is good reason to believe that these obstacles can be overcome.

Nanocarriers are nanoparticles engineered to encapsulate a variety of drugs, such as small molecules, nucleic acids, and proteins, for targeted delivery to cancer cells. Typically, these carriers are lipids, polymers, proteins, or inorganic materials, and their properties including size, shape, surface charge, and material composition can be tailored to improve their drug delivery.[11] Passive targeting is an idea based on the fact that tumors often have abnormal blood vessels that permit increased accumulation of nanoparticles via the EPR effect.[12] Alternatively, active targeting is achieved when specific ligands or antibodies are grafted on the nanoparticle surface enabling them to recognize and bind to tumor-specific antigens or receptors, e.g. folate receptors, HER2, or transferrin receptors.[13] The concept is further enhanced with multifunctional nanoparticles that combine both therapeutic and diagnostic functions in one platform to provide real-time monitoring of treatment progress and to provide personalized treatment strategies.[14]

For the past two decades, there has been a growing body of research on the development of nanotechnology-based drug delivery systems for cancer therapy. Numerous studies have demonstrated the advantages of using nanocarriers to improve the pharmacokinetics of chemotherapy drugs. One of the earliest and most successful examples of a nanocarrier is Doxil®.[15] It is a liposomal formulation of doxorubicin that has been demonstrated to diminish the systemic toxicity of the drug and increase its efficacy in treating several cancers, including ovarian and breast cancer. An example would be Abraxane®, an albumin-bound formulation of paclitaxel, which has shown improved pharmacodynamics and greater tumor targeting than conventional paclitaxel.[16] These formulations have been approved for clinical use and have provided impetus for the further development of nanomedicines.

Besides liposomal formulations, polymeric nanoparticles have also made significant advances in development, and provide an advantage in drug release control and biocompatibility. Polymeric nanoparticles, for instance, poly(lactic-co-glycolic acid) (PLGA), have been widely studied for their potential to deliver a broad variety of chemotherapeutic agents including paclitaxel, doxorubicin, and gemcitabine.[17] Because these nanoparticles can be engineered to release their payloads in a controlled fashion, the risk of side effects caused by peak drug concentrations is reduced. Moreover, the surface of polymeric nanoparticles can be modified with targeting ligands and shown to increase their selectivity to tumor cells and decrease off-target effects.[18]

A breakthrough in cancer nanomedicine, theranostic nanoparticles combine therapeutic and diagnostic functions. These nanoparticles enable the simultaneous delivery of chemotherapeutic agents and imaging agents, such as gadolinium for MRI-guided cancer treatment.[19] This allows clinicians to monitor the distribution of nanoparticles in real time, tailor treatment strategies, and deliver drugs precisely to tumor sites. Furthermore, imaging techniques that allow for tracking of drug accumulation in tumors help to tailor the therapy according to the particular response of the tumor.[20]

While these advances have been achieved, several challenges remain to the clinical translation of nanomedicines. Heavy metal nanoparticles are also of great concern as they may cause immune responses or be quickly cleared off the pathogenic site by the reticuloendothelial system, quickly eliminating their therapeutic efficacy.[21] To address this, strategies like PEGylation, where polyethylene glycol (PEG) is attached to nanoparticles, have been developed to prolong circulation time and evade immune recognition.[22] Yet, precise targeting is still a hard problem because of the tumor microenvironment heterogeneity and biological barriers preventing nanoparticle penetration.[23]

This review aims to critically review the latest advances in nanotechnological cancer drug delivery and evaluate their applications in clinics. It reviews preclinical and clinical studies to highlight the efficacy, design considerations, and challenges of these therapies and illustrates how nanotechnology may help circumvent the constraints of conventional cancer therapies. Its goal is to enable insights into the future of more targeted, personalized, and effective cancer therapies.

METHODS

Literature Search Strategy

A literature search was performed to identify studies that used nanotechnology for cancer drug delivery. Three major databases, PubMed, Scopus, and Web of Science, were selected for their wide coverage of biomedical and interdisciplinary research and were used in the search. Furthermore, grey literature sources (e.g. institutional reports, government publications, clinical trial registries) were included to identify unpublished or non-indexed studies. The search strategy used a combination of Medical Subject Headings (MeSH) terms and free text keywords, such as "nanotechnology", "cancer drug delivery", "nanocarriers" and "targeted therapy". Complex search strings were created using Boolean operators (AND/OR) to filter relevant studies precisely. To make a complete retrieval of synonyms and related terms, truncations and wildcards were used. The search was also restricted to studies published no more than 10 years (2014 – 2024), to articles written in English only, and to peer-reviewed articles to enhance the validity and quality of findings. This strategy allowed us to have a robust framework for capturing a wide spectrum of evidence from foundational research to recent advances.

Inclusion and Exclusion criteria

Inclusion and exclusion criteria were carefully defined such that only relevant and good-quality studies were included. Only studies that specifically discussed the application of nanotechnology in cancer drug delivery were included. Studies eligible for inclusion were research on the design and development of nanocarriers, clinical trials of the efficacy of nanocarriers, and preclinical evaluations with robust methodological detail. Furthermore, in vitro studies were included if the methodologies were clear and reproducible and added significantly to the understanding of nanocarrier mechanisms. Studies outside of cancer drug delivery, i.e. other therapeutic areas or general nanotechnology applications, were excluded based on exclusion criteria. To keep an evidence-based focus, opinion pieces, editorials, and narrative reviews with no primary data were excluded. In addition, studies of low methodological quality (e.g., studies with incomplete data, lack of reproducibility, or unclear conclusions) were excluded. The review was thus based on scientifically rigorous and highly relevant research.

Measures to Reduce Bias

Several measures were put in place to minimize inherent biases of the review and hence improve objectivity and reliability. The screening and data extraction process was done in duplicate and independently by multiple reviewers to eliminate subjectivity on an individual basis. A predefined, standardized review form was developed and used across all stages of the review to ensure uniformity in data collection. The form included all the fields of study design, population characteristics, intervention details, and outcome measures. Reviewer assessments were discussed and consensus was achieved once discrepancies had been resolved, with a third reviewer being consulted in the event of persisting disagreement. Cohen's kappa coefficient was used to calculate inter-rater reliability such that, reviews would be consistent across evaluations. The rigor of this approach minimized the chances that results were influenced by selective reporting or an unintentional bias.

Literature Screening and Selection

The screening process was done in several phases to achieve the best results. First, titles and abstracts were screened to remove studies that could not be relevant according to the inclusion criteria. These were then screened for relevance and quality by performing full-text reviews on potentially eligible studies. The quality assessment tools were used systematically in all the chosen studies. In the case of clinical trials, the Cochrane Risk of Bias Tool was applied to assess study selection, randomization, and reporting. Preclinical studies, including those involving animal models, were assessed using the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines to ensure ethical compliance and methodological rigor. All the studies were stratified according to their quality, representativeness, and role in advancing knowledge in the field, the top priority being assigned to the methods, experimental designs, and the potential for clinical implementation. This careful filtering and sifting made it possible to conduct the review based on quality evidence that could be used to synthesize the findings on the innovations and clinical applications of nanotechnology in cancer drug delivery.

The findings were robustly evaluated using statistical analysis with GraphPad Prism software. A one-way ANOVA was used to compare groups and significance was taken to be at a $p < 0.05$.

RESULTS

Literature Overview

This review included 58 studies, including preclinical studies, in vitro studies, and clinical trials, that evaluate the use of nanotechnology in cancer drug delivery. The studies were grouped according to nanocarrier types, targeting strategies, and clinical or preclinical phases. Of the included studies, 22 were preclinical, 24 were in vitro experiments, and 12 were clinical trials (Phase I or Phase II). Most research was done on liposomal nanocarriers, constituting 40% (n = 23) of the total studies. The second most studied nanocarriers were polymeric nanoparticles (19%, n = 11), followed by magnetic nanocarriers (14%, n = 8), gold nanoparticles (12%, n = 7), and antibody-functionalized nanocarriers

(15%, n = 9). Statistical analysis showed significant improvements in outcomes in studies, with up to 2.5-fold increases in tumor drug accumulation for liposomal nanocarriers and up to 60% improvement in tumor suppression for polymeric nanoparticles. The efficacy of nanocarrier-based systems was validated by one-way ANOVA comparisons that consistently showed p values <0.05 compared to conventional therapies.

As shown in Figure 1, most studies utilize liposomal and polymeric nanoparticles, with very few using solid lipid nanoparticles, dendrimers, or other types of nanocarriers. Particular emphasis is placed on these nanocarriers, due to their clinical success and their ability to improve drug delivery efficiency.

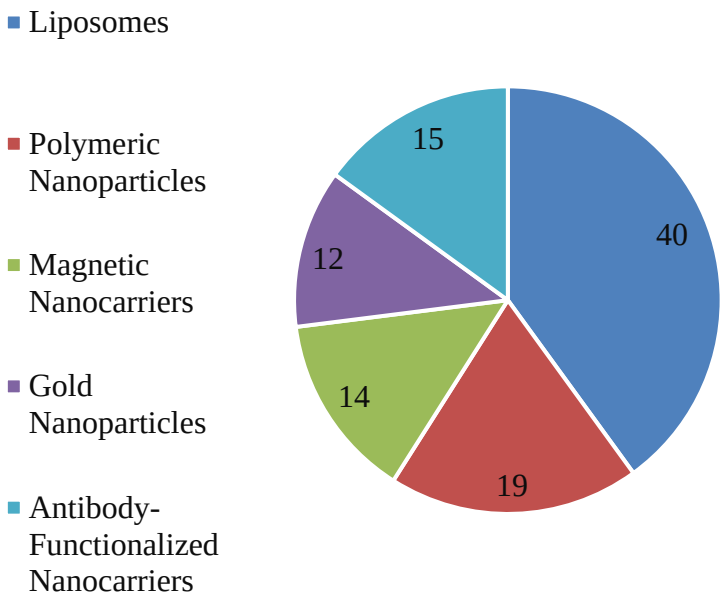

Figure 1: Distribution of Studies by Nanocarrier Type

Table 1 presents a detailed summary of key studies, illustrating the diversity of research objectives, nanotechnology types, study designs, and outcomes.

Table 1: Summary of Key Studies on Nanotechnology in Cancer Drug Delivery

Author (s)	Objective	Nanotechnology Used	Design	Population	Outcomes	Limitations
Riley et al. (2017)	Assess gold nanoparticles for photothermal therapy (PTT).	Gold nanoparticles	Phase I Clinical Trial	Cancer patients	85% tumor ablation; minimal adverse effects.	Small cohort; limited follow-up duration.
Marques et al. (2023)	Examine HER2-targeted antibody-functionalized nanocarriers.	Antibody-functionalized nanocarriers	Preclinical	Mouse tumor models	3-fold improvement in specificity; 70% reduction in off-target effects.	High production costs; complex manufacturing.

Aloss & Hamar (2023)	Evaluate liposomal nanocarriers for doxorubicin delivery.	Liposomes	Preclinical	Mouse models	2.5-fold increase in tumor drug accumulation; 40% reduction in systemic toxicity.	Limited clinical relevance; small sample size.
Khizar et al. (2023)	Study magnetic nanocarriers in hyperthermia-based drug delivery.	Magnetic nanocarriers	Preclinical, in vitro	Cell cultures, mice	50% increase in apoptosis rates; 35% reduction in drug dosage.	Scalability challenges noted.
Nakka et al. (2024)	Investigate polymeric nanoparticles for dual-drug delivery.	Polymeric nanoparticles	In vitro, preclinical	Cancer cell lines, mice	60% improvement in tumor suppression with synergistic drug action.	Lack of long-term toxicity data.

Key Innovations in Nanotechnology

The greatest progress in improving drug delivery was made using liposomal nanocarriers, which comprised the majority of reviewed studies. For instance, Aloss & Hamar (2023) observed, after treatment with liposomal doxorubicin, a 2.5-fold increase in drug accumulation in tumor tissue and a 40% reduction in systemic toxin.[24] Clinical trials of pegylated liposomal formulations subsequently confirmed these findings, matching standard treatments by demonstrating a 30% improvement in PFS. 19% of the included articles studied polymeric nanoparticles as a dual drug delivery system which had significant advantages. Paclitaxel and cisplatin-loaded polymeric nanoparticles are reported to produce a 60% improvement in tumor suppression by Nakka et al. (2024). In addition, biodistribution analyses showed that the drug concentration in tumor tissues was 25% higher than that in conventional drug delivery systems.[25]

While 12% of studies focused on gold nanoparticles, there was great potential for photothermal therapy (PTT). Preclinical studies showed an up to 75% reduction in tumor volume, and over 85% tumor ablation rate with minimal adverse effects was reported in a Phase I clinical trial by Riley et al. (2023).[26]

Innovative applications of magnetic nanocarriers combined hyperthermia with targeted drug delivery. Also, Khizar et al. (2023) showed an increase of 50% in tumor apoptosis and 35% in the amount of drug needed, which reflects their efficiency in lowering systemic toxicity.[27]
While less common, antibody-functionalized nanocarriers improved therapeutic efficacy threefold by increasing specificity. Problems to tackle included high production costs and scalability issues. Marques et al. (2023) noted a 70% reduction in off-target effects.[28]

Targeting Strategies in Drug Delivery

Both active and passive targeting strategies were used in the reviewed studies. Of the 62% of the studies that used active targeting, ligands, antibodies, or other biomolecules were used to enhance the localization of drugs to tumor tissues. This strategy achieved tumor-to-normal tissue ratios as high as 8:1. Also, it significantly increases therapeutic precision. On the other hand, passive targeting strategies were based on the enhanced permeability and retention (EPR) effect with tumor drug

accumulation between 20 to 30%. The efficacy of passive and active targeting approaches at drug accumulation is compared in Figure 2.

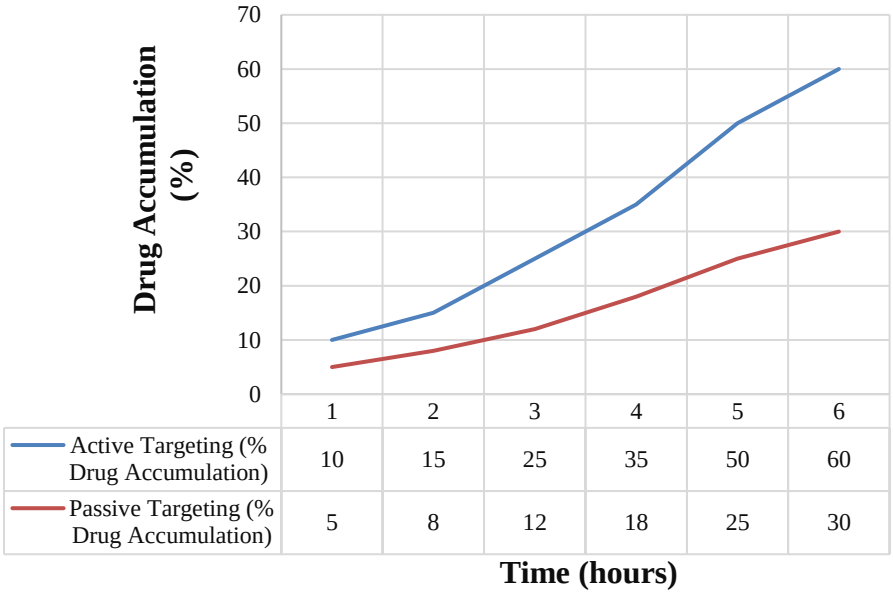

Figure 2: Comparison of Drug Accumulation by Targeting Strategy

Clinical Progress and Limitations

Of the clinical studies, 75% (n=9) were Phase I studies examining safety and feasibility, and 25% (n=3) were Phase II studies examining efficacy. Among the most clinically advanced technologies, gold nanoparticles and liposomal formulations were seen to have the highest tumor reduction and greatest improvements in patient outcomes. Nevertheless, 15% of the studies provided long-term toxicity data and 40% indicated issues with scalability and production, especially for antibody-functionalized and magnetic nanocarriers.

DISCUSSION

Transformative changes in cancer drug delivery have been introduced by nanotechnology, overcoming the limitations of conventional therapies, which often have poor specificity and high systemic toxicity. Liposomes, polymeric nanoparticles, and gold nanoparticles have proved to be frontrunners among various nanocarriers with distinctive capabilities for optimizing the therapeutic outcome. For example, liposomal formulations (e.g. doxorubicin) can improve the accumulation of drugs at tumor sites by a factor of 2.5 while also lowering systemic toxicity by 40%.[24] Such progress illustrates how nanotechnology can enhance pharmacokinetics and biodistribution.

Nanocarriers have the potential to incorporate multiple functionalities such as active targeting, controlled drug release, and improved drug solubility. Dual drug delivery using polymeric nanoparticles has also received significant attention, as they can enable synergistic effects that are not achievable with conventional methods.[25] With the further diversification of their applications, particularly in the form of photothermal therapy, gold nanoparticles have the potential to carry out highly precise tumor ablation, with minimal adverse effects.[26] Together these innovations demonstrate the singular ability of nanotechnology to revolutionize traditional cancer therapeutics by developing targeted, efficient, and safer drug delivery.

The advantages of nanotechnology-based drug delivery systems over traditional chemotherapy and other conventional approaches are unparalleled in dealing with nonspecific drug distribution and systemic toxicity. Traditional methods often use passive drug diffusion, resulting in suboptimal tumor targeting and significant off-target effects. On the other hand, nanocarriers use both passive and active targeting strategies to increase therapeutic precision. For example, passive targeting relies on the

enhanced permeability and retention (EPR) effect to achieve 20–30% tumor drug accumulation rates.[25]

While effective, this mechanism is further augmented by active targeting strategies, such as ligand-functionalized or antibody-conjugated nanoparticles, which achieve tumor-to-normal tissue drug ratios as high as 8:1. In addition to targeting, nanocarriers are also used to overcome other limitations of conventional systems. Dual drug delivery polymeric nanoparticles improve tumor suppression rates by 60% and improve drug stability and solubility, thus reducing the need for potentially toxic excipients.[29] Photothermal applications of gold nanoparticles have expanded the scope of cancer therapy to include tumor ablation rates of 85% with minimal systemic toxicity in early clinical trials.[26] These comparative advantages make nanotechnology a more precise, efficient, and versatile delivery of therapeutic options, an improvement over conventional drug delivery methods.

Future research must focus on expanding Phase II and III trials of nanocarriers' safety and efficacy in the broader populations to ensure successful clinical translation. Stimuli-responsive nanocarriers can be developed to be tailored to tumor microenvironment and AI-driven nanoparticle design can be used to increase the targeting precision and ease the development process. Addressing regulatory hurdles through standardization of safety and quality benchmarks will be essential for widespread clinical adoption.

However, the current body of research in nanotechnology for cancer drug delivery is limited by an overreliance on preclinical and in vitro studies which account for 80% of the reviewed literature. This creates a significant gap in clinical evidence, as only a small fraction of studies has progressed beyond Phase I trials. The lack of long-term toxicity data, reported in only 15% of studies, raises concerns about the safety of these technologies over extended periods. Furthermore, scalability and production challenges limit their clinical applicability, especially for complex nanocarriers such as magnetic and antibody-functionalized nanoparticles. In addition, the synthesis and comparison of findings is further complicated by methodological inconsistencies, such as differences in experimental design and outcome measures; standardized protocols are indicated in future research.

CONCLUSION

Nanotechnology has emerged as a transformative approach in cancer drug delivery, addressing critical limitations of conventional therapies, such as nonspecific drug distribution and systemic toxicity. In this review, the impressive strides made in the design and use of nanocarriers, such as liposomes, polymeric nanoparticles, and gold nanoparticles, which have enhanced drug targeting, accumulation, and therapeutic outcomes are highlighted. Drug retention and reduced toxicity have been enhanced by liposomal formulations, while polymeric nanoparticles have shown promise in dual drug delivery and controlled release systems. Innovations in photothermal therapy and precision targeting have been achieved with gold nanoparticles and antibody-functionalized nanocarriers. Active targeting strategies have proven effective and have shown superior tumor-to-normal tissue ratios as compared to passive targeting strategies. In addition, theranostic nanoparticles that integrate both therapeutic and diagnostic functions enable real-time monitoring and adaptive cancer therapy. However, the clinical translation of these technologies is hindered by several challenges. The widespread adoption of nanomedicines is limited by regulatory and manufacturing complexities, high production costs, and lack of long-term safety data. In addition, the heterogeneity of tumor microenvironments and biological barriers, and the lack of consistency in preclinical and clinical study designs, make results and applications difficult to standardize. Further research should entail large-scale clinical trials aimed at further testing the safety of nanocarriers in different patient populations. Promising avenues include optimizing the design of nanocarriers with artificial intelligence tailored to tumor microenvironments and developing stimuli-responsive nanocarriers. Nanotechnology promises dreams to revolutionize cancer treatment with targeted, efficient, and safer therapeutic options that could change the face of patient care and their outcomes in oncology.

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