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Multifunctional Nanotheranostics in Precision Oncology: Integrating Diagnosis, Imaging, and Targeted Therapy Across Solid Tumors

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Abstract:

Its value as a health burden is still important because cancer has been one of leading causes in the world where liver, lung, pancreatic, breast and brain cancers make up copious mortality and finalities. Conventional diagnostic and therapeutic modalities are frequently faced with delayed detection, insufficient tumor specificity, systemic toxicity, and the development of therapeutic resistance, emphasizing an imperative to develop integrated and selective strategies. To be consonant with above-mentioned definition led us to this systematic review summarizing the advances made from 2020 to 2025 in almost five main types of nanotheranostics (i.e. nansystems for simultaneous diagnosis and therapy) in cancer biology. Methods. A systematic literature search with PubMed, Scopus and Web of Science was conducted to identify any studies assessing the relationship between COVID-19 risk factors defined as a history of or concurrent chronic disease and COVID-19 infection or COVID-19-related mortality from January 2020 to June 2025. Inclusion Criteria Eligible studies were defined as those reporting on nanoplatforms having both diagnostic imaging and therapeutic function in liver, lung, pancreatic, breast or brain tumors; Data extracted included nanomaterial composition, imaging modality, therapeutic mechanism and experimental outcomes as well as physical indicators of translational feasibility. Results illustrate major advancements in metallic nanoparticles, polymeric and liposomal carriers, carbon-based nanomaterials and hybrid multifunctional systems that improve imaging sensitivity via different modalities including magnetic resonance imaging (MRI), positron emission tomography (PET) fluorescence and photoacoustic imaging while providing targeted therapeutic delivery through chemotherapy, photothermal therapy, photodynamic therapy and immunotherapy. Organ-targeting innovations such as blood brain barrier–permeable carriers, inhalable nano-platforms, stroma-modulating systems and receptor-targeted construct add to this precision. While preclinical and early clinical results have been promising, safety validation, regulatory approval, manufacture at scale and cost-effectiveness for healthcare delivery continue to pose challenges. Interdisciplinary collaboration and ongoing refinement of the technology are likely to foster clinical translation, paving the way toward global precision oncology.

Keywords: Nanotheranostics, multi-organ cancer, precision oncology, imaging-guided therapy, targeted drug delivery, clinical translation.

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1. Introduction

Cancer remains a leading cause of morbidity and mortality worldwide, with the global incidence projected to rise significantly in the coming decades. Among the most challenging cancers are liver (hepatocellular carcinoma), lung, pancreatic, breast, and brain tumors, which collectively contribute to millions of deaths annually[1]. Lung cancer continues to hold the highest mortality rate, followed by liver and pancreatic cancers, both of which are often diagnosed at advanced stages. Breast cancer is the most prevalent malignancy among women, while brain tumors such as glioblastoma represent some of the most aggressive and treatment-resistant cancers[2] (Table 1).

Traditional methods, including imaging (CT, MRI, and PET) and systemic chemotherapy or radiotherapy, have improved outcomes but remain limited by delayed diagnosis, non-specificity, toxicity, and drug resistance. Early detection is often hindered by the lack of sensitive biomarkers, while conventional treatments are plagued by systemic side effects and poor targeting efficiency. Furthermore, invasive biopsies are not always feasible for tumors located in sensitive regions such as the brain.

The convergence of nanotechnology and theranostics has opened a transformative pathway in oncology[8]. Nanotheranostics are multifunctional nanosystems that integrate diagnostic imaging and therapeutic modalities into a single platform. These nanosystems can:

- Enhance imaging sensitivity and specificity (MRI, PET, fluorescence, and photoacoustic imaging).
- Deliver drugs in a targeted manner, reducing systemic toxicity.
- Provide combinatorial therapies (chemotherapy, photothermal therapy, photodynamic therapy, and immunotherapy).
- Enable real-time monitoring of treatment response.

This paradigm shift from one-size-fits-all therapies to precision-guided, image-assisted treatments positions nanotheranostics as a frontier in personalized cancer management.

While numerous reviews exist for organ-specific nanotheranostic applications, there is limited systematic integration across multiple cancer types[9] (Figure 1). Given the distinct biological barriers associated with different cancers, such as the dense stroma in pancreatic tumors and the blood-brain barrier (BBB) in glioblastoma, comparing organ-specific advances can provide valuable insights into both universal design principles and unique therapeutic challenges. Between 2020 and 2025, nanotheranostic research has accelerated, yielding novel multifunctional nanoplatforms, translational models, and early-stage clinical applications[10].

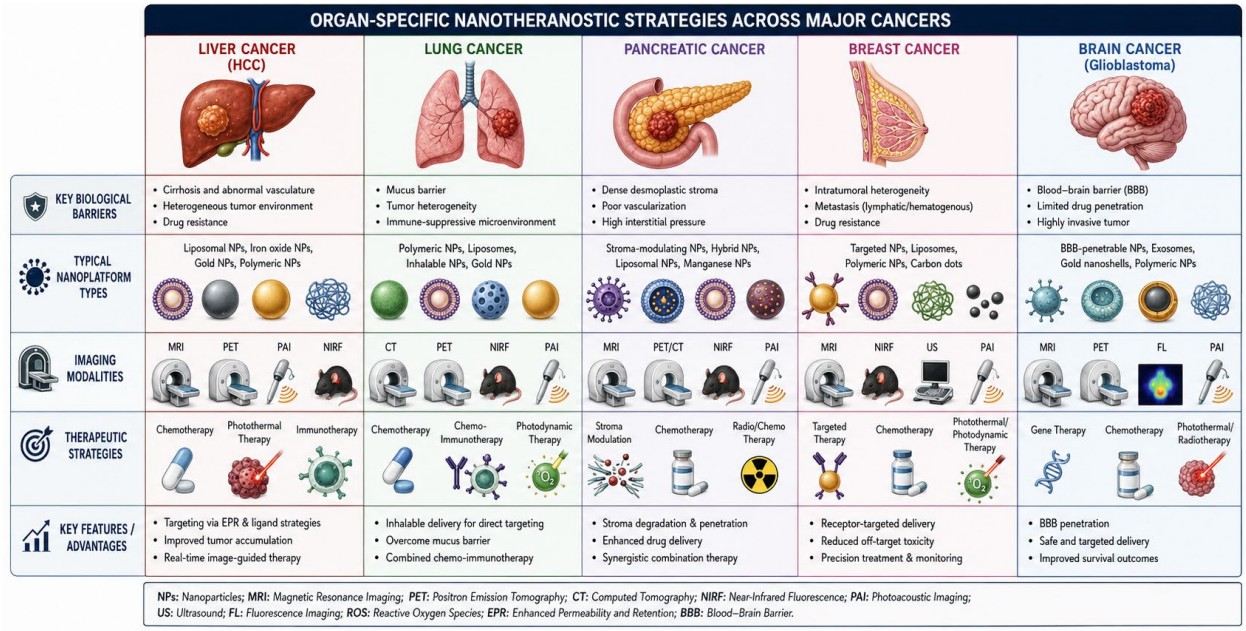

Figure 1. Organ-specific nanotheranostic strategies across major cancers. The schematic illustrates key biological barriers, nanoplatform types, imaging modalities, therapeutic strategies, and pecision oncology outcomes associated with liver, lung, pancreatic, breast, and brain cancers.

Table 1. Global Burden and Clinical Challenges of Major Cancers

Cancer Type	**Global Incidence**	**Major Clinical Challenges**	**Survival Rate**
Liver Cancer (HCC)	High	Late diagnosis, cirrhosis, drug resistance	Low
Lung Cancer	Highest mortality	Metastasis, late detection	Low
Pancreatic Cancer	Increasing	Dense stroma, poor drug penetration	Very Low
Breast Cancer	Most common in women	Recurrence, metastasis	Moderate-High
Brain Cancer (Glioblastoma)	Lower incidence	BBB barrier, therapy resistance	Very Low

2. Methodology

The data were collected from PubMed, Scopus and Web of Science relevant studies published between January 2020 and June 2025. We utilized keywords relevant to nanotheranostics, cancer and organ-specific cancers (liver, lung, pancreatic, breast and brain). The search was refined thanks to Boolean operators (AND, OR). Reference lists for selected papers were also checked. Only one peer-reviewed article published in English was included. We included studies that reported nanotheranostic systems with diagnostic and therapeutic components specific to liver, lung or pancreatic or breast or brain cancers. Laboratory and clinical studies were both included. Exclusion criteria included: reviews, editorials, conference abstracts and studies that did not specify combined diagnostic and therapeutic roles. Articles were excluded if they were not published in English, if their content reffered to another topic besides cancer or if the full text was unavailable. Methods: Two reviewers independently screened titles,

abstracts and full texts. Relevant information like the cancer type, nanoplatform design, imaging mode, therapy type and study results were logged using a standardized format. Discrepancies between reviewers were discussed to arrive at a consensus. A summary of the collected data was created and grouped by type of cancer. Comparing nanoplatform designs, imaging modalities, therapeutic approaches and highlighting key findings allowed us to assess research trends and breakthroughs as well as current challenges in the field of nanotheranostics.

Table 2. Classification of Nanotheranostic Platforms

Nanoplatform	**Examples**	**Imaging Modality**	**Therapeutic Function**	**Advantages**
Metallic Nanoparticles	Gold, Iron Oxide, Silver	MRI, CT, Photoacoustic	PTT, Drug Delivery	High imaging sensitivity
Polymeric Nanoparticles	PLGA, Dendrimers	MRI, Fluorescence	Controlled Drug Release	Biocompatible
Liposomes	PEGylated Liposomes	MRI, Fluorescence	Chemotherapy	FDA-approved
Carbon-based Nanomaterials	CNTs, Graphene, Carbon Dots	Fluorescence, Photoacoustic	PTT, Gene Delivery	High surface area
Hybrid Nanoplatforms	Gold-Iron Oxide, Liposome-Metal Hybrids	Multimodal Imaging	Combination Therapy	Multifunctionality

3. Nanotheranostic Platforms: An Overview

Nanotheranostics represent an innovative class of nanosystems that integrate diagnostic imaging and therapeutic functions into a single platform[11]. The versatility of these systems arises from the diversity of nanomaterials available and the ability to functionalize them with targeting ligands, imaging agents, and therapeutic payloads. Broadly, nanotheranostics can be classified into metallic nanoparticles, polymeric and liposomal nanocarriers, carbon-based nanomaterials, and hybrid/multifunctional systems. Each category offers unique physicochemical properties that can be exploited for precise cancer imaging and therapy. The following sections summarize their roles and mechanisms of action[12].

3.1 Types of Nanomaterials

3.1.1 Metallic Nanoparticles

Metallic nanoparticles, including gold, iron oxide, and silver nanoparticles, are among the most extensively investigated platforms. Gold nanoparticles (AuNPs) exhibit strong surface plasmon resonance properties, enabling their use in photothermal therapy (PTT) and photoacoustic imaging. Their surface can be readily functionalized with drugs, antibodies, or nucleic acids, making them adaptable for targeted cancer therapy[13]. Iron oxide nanoparticles (IONPs) serve as excellent magnetic resonance imaging (MRI) contrast agents and can be guided to tumor sites using external magnetic fields, thereby enhancing localized drug delivery. Silver nanoparticles, though less explored clinically due to toxicity concerns, have demonstrated intrinsic cytotoxic and antimicrobial activities, and when engineered appropriately, they can function as potent theranostic agents[14].

3.1.2 Polymeric and Liposomal Nanocarriers

Polymeric nanoparticles and liposomes provide biocompatibility and controlled drug release profiles. Polymeric nanocarriers such as poly(lactic-co-glycolic acid) (PLGA) or dendrimers can encapsulate hydrophobic and hydrophilic drugs simultaneously, offering dual- or multi-drug loading capabilities. Liposomes, on the other hand, are well-established nanocarriers approved for clinical use (e.g., liposomal doxorubicin)[15]. Their flexible bilayer structure enables co-delivery of chemotherapeutics with imaging agents, creating imaging-guided drug delivery systems. Modifications with polyethylene glycol (PEG) and targeting ligands extend their circulation half-life and tumor-specific accumulation via the enhanced permeability and retention (EPR) effect[16].

3.1.3 Carbon-Based Nanomaterials

Carbon-based nanostructures such as graphene, carbon nanotubes (CNTs), and carbon dots offer high surface-to-volume ratios, excellent electronic conductivity, and tunable optical properties. Graphene oxide (GO) provides a versatile platform for loading multiple drugs and imaging probes, while its photothermal conversion efficiency makes it suitable for PTT[17]. Carbon nanotubes penetrate cell membranes efficiently, serving as carriers for drugs and genes, and can also act as radiofrequency absorbers for hyperthermia therapy. Carbon dots are small (<10 nm) and exhibit inherent fluorescence, which facilitates real-time bioimaging along with drug delivery[18].

3.1.4 Hybrid and Multifunctional Systems

Recent advances have led to the design of hybrid nanotheranostic platforms that integrate two or more functional components into a single construct. For example, gold-coated iron oxide nanoparticles combine MRI contrast with photothermal properties, while liposome-metallic hybrids enable simultaneous controlled drug release and imaging[18]. Multifunctional nanosystems are increasingly being engineered for stimuli-responsive behavior, releasing therapeutic agents in response to pH, enzymes, or external triggers (light, magnetic field, and

ultrasound) (Table 2). Such hybrid platforms offer the potential for real-time monitoring of therapy outcomes, reducing off-target effects and improving treatment precision[19].

3.2 Mechanisms of Action

The efficacy of nanotheranostic systems lies in their ability to diagnose, deliver therapy, and monitor response simultaneously.

3.2.1 Imaging Applications

Nanotheranostic platforms enable a spectrum of therapeutic strategies:

• **Chemotherapy Delivery:** Nanocarriers enhance tumor accumulation and reduce systemic toxicity.
• **Photothermal Therapy (PTT):** Gold nanoparticles and graphene convert light energy into heat, selectively ablating cancer cells.
• **Photodynamic Therapy (PDT):** Nanoparticles deliver photosensitizers that, upon light activation, generate reactive oxygen species to kill tumor cells.
• **Immunotherapy:** Some nanosystems are engineered to deliver immune checkpoint inhibitors or stimulate dendritic cells, enhancing antitumor immunity[20,21].

This dual functionality, combining imaging and therapy, provides clinicians with the ability to tailor interventions, monitor therapeutic responses in real time, and adjust treatment strategies accordingly.

4. Organ-Specific Applications

4.1 Liver Cancer (Hepatocellular Carcinoma)

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and ranks among the leading causes of cancer-related deaths worldwide. Its high mortality is largely attributed to late-stage diagnosis, underlying liver dysfunction, and limited therapeutic options[26]. Conventional diagnostic imaging modalities such as MRI, CT, and ultrasound provide valuable information but often lack the sensitivity to detect early-stage disease or monitor therapeutic responses accurately. Nanotheranostics have emerged as a promising approach to overcome these limitations by integrating sensitive diagnostic imaging with localized and effective therapeutic strategies[27].

Table 3. Liver Cancer Nanotheranostic Systems

Nanocarrier	Imaging Technique	Drug/Therapy	Targeting Strategy	Outcome
Iron Oxide NP	MRI	Sorafenib	GPC3 targeting	Improved imaging
Liposomes	Fluorescence	Doxorubicin	Lactobionic acid	Enhanced accumulation

Gold NP	Photoacoustic	PTT	Passive targeting	Tumor ablation
ICG-loaded NP	Fluorescence	Surgery guidance	Tumor selective	Improved resection

4.1.1 Progress in Imaging-Guided Nanotheranostics

Recent years have witnessed significant progress in imaging-guided nanoplatforms for HCC. Iron oxide nanoparticles remain the cornerstone for MRI-based diagnosis, offering excellent contrast for liver lesions. Functionalization with targeting ligands such as glypican-3 (GPC3) antibodies or folate has further improved tumor selectivity[28]. In parallel, ultrasound-responsive nanoparticles have been engineered to act as both contrast agents and therapeutic carriers, enabling real-time imaging-guided interventions. Dual-modality systems that combine MRI with fluorescence or photoacoustic imaging have also been developed to enhance sensitivity and precision in tumor localization[29].

4.1.2 Targeted Drug Delivery

Nanotheranostics have advanced the targeted delivery of frontline chemotherapeutics such as sorafenib and doxorubicin. Sorafenib, the standard systemic therapy for advanced HCC, suffers from poor bioavailability and off-target toxicity. Nanocarriers such as liposomes, PLGA nanoparticles, and polymeric micelles have been designed to encapsulate sorafenib and deliver it preferentially to tumor tissue, significantly enhancing therapeutic efficacy while reducing systemic side effects[30]. Similarly, doxorubicin-loaded nanoparticles, often surface-modified with targeting moieties such as transferrin or lactobionic acid, have demonstrated superior tumor penetration and retention. The combination of imaging agents with these nanocarriers enables clinicians to track drug distribution in real time, paving the way for precision medicine.

4.1.3 Photothermal and Photodynamic Advances

The integration of photothermal therapy (PTT) and photodynamic therapy (PDT) into nanotheranostic designs has provided new therapeutic options for HCC. Gold nanoparticles, graphene oxide nanosheets, and carbon nanodots have been employed as photothermal agents capable of converting near-infrared (NIR) light into localized heat to ablate tumor cells. PDT has similarly benefited from nanoparticle carriers that deliver photosensitizers such as chlorin e6 or indocyanine green (ICG) directly to the tumor site[31]. Multifunctional platforms combining chemotherapy with PTT or PDT have shown synergistic effects, overcoming drug resistance and improving overall survival in preclinical liver cancer models.

4.1.4 Clinical and Preclinical Updates

Preclinical research has expanded rapidly, with numerous animal studies demonstrating enhanced therapeutic efficacy and safety of nanotheranostic approaches in HCC. Notably, iron oxide and liposomal nanoparticles carrying sorafenib have entered early-phase clinical trials,

highlighting their translational potential (Table 3). Clinical evaluations of ICG-loaded nanoparticles for fluorescence-guided liver cancer surgery have also shown encouraging results, improving tumor resection accuracy[32]. Despite these advances, challenges remain in addressing hepatic clearance, potential toxicity, and variability in patient liver function. Nevertheless, the convergence of nanotechnology with molecular imaging and targeted therapy is poised to transform HCC management in the coming decade[33] (Figure 4).

4.2 Lung Cancer

Lung cancer remains the leading cause of cancer-related mortality globally, with poor survival outcomes due to late-stage diagnosis and therapeutic resistance. Nanotheranostics have gained momentum in addressing these challenges by enabling early detection, targeted delivery, and combined therapies tailored to the tumor microenvironment.

4.2.1 Nanoparticles for Early Diagnosis (Liquid Biopsy Integration)

Traditional imaging (CT/PET) often identifies lung cancer only at advanced stages. Nanoparticles functionalized with tumor-specific markers have been developed for liquid biopsy integration, enabling detection of circulating tumor DNA (ctDNA), exosomes, and circulating tumor cells (CTCs)[40]. For instance, gold nanoparticles conjugated with DNA probes allow highly sensitive fluorescence and surface plasmon resonance-based detection of early-stage lung cancer biomarkers. These platforms provide a minimally invasive, rapid, and sensitive diagnostic alternative.

4.2.2 Tumor Microenvironment-Targeted Delivery

The lung tumor microenvironment (TME) is characterized by hypoxia, acidic pH, and immunosuppressive cells. Nanotheranostics designed with pH-sensitive, hypoxia-responsive, and redox-sensitive coatings have shown remarkable efficacy in releasing drugs selectively within the TME. For example, polymeric nanoparticles carrying doxorubicin and imaging agents have achieved deeper tumor penetration, improved MRI contrast, and minimized systemic toxicity[41].

4.2.3 Combined Chemo-Immunotherapy Nanoplatforms

Recent studies have demonstrated the use of multifunctional nanoplatforms that combine chemotherapy with immune checkpoint inhibitors. Nanoparticles delivering cisplatin along with PD-L1-blocking antibodies have enhanced immune cell infiltration and tumor regression. Real-time monitoring of drug release using fluorescence or MRI further strengthens their therapeutic applicability[42].

4.2.4 Advances in Inhalable Theranostic Nanocarriers

A unique approach for lung cancer is inhalable nanotheranostics, which enable direct deposition into the lungs, maximizing drug concentration at the tumor site while minimizing systemic exposure (Table 4). Inhalable liposomes and polymeric nanoparticles loaded with

paclitaxel, coupled with fluorescent probes, have been developed for imaging-guided therapy. These advances hold promise for non-invasive and patient-friendly treatment regimens[43] (Figure 4).

4.3 Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies due to its dense stromal barrier, late diagnosis, and resistance to therapy. Nanotheranostics provide unique opportunities to overcome these hurdles.

4.3.1 Overcoming Stromal Barriers with Nanotheranostics

The pancreatic TME is highly fibrotic, limiting drug penetration. Smart nanoparticles engineered with stromal-disrupting agents (e.g., hyaluronidase-loaded nanocarriers) have improved the accumulation of chemotherapeutics and imaging agents within tumors. Iron oxide-based nanoparticles, functionalized with stroma-targeting peptides, have also been used to enhance MRI visualization of PDAC[49].

4.3.2 Synergistic Therapies (Chemo-Radiotherapy with Nanoparticles)

Combination strategies using nanoparticles as radiosensitizers have gained traction. Gold nanoparticles improve tumor response to radiotherapy while also acting as PTT agents. Polymeric nanocarriers encapsulating gemcitabine combined with imaging probes have shown synergistic effects with radiotherapy, leading to improved survival in animal models.

4.3.3 Imaging-Guided Nanoparticle Delivery for Deep-Seated Tumors

Given the anatomical challenges of the pancreas, nanoplatforms designed for dual-mode imaging (MRI + PET/CT) facilitate precise localization and guided delivery. For instance, manganese oxide nanoparticles loaded with chemotherapeutics provide strong MRI contrast and controlled drug release. These imaging-guided systems are crucial for ensuring accurate delivery to deep-seated tumors[50].

4.4 Breast Cancer

Breast cancer is the most frequently diagnosed cancer worldwide. Nanotheranostics have focused on HER2-targeted therapies, dual-mode imaging, and treatment monitoring.

4.4.1 HER2-Targeted Nanotheranostics

HER2-overexpressing breast cancers benefit from nanoparticles functionalized with trastuzumab or HER2 aptamers. These nanoplatforms co-deliver drugs such as doxorubicin or paclitaxel while enabling MRI or fluorescence imaging, thereby enhancing therapeutic specificity.

4.4.2 Dual-Mode Imaging (MRI/Fluorescence, PET/CT)

Gold nanoparticles and liposomes labeled with radioactive isotopes enable PET/CT-based tracking of tumor burden. Dual-mode imaging (e.g., MRI combined with near-infrared fluorescence) allows real-time assessment of drug biodistribution and therapeutic response[51].

4.4.3 Nanoplatforms for Monitoring Treatment Response

Carbon dots and polymeric nanoparticles conjugated with pH- or enzyme-sensitive probes provide dynamic monitoring of treatment response, including tumor shrinkage and drug resistance. This feedback mechanism enables adaptive treatment strategies.

4.5 Brain Tumors (Glioblastoma and Others)

Glioblastoma multiforme (GBM) is the most aggressive brain tumor, characterized by poor prognosis due to blood-brain barrier (BBB) restrictions and therapy resistance. Nanotheranostics aim to bridge these gaps.

4.5.1 Blood-Brain Barrier (BBB) Penetration Strategies

Nanoparticles modified with transferrin, lactoferrin, or angiopeptide ligands have shown enhanced BBB penetration. Exosome-based nanocarriers have also emerged as natural BBB-crossing vehicles for theranostics[52].

4.5.2 Theranostic Nanoparticles for Glioblastoma

Iron oxide nanoparticles conjugated with glioma-targeting peptides allow MRI visualization and localized delivery of temozolomide. Multifunctional nanoplatforms integrating PET/CT with drug delivery have shown promising results in extending survival in animal models.

4.5.3 Imaging-Guided Photothermal and Gene Therapy Approaches

Gold nanoshells and carbon-based platforms have been employed for NIR-based PTT, achieving selective glioblastoma ablation. Additionally, nanoparticles carrying gene-editing tools (CRISPR-Cas9, siRNA) allow simultaneous imaging and correction of tumor-driving mutations.

4.5.4 Nanoparticle-Assisted Radiosensitization

Gold and hafnium oxide nanoparticles act as potent radiosensitizers, amplifying radiation damage in glioblastoma cells. Imaging integration ensures precise localization of nanoparticles within the tumor before therapy[53].

5. Comparative Analysis across Organs

Nanotheranostics are a seductive promise: one platform that can both find and finish a tumor. In reality, however, the utility of any nanotheranostic design is shaped more by the organ than by the nanoparticle itself. This section synthesizes common challenges encountered across organs, contrasts two extremes (liver versus brain), and identifies trends in whether researchers

pursue universal (one-size-fits-many) or organ-specific designs[54]. The goal is to make explicit where shared engineering solutions exist and where bespoke, organ-aware approaches are unavoidable.

5.1 Common Challenges in Multi-Organ Nanotheranostic Applications

Across liver, lung, pancreas, breast, and brain cancers, researchers repeatedly encounter several technical and translational obstacles. First, biodistribution and off-target accumulation remain persistent problems: nanoparticles introduced intravenously face opsonization, rapid clearance by the mononuclear phagocyte system (MPS), and sequestration in the liver and spleen, which reduces tumor uptake and raises safety concerns. Second, heterogeneous tumor microenvironments (TMEs), including differences in vascular permeability, interstitial pressure, pH, and immune cell composition, undermine predictable nanoparticle penetration and payload release[55]. Third, safety and long-term toxicity (material persistence, immunogenicity, and organ-specific toxicity) slow clinical translation and raise regulatory hurdles. Fourth, scalability and reproducibility of complex multifunctional constructs (hybrids, multilayered coatings, and ligand arrays) are nontrivial for manufacturing under GMP. Lastly, imaging-therapy co-optimization is challenging: optimizing for maximal imaging contrast may conflict with optimal drug loading, release kinetics, or biodegradation profiles. These recurring barriers demand cross-disciplinary solutions spanning materials chemistry, pharmacology, regulatory science, and clinical trial design[56].

5.2 Differences: Liver versus Brain (Accessibility, Microenvironment, Barriers)

Contrasting liver and brain cancers highlights how organ biology dictates nanotheranostic strategy. The liver (HCC) is comparatively accessible to nanoparticles delivered systemically: the organ's fenestrated sinusoidal endothelium and high perfusion often favor hepatic accumulation, which explains why many nanoparticles accumulate in the liver regardless of targeting. This is a double-edged sword: it facilitates delivery to hepatic tumors but increases off-target hepatic exposure and complicates dosage[57]. The liver microenvironment is also influenced by chronic disease (fibrosis and cirrhosis), which alters vascular architecture and nanoparticle transport. Thus, liver-directed nanotheranostics often exploit passive targeting (EPR) plus active targeting (GPC3 and ASGPR ligands) and focus on controlling hepatic clearance and hepatotoxicity[58].

Brain tumors (e.g., glioblastoma), by contrast, are defined by inaccessibility. The blood-brain barrier (BBB) and blood-tumor barrier (BTB) severely restrict nanoparticle entry. Successful strategies require either transient BBB disruption (focused ultrasound and hyperosmotic agents), active receptor-mediated transcytosis (transferrin and angiopep), or leveraging endogenous carriers such as exosomes. The brain TME is also highly immunosuppressive and spatially heterogeneous, necessitating precise intratumoral dosing and careful toxicity profiling to avoid neurotoxicity. Consequently, brain nanotheranostics prioritize BBB-penetrating ligands, minimized systemic exposure, and highly biocompatible, often degradable materials[59]. In short, the liver asks, “How do we avoid killing the liver while exploiting its permissiveness?” whereas the brain asks, “How do we get anything in there safely and selectively?” These constraints push design decisions in opposite directions.

5.3 Trends in Multi-Organ Targeting: Universal versus Organ-Specific Designs

Two broad trends have emerged in the literature: (1) pursuit of universal, modular platforms that are tunable across organs, and (2) development of organ-specific systems optimized for the unique biophysics and biology of a target site.

Universal or modular platforms emphasize a common core (e.g., iron oxide or polymeric nanoparticles) with plug-and-play modules for imaging labels, targeting ligands, and therapeutic payloads. The attraction lies in simplified manufacturing pipelines, standardized safety profiles, and the ability to tailor modules to different cancers without redesigning the entire nanoparticle[60]. These are particularly popular for diagnostic imaging agents and immunomodulatory cargos that act systemically.

Organ-specific systems, however, dominate where biological barriers are extreme (brain and pancreas) or where local delivery routes exist (inhalation for lung cancer). These designs incorporate organ-aware features such as enzyme-cleavable coatings for pancreatic stroma, mucus-penetrating aerosols for lung tumors, hepatic-targeting ligands for HCC, and BBB-transcytosis ligands for brain tumors. Evidence increasingly supports that organ-specific tailoring yields superior target engagement and therapeutic indices for difficult sites, even if at a higher development cost[61].

A pragmatic strategy in the field is hybridization: starting from a validated universal scaffold and adding organ-specific modules to overcome local barriers. This approach balances translational feasibility with biological necessity.

5.4 Translational Implications and Clinical Priorities

Translational success will hinge on reconciling biological complexity with regulatory and manufacturing realities. For organs where passive accumulation is favorable (e.g., liver and breast), focus should be on safety optimization, predictable pharmacokinetics, and imaging biomarkers that demonstrate target engagement[62]. For organs with severe access barriers (e.g., brain and pancreas), early investment in robust preclinical models that mimic human barriers and in translational delivery technologies (focused ultrasound, localized infusion, and inhalation devices) is essential. From a clinical-trial design perspective, imaging endpoints (real-time biodistribution and target saturation) can be used as early proof-of-concept biomarkers to de-risk therapeutics, enabling smaller and better-informed Phase I/II studies. Harmonizing characterization assays (size, charge, ligand density, and release kinetics) across laboratories will further accelerate regulatory dialogue[63].

6. Translational and Clinical Advances

6.1 Preclinical → Clinical Pipeline Updates

The past five years have seen several nanotheranostic platforms progress from robust preclinical evidence into clinical testing, notably radiosensitizing nanoparticles and multifunctional imaging-therapy constructs. The hafnium oxide nanoparticle NBTXR3 completed pivotal clinical studies in soft-tissue sarcoma and has multiple ongoing trials evaluating its activity with external beam radiation across different solid tumors, illustrating a clear preclinical-to-clinical trajectory for radiation-activated nanomaterials.

Another high-profile example is AGuIX®, a gadolinium-based ultrasmall nanoparticle designed to function as an MRI-visible radiosensitizer. AGuIX has progressed through Phase I/IB studies in brain tumors and brain metastases with encouraging safety and biodistribution data and is advancing into randomized Phase II testing for glioblastoma and malignant gliomas. It also received FDA Fast Track designation in 2024[65].

Beyond radiosensitizers, liposomal and polymeric nanocarriers with combined imaging labels and drugs continue to populate late preclinical pipelines. However, comparatively few multifunctional theranostic systems have reached large multicenter Phase II/III trials. Recent reviews and meta-analyses note steady growth in preclinical sophistication but a modest conversion rate into late-phase clinical testing[66].

6.2 Ongoing Clinical Trials Involving Nanotheranostics

Clinical trial registries and published Phase I/II reports demonstrate an active, though selective, clinical agenda:

• **NBTXR3 (hafnium oxide):** Multiple trials across sarcoma, head and neck, lung, and other solid tumors are evaluating NBTXR3 with radiotherapy.

• **AGuIX (gadolinium nanoparticles):** Phase IB studies in glioblastoma and brain metastases have reported broad intratumoral dispersion without major AGuIX-related toxicity. Larger randomized studies are ongoing, and the platform has received FDA Fast Track designation for malignant gliomas.

• **Additional early-phase studies:** Nanoparticle-enabled fluorescence agents for intraoperative guidance and inhalable nanoparticle formulations for lung cancer continue to advance, although most remain at pilot or Phase I stages[67].

6.3 Regulatory Hurdles and Safety Concerns

Regulatory agencies, including the FDA and EMA, recognize both the promise and complexity of nanomedicines. Key regulatory challenges include product heterogeneity, complex characterization requirements, interdependence of imaging and therapeutic functions, and the need for robust nonclinical models capable of predicting human biodistribution and long-term fate.

Safety concerns remain central to regulatory evaluation. Although several studies have reported acceptable biodistribution and no major nanoparticle-related toxicity at recommended doses,

long-term retention of non-biodegradable materials, immunogenicity, and organ-specific toxicity remain important issues. Comprehensive pharmacokinetic, toxicokinetic, and clearance data are generally required before progression to larger clinical trials[68].

6.4 Cost-Effectiveness and Scalability Issues

From a clinical adoption perspective, manufacturing scalability and cost-effectiveness remain major barriers. Multifunctional nanotheranostics often require complex, multistep syntheses that are difficult to scale under GMP conditions without altering critical quality attributes. Reviews and industry analyses suggest that standardized, modular nanoparticle scaffolds are more likely to achieve successful translation.

Economic evaluations remain limited. Although several nanomedicines have demonstrated clinically meaningful benefits, theranostic systems must demonstrate not only efficacy but also cost-effectiveness through reduced procedures, improved patient selection, and optimized healthcare utilization. Regulatory and reimbursement frameworks remain immature, making early health-economic evidence generation essential[69].

7. Future Perspectives

The field of nanotheranostics has matured beyond proof-of-concept studies and is now moving toward robustness, personalization, and responsible clinical translation. Four converging directions are expected to shape the future: smart stimuli-responsive systems, artificial intelligence and machine learning integration, personalized nanomedicine, and ethical and societal considerations[70].

7.1 Smart and Stimuli-Responsive Nanotheranostics

The next generation of theranostic platforms will be reactive rather than passive. Stimuli-responsive systems, tuned to endogenous cues (pH, redox potential, enzymatic activity, and hypoxia) or exogenous triggers (light, ultrasound, and magnetic fields), allow on-demand drug release and spatiotemporal control of therapy while minimizing off-target toxicity.

Examples include pH-sensitive PEG coatings, hypoxia-activated prodrug carriers, and magneto- or photo-responsive nanoparticles that combine localized heating with imaging readouts. Future efforts will focus on predictable response kinetics, reproducible manufacturing, and rigorous validation under clinically relevant conditions[71].

7.2 AI and Machine Learning Integration for Imaging and Therapy Optimization

Artificial intelligence will increasingly support nanoparticle design, image analysis, and treatment optimization. Machine learning can predict biodistribution, automate imaging interpretation, and optimize treatment parameters using real-time feedback. Closed-loop systems integrating imaging data with therapeutic adjustments may substantially improve therapeutic indices[72].

Digital twins that combine imaging, genomic, and pharmacokinetic data may eventually allow in silico testing of nanotheranostic regimens before clinical implementation.

7.3 Personalized Nanotheranostics (Genomics + Nanomedicine)

Personalized nanotheranostics represent one of the most promising future directions. Integration of tumor genomics, single-cell profiling, and molecular diagnostics with nanomedicine design may allow patient-specific selection of nanoparticle platforms and targeting strategies.

Examples include ligand-functionalized carriers directed toward tumors with specific molecular signatures and personalized neoantigen-based systems that combine immune activation with image-guided delivery. Liquid biopsies may further support personalized treatment by monitoring minimal residual disease and guiding re-dosing decisions[73].

7.4 Ethical, Safety, and Societal Implications

Ethical and societal considerations will become increasingly important as nanotheranostics enter routine clinical practice. Key concerns include equitable access, informed consent for multifunctional agents with uncertain long-term biodistribution, and data privacy associated with AI-driven imaging and genomic analysis.

Safety considerations extend beyond patient toxicity to include environmental impacts arising from manufacturing waste and nanoparticle disposal. Public trust will depend on transparent reporting of benefits and risks, long-term outcome registries, and active engagement with diverse patient populations.

Regulatory and ethical frameworks should incorporate environmental impact assessments, long-term surveillance programs for persistent nanomaterials, and clear pathways for compassionate or personalized use of nanotheranostic systems[74].

8. Conclusion

Nanotheranostics represent one of the most revolutionary frontiers in oncology by providing a single platform that integrates early, sensitive and specific diagnosis with targeted, multimodal therapy. Advances in liver, lung, pancreatic, breast, and brain cancers over the past five years have demonstrated the potential and complexity of these nanosystems. We contrast universal design principles for modular nanocarriers with multifunctional imaging–therapy integration against organ-specific challenges, such as the blood–brain barrier in glioblastoma and the stromal barrier in pancreatic cancer. There is strong preclinical evidence, but translation into clinical practice is more prudent; only a small number of nanotheranostics (i.e. NBTXR3, AGuIX) have reached late-stage trials. One of the hurdles is long-term safety, manufacturability, regulatory ambiguity and cost-effectiveness. However, timely advancement within the discipline via stimuli-responsive designs, AI-driven optimization, and personalized nanomedicine promises that image-guided, patient-specific cancer treatment will enter routine clinical care in the near future. Simply put, nanotheranostics are transitioning from bench to

bedside but success will rely on utilizing synergistic interdisciplinary efforts, a uniform standard of assessment and ethical governance. If these challenges can be overcome, this may herald the transition of nanotheranostics from a novel experimental field to a key pillar of precision oncology over the next decade.

9. References

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