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Nanotheranostics for Early Detection and Treatment of Minimal Residual Disease in Cancer

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ABSTRACT

Minimal residual disease (MRD) refers to the small population of malignant cells that persist after apparently successful cancer treatment and remain below the detection limit of conventional diagnostic tools. MRD is a major driver of cancer relapse, metastasis, and therapeutic resistance, representing a critical unmet need in oncology. Nanotheranostics—integrated nanoscale platforms that combine diagnostic and therapeutic functions—have emerged as a promising strategy for the early detection and targeted eradication of MRD. By exploiting unique tumor-associated biomarkers, microenvironmental cues, and cellular vulnerabilities, nanotheranostic systems enable highly sensitive imaging, real-time disease monitoring, and precision drug delivery. This review examines the role of nanotheranostics in addressing the biological and clinical challenges of MRD. We discuss the molecular basis of MRD, limitations of current detection and treatment approaches, and the design principles underlying nanotheranostic platforms. Emphasis is placed on multifunctional nanoparticles capable of simultaneous imaging and therapy, as well as stimulus-responsive systems tailored to the MRD niche. Preclinical advances, translational challenges, and future directions toward clinical implementation are critically analyzed. Collectively, nanotheranostics represent a transformative approach for improving long-term cancer control by enabling earlier intervention and preventing disease recurrence.

Keywords: nanotheranostics; minimal residual disease; early cancer detection; targeted therapy; precision oncology

INTRODUCTION

Minimal residual disease (MRD) represents a clinically elusive yet biologically consequential phase of cancer progression. Defined as the persistence of malignant cells after definitive therapy, MRD remains undetectable by standard imaging and histopathological techniques[1]. Despite low tumor burden, these residual cells retain the capacity to drive relapse, metastasis, and therapeutic resistance, making MRD one of the strongest predictors of poor long-term outcomes across both hematological malignancies and solid tumors[2, 3].

Biologically, MRD cells are distinct from bulk tumor populations. They often exhibit stem-like properties, including quiescence, enhanced DNA repair capacity, metabolic adaptability, and resistance to apoptosis[4, 5]. These features allow MRD cells to survive cytotoxic therapies that primarily target rapidly dividing cancer cells. In addition, MRD cells frequently reside in protective niches such as bone marrow, perivascular regions, or fibrotic tumor beds, where interactions with stromal cells, immune components, and extracellular matrix further promote survival. Epigenetic plasticity and phenotypic heterogeneity enable MRD cells to dynamically adapt to therapeutic pressure, contributing to disease recurrence months or even years after apparent remission[6].

Clinically, MRD has been extensively studied in leukemia and lymphoma, where sensitive molecular and flow cytometric assays have demonstrated strong correlations between MRD positivity and relapse risk. In solid tumors, however, MRD detection remains far more challenging due to anatomical complexity, limited accessibility, and the absence of universally applicable biomarkers[7]. Circulating tumor cells (CTCs),

circulating tumor DNA (ctDNA), and extracellular vesicles have emerged as surrogate indicators of MRD, yet their sensitivity and specificity vary widely depending on tumor type and disease stage[8].

Current therapeutic strategies largely fail to address MRD effectively. Adjuvant chemotherapy and radiotherapy aim to eliminate residual disease but often lack selectivity, leading to systemic toxicity without guaranteed eradication of MRD cells. Immunotherapies have shown promise, particularly in hematological cancers, but their efficacy can be limited by immune evasion mechanisms and the immunosuppressive microenvironment surrounding MRD niches[9]. Consequently, there is a pressing need for technologies that can both sensitively detect MRD at its earliest stages and deliver targeted therapy to eradicate residual malignant cells before overt relapse occurs[9].

Nanotheranostics offer a conceptual and practical framework to address this challenge. By integrating diagnostic and therapeutic functionalities within a single nanoscale system, nanotheranostics enable simultaneous detection, monitoring, and treatment of MRD. Such systems can be engineered to recognize tumor-specific biomarkers, respond to microenvironmental cues, and deliver therapeutic payloads with high precision[10]. Importantly, nanotheranostics have the potential to shift cancer management from reactive treatment of relapse to proactive intervention during the MRD phase, fundamentally altering the trajectory of disease progression[11, 12].

2. Principles and Design of Nanotheranostic Platforms

Nanotheranostics are multifunctional nanosystems designed to combine diagnostic imaging and therapeutic action within a single construct. Their design is guided by principles of nanotechnology, molecular targeting, and biomedical engineering, with the overarching goal of maximizing sensitivity, specificity, and therapeutic efficacy while minimizing off-target effects[13–15].

At the core of nanotheranostic platforms is the nanoscale carrier, which may consist of inorganic materials (e.g., gold nanoparticles, iron oxide, quantum dots), organic systems (e.g., liposomes, polymeric nanoparticles), or hybrid structures[16]. These carriers serve as scaffolds for the incorporation of imaging agents, targeting ligands, and therapeutic payloads. The nanoscale size range (typically 10–200 nm) allows favorable pharmacokinetics, prolonged circulation, and enhanced tissue penetration, which are critical for detecting and treating sparse MRD cell populations[16].

Targeting specificity is achieved through surface functionalization with ligands such as antibodies, peptides, aptamers, or small molecules that recognize MRD-associated biomarkers. In addition to molecular targeting, nanotheranostics can exploit physiological differences between residual tumor niches and normal tissues, including altered pH, redox state, enzyme expression, and immune composition[17]. Stimulus-responsive designs enable conditional activation of imaging signals or drug release, enhancing precision.

Imaging modalities integrated into nanotheranostics include fluorescence, magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), and photoacoustic imaging[18]. The choice of modality depends on sensitivity requirements, tissue depth, and clinical applicability. Therapeutic components may include chemotherapeutic agents, nucleic acids, immunomodulators, or photothermal and photodynamic elements. The co-localization of diagnostic and therapeutic functions enables real-time monitoring of drug delivery, target engagement, and treatment response.

3. Nanotheranostics for Early Detection of Minimal Residual Disease

Minimal residual disease (MRD) represents a clinically elusive yet biologically critical stage of cancer progression, characterized by small populations of malignant cells that persist following primary therapy[19, 20]. These residual cells often evade conventional diagnostic tools due to their low abundance and spatial dispersion, ultimately serving as the seed for relapse and metastasis. Consequently, early and precise detection of MRD is essential for timely intervention and improved patient outcomes. Nanotheranostic platforms—integrating diagnostic and therapeutic functionalities within a single nanoscale system—offer unprecedented sensitivity and specificity for MRD detection[21].

A key advantage of nanotheranostics lies in their ability to amplify diagnostic signals. Nanoparticles can encapsulate or conjugate large payloads of imaging agents, including fluorophores, magnetic resonance contrast agents, radionuclides, or photoacoustic probes[22]. This multivalent loading substantially enhances signal intensity compared to free probes, enabling the detection of extremely low tumor burdens. Furthermore, the physicochemical tunability of nanoparticles allows optimization of size, surface charge, and pharmacokinetics, promoting prolonged circulation and enhanced accumulation in MRD niches[22].

Liquid biopsy–based detection has emerged as a particularly promising application of nanotheranostics for MRD monitoring. Circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and tumor-derived extracellular vesicles are present at exceedingly low concentrations, especially in early residual disease[23]. Nanoparticles functionalized with tumor-specific antibodies, aptamers, or peptides can selectively bind these biomarkers, enabling magnetic, optical, or electrochemical enrichment and detection. Plasmonic nanoparticles enhance surface-enhanced Raman scattering or fluorescence signals, while magnetic nanoparticles facilitate rapid isolation from complex biological fluids. These approaches allow non-invasive, longitudinal monitoring of MRD dynamics, supporting real-time assessment of disease status[24].

For solid tumor MRD, nanotheranostics enable high-resolution imaging of microscopic residual lesions that are undetectable by conventional radiological techniques. Activatable nanoprobes represent a particularly powerful

strategy, generating imaging signals only in response to tumor-associated stimuli such as protease activity, acidic pH, hypoxia, or aberrant metabolic pathways[25]. This conditional activation significantly reduces background noise and false-positive signals, improving diagnostic accuracy. By revealing the presence and spatial distribution of MRD at earlier time points, nanotheranostics create a critical window for therapeutic escalation before overt relapse occurs[25].

4. Therapeutic Targeting of MRD Using Nanotheranostic Systems

While early detection of MRD is essential, its clinical value ultimately depends on the ability to eradicate residual malignant cells. MRD is frequently composed of therapy-resistant subpopulations, including dormant cells, cancer stem-like cells, and immune-evasive clones[26]. These cells often reside in protective microenvironments and exhibit altered metabolic and signaling profiles, rendering them refractory to conventional systemic therapies. Nanotheranostic systems are uniquely suited to address these challenges by enabling precise, localized therapeutic delivery coupled with real-time monitoring[26].

Nanotheranostics can selectively target MRD niches through surface functionalization with ligands recognizing tumor-specific antigens, stromal markers, or microenvironmental features. Once localized, these platforms deliver high local concentrations of chemotherapeutic agents, molecular inhibitors, nucleic acids, or protein therapeutics, minimizing systemic toxicity[27]. Microenvironment-responsive nanotheranostics further enhance selectivity by releasing their therapeutic payload only under specific conditions, such as acidic pH, elevated reactive oxygen species, or tumor-associated enzyme activity. This spatiotemporal control is particularly valuable in MRD, where overtreatment of normal tissues must be avoided[28].

Externally activatable nanotheranostics, including photothermal and photodynamic systems, offer additional precision. Upon exposure to near-infrared light, these nanoparticles generate localized heat or reactive oxygen species, inducing selective cytotoxicity in MRD cells while sparing surrounding healthy tissue[29]. Because activation is externally controlled, clinicians can precisely define the treatment field, making these approaches well-suited for eradicating residual disease in anatomically sensitive sites.

A defining feature of nanotheranostics is their ability to integrate therapeutic delivery with imaging feedback. Real-time visualization of nanoparticle accumulation, drug release, and treatment response enables adaptive therapy, where dosing and scheduling are adjusted based on MRD dynamics[30]. This closed-loop approach supports personalized treatment strategies, reduces unnecessary exposure, and increases the likelihood of complete MRD eradication before clinical relapse.

5. Immune-Modulating Nanotheranostics in MRD Control

The immune system plays a central role in controlling minimal residual disease, often determining whether residual cancer cells are eliminated or progress to overt relapse. Nanotheranostic platforms designed to modulate immune responses represent a powerful strategy for sustained MRD suppression, particularly when complete physical eradication of residual cells is not feasible[31].

Immune-modulating nanotheranostics can deliver immunotherapeutic agents directly to MRD niches, enhancing efficacy while minimizing systemic immune-related toxicity. These systems have been engineered to transport immune checkpoint inhibitors, cytokines, toll-like receptor agonists, and cancer vaccines. Targeted delivery enhances local immune activation, promoting cytotoxic T-cell infiltration and reprogramming immunosuppressive tumor microenvironments[32, 33]. For MRD, where tumor burden is low, even modest immune activation may be sufficient to maintain long-term disease control.

Importantly, nanotheranostics enable simultaneous imaging of immune engagement and therapeutic response. Imaging probes integrated into these platforms can visualize immune cell recruitment, cytokine release, or changes in tumor-associated inflammation[34]. This dual diagnostic–therapeutic capability allows clinicians to assess whether immune modulation is effectively controlling MRD, providing critical insight into treatment durability.

Additionally, nanotheranostic systems can be designed to induce immunogenic cell death, releasing tumor-associated antigens and danger signals that further stimulate antitumor immunity[35]. This approach transforms MRD from a hidden threat into a source of immune education, potentially establishing long-term immune surveillance and reducing the risk of recurrence.

6. Translational Challenges and Clinical Perspectives

Despite the compelling promise of nanotheranostics for MRD detection and treatment, several challenges impede their clinical translation. Manufacturing complexity remains a major obstacle, as multifunctional nanotheranostic systems require precise control over size, composition, surface chemistry, and payload integration[36]. Achieving large-scale reproducibility while maintaining consistent performance is essential for regulatory approval and clinical adoption. Long-term safety is another critical concern. Nanoparticles may accumulate in off-target organs such as the liver or spleen, raising questions about chronic toxicity, immunogenicity, and biodegradability. Comprehensive pharmacokinetic and toxicological studies are therefore required, particularly for systems intended for repeated MRD monitoring and treatment[37, 38].

Biological heterogeneity further complicates translation. MRD varies significantly across cancer types, treatment histories, and individual patients, necessitating adaptable and stratified nanotheranostic designs. Integration into existing clinical workflows will require robust biomarkers, standardized imaging protocols, and clear decision-making frameworks[39].

Looking forward, advances in materials science, systems biology, and artificial intelligence–guided nanoparticle design are expected to accelerate translation. By enabling rational optimization and patient-specific customization, these innovations may ultimately establish nanotheranostics as a cornerstone technology for MRD management and durable cancer control.

7. Conclusion and Future Directions

Nanotheranostics represent a paradigm-shifting approach for the early detection and targeted treatment of minimal residual disease in cancer. By unifying sensitive diagnostics with precision therapy, these platforms address the fundamental challenges that drive relapse and therapeutic failure. Continued progress in nanomaterial engineering, biomarker discovery, and clinical integration will be essential for realizing their full potential. As technologies mature, nanotheranostics are poised to transform MRD management from passive surveillance to active, personalized intervention, ultimately improving long-term cancer outcomes and patient survival.

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