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REVIEW

Theranostic Role of Advanced Nanotechnological Tools in Early Brain Metastases in Lung Cancer: An Updated Review

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Abstract: Lung cancer with brain metastases remains a clinical challenge and is often diagnosed at advanced stages when treatment options are limited. Nanotechnological tools have emerged as pivotal in enhancing both diagnostic and therapeutic approaches. Herein, we explore the theranostic potential of nanotechnology for the detection and treatment of lung cancer brain metastases, focusing on nanomaterials such as liposomes, polymeric nanoparticles, quantum dots, and magnetic nanoparticles, and their applications in imaging techniques like MRI, PET, fluorescence imaging, and CT. The role of nanotechnology in overcoming the blood-brain barrier and facilitating targeted drug delivery through passive and active targeting is also discussed. Additionally, it examines the application of nanocarriers in chemotherapy, radiotherapy, immunotherapy, and combination therapies. Special attention is given to immune-modulating nanoparticles, including checkpoint inhibitors and nano vaccines, as key innovations in immunotherapy. Theranostic nanoparticles are highlighted for their potential in real-time treatment monitoring. In summary, nanotechnological tools offer transformative potential in oncology, advancing diagnostics, enabling targeted therapies, and improving patient survival outcomes.

Keywords: nanotechnology, brain metastases, lung cancer, theranostics, real-time monitoring, nanomaterials

Introduction

Non-small cell lung cancer (NSCLC) represents approximately 85% of all lung cancer cases, with brain metastasis occurring frequently and significantly impacting patient prognosis.[1] Advancements in early detection and targeted therapies have modestly improved survival rates for non-small cell lung cancer, with the five-year survival rate increasing from 13% in the 1970s to 25% in recent years.[2] However, these improvements are mainly seen in early-stage diagnoses, while survival remains poor for patients with advanced-stage disease and brain metastases. Additionally, recent studies reveal a concerning rise in lung cancer incidence among women under 65, surpassing rates in men, with factors like smoking patterns, delayed childbirth, obesity, inactivity, and alcohol consumption contributing to this trend. Research indicates that 40–50% of lung cancer patients develop brain metastases as the disease progresses, which severely affects neurological function and quality of life.[3] Cancer cells from the primary tumor can invade the bloodstream or lymphatic system and spread to distant organs, including the brain.[4] The brain's microenvironment is conducive to lung cancer cell proliferation, particularly in the cerebral hemispheres, though metastases can also affect the cerebellum and brainstem, leading to symptoms such as seizures and cognitive decline.[5] In the absence of treatment, survival for patients with brain

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metastases is generally limited to three to six months. While targeted therapies Tyrosine kinase inhibitors (TKIs), have shown promise, the impermeability of the blood-brain barrier (BBB) often hampers the efficacy of systemic treatments.[6]

Nanotechnological platforms, particularly those integrating diagnostic and therapeutic functions (theranostics), have garnered increasing attention for their potential to address these challenges.[7] With the ability to manipulate materials at the atomic level, nanotechnology offers transformative opportunities for diagnosing and treating brain metastases.[8] Standard imaging techniques are commonly used to detect brain metastases; however, they typically identify metastases only when they exceed 5 mm in size. This delayed detection often results in a poorer prognosis and limits therapeutic options.[9]

Recent advancements in nanotechnology offer the potential for earlier detection of brain metastases. Due to their small size and ability to influence biological processes, nanoparticles can penetrate the blood-brain barrier and detect metastatic cells more efficiently than traditional imaging methods. Additionally, nanoparticles engineered with cancer-specific ligands can bind to brain cells, and enhance imaging contrast that may be undetectable by conventional techniques.[10]

Liquid biopsies, which detect tumor-derived exosomes and circulating tumor cells (CTCs) in blood or cerebrospinal fluid, offer potential for early diagnosis of brain metastases.[11] Recent advancements integrating nanoparticle technology with liquid biopsies have improved the detection of biomarkers and enhanced the accuracy of CTC identification, achieving over 90% sensitivity. These innovations facilitate continuous monitoring of tumor progression and therapeutic response, providing critical real-time data for optimizing treatment strategies in the management of metastatic cancer.[12]

This review examines the role of advanced nanotechnological tools in diagnosing and treating lung cancer brain metastases. It highlights recent advancements in nanotechnology-based diagnostics, theranostic drug delivery across the blood-brain barrier, and current challenges in clinical oncology. Additionally, it explores future directions for the development of precision nanotherapies to overcome therapeutic barriers in cancer treatment.

Lung Cancer Brain Metastases: Pathophysiology and Clinical Challenges

Brain metastasis has a major role in the high death rate of lung cancer, the world's most common cause of cancer-related fatalities.[13] Brain metastases affect about 10–20% of patients with non-small cell lung cancer at the time of diagnosis, and another 30–40% acquire them as the disease advances. The large clinical impact is caused by the high prevalence of brain metastases, which complicates both the prognosis and therapy.[14,15]

Mechanisms of Brain Metastasis in Lung Cancer

A series of steps in the metastatic process include the separation of cancer cells from the initial lung tumor, their migration into the surrounding vasculature, and their passage through the bloodstream, as illustrated in Figure 1. To create secondary lesions, tumor cells that make it across the BBB and adapt to the distinct microenvironment of the brain are required. Lung cancer cells use a variety of cellular and molecular pathways as part of a highly coordinated process to invade the brain.[16,17]

The Seed and Soil Hypothesis and the Brain Microenvironment

Stephen Paget's "seed and soil" theory, proposed in 1889, remains a critical framework for understanding the process of cancer metastasis.[18] This theory posits that specific organ microenvironments termed the "soil", can either promote or impede the colonization of metastatic tumor cells, the "seeds." In the case of brain metastasis, lung cancer cells (the "seeds") preferentially colonize the brain's microenvironment, which is rich in vascularity, neurotrophins, and exhibits a degree of immunological privilege factors that collectively facilitate the establishment and growth of metastatic tumors.[19,20] A key determinant in the metastatic spread of lung cancer to the brain is the expression of chemokine receptors, particularly CXCR4 and CXCR7, on the surface of tumor cells.[21,22] These receptors mediate the directed migration of cancer cells toward the brain in response to elevated concentrations of chemokine ligands, CXCL12, which are abundantly present in brain tissues. Furthermore, brain-derived neurotrophic factors (BDNF) play an integral role in shaping the brain's microenvironment, fostering conditions that enable tumor cells to proliferate and sustain growth within this niche.[23–25]

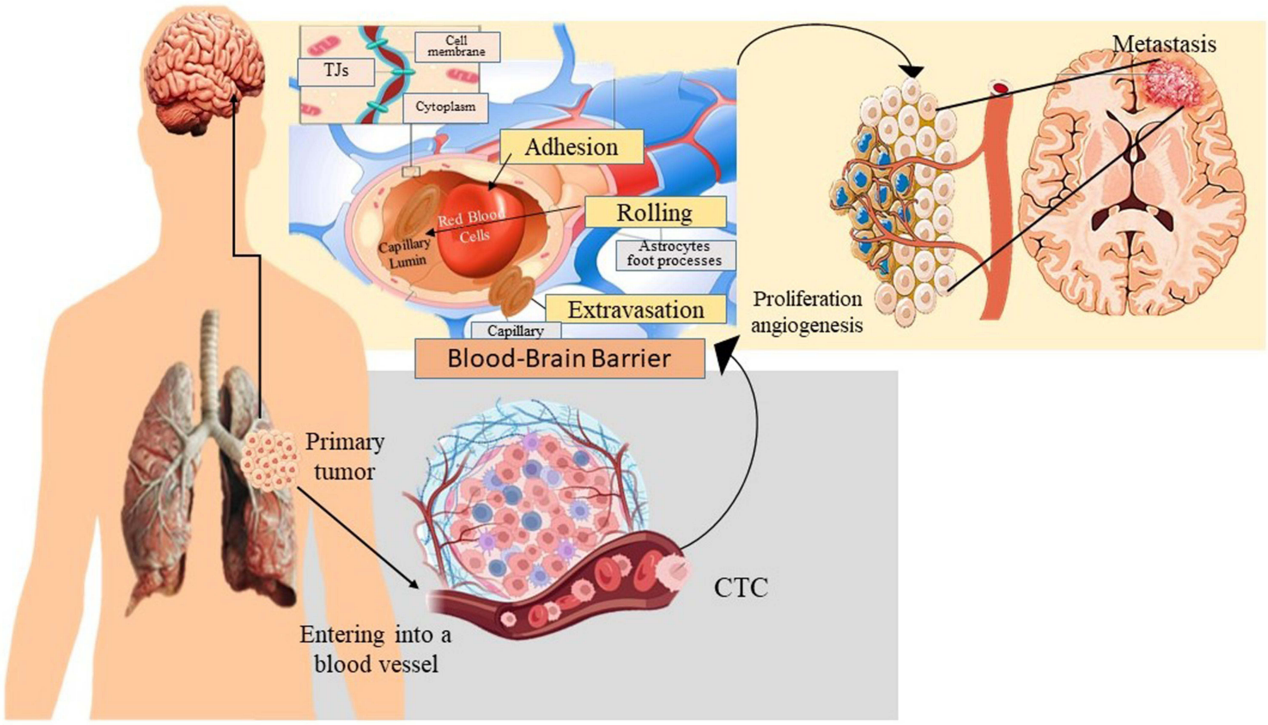

Figure 1 Mechanisms of Brain Metastasis in Lung Cancer. Primary lung cancer cells move from the primary tumor site to overspread and circulate in blood vessels, called circulating tumor cells (CTC). In response to chemokines, CTCs can reach the brain and cross the blood-brain barrier by rolling, adherence and extravasation Angiogenesis leads to brain metastasis.
Abbreviation: TJs, tight junctions.

Crossing the Blood-Brain Barrier (BBB)

The BBB presents an important challenge for both the therapeutic drug and the metastasizing tumor cell. The BBB, which is made up of astrocytes, pericytes, and endothelial cells connected by tight junctions, strictly controls the flow of chemicals from the blood into the brain. However, there are a few ways for lung cancer cells to get across the BBB.[26] For example, cancer cells frequently release matrix metalloproteinases (MMPs), namely MMP-2 and MMP-9, which break down the BBB's components and enable tumor cells to spread into the brain parenchyma.[27] Lung cancer cells can also alter the blood-brain barrier by making endothelial cells more permeable. According to studies, vascular endothelial growth factor (VEGF) secreted by metastatic lung cancer cells disrupts the tight connections between BBB endothelial cells, allowing tumor cells to penetrate the barrier. Furthermore, by stimulating lung cancer cells to attach to brain endothelial cells, astrocyte-derived exosomes boost lung cancer cells' metastatic potential.[28,29]

Epithelial-Mesenchymal Transition (EMT) and Cellular Plasticity

In cancer metastasis, one important mechanism is the EMT. Lung cancer cells undergo epithelial traits like adherence during EMT, but they also acquire mesenchymal characteristics that enhance invasion and Lung cancer cells have phenotypic plasticity, allowing them to proliferate outside of their primary tumor, persist in the circulation, and spread to other organs like the brain.[30] In metastatic lung cancer cells, several signaling pathways are extremely active and mutually regulating, as TGF-β, Wnt/β-catenin, and Notch. Transcription factors linked with EMT, including Snail, Slug, and ZEB1, have been identified as critical modulators of the metastatic spread of lung cancer to the brain.[31,32] Furthermore, current research highlights the role extracellular vesicles like exosomes which play in the transmission of signals from tumors that promote epithelial-mesenchymal transition.[33]

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Immune Evasion in the Brain Microenvironment

The BBB restricts immune cells' ability to enter the brain and encourages the cooperative participation of local immune cells, astrocytes and microglia, in tumor cells to build immunological tolerance. Lung cancer cells are known to upregulate immune checkpoint proteins, PD-L1, which attach to T cells' PD-1 receptors and prevent them from acting as antitumor agents. Furthermore, TGF-β and IL-10, two immunosuppressive cytokines that contribute to an immunosuppressive environment and a propensity for brain tumor development, can be released by lung cancer cells. This immune evasion is one of the reasons immunotherapies has been less successful in treating brain metastases than extracranial metastases.[34,35]

Clinical Presentation and Diagnosis of Brain Metastasis

Clinically, brain metastases in lung cancer patients manifest as differentiating lesions in terms of size, quantity, and location. The most typical symptoms are localized neurological abnormalities motor weakness or sensory loss, headaches, seizures, and cognitive failure. Increased intracranial pressure or the metastatic invasion of functioning brain areas are the causes of these symptoms.[36,37]

The gold standard for diagnosing brain metastases is MRI with contrast enhancement, more especially with gadolinium, as even tiny metastatic lesions increase the sensitivity of the scan. MRI is particularly helpful in identifying lesions in the brainstem and posterior fossa, as it has higher sensitivity and resolution than computed tomography (CT).[38,39] A compromised blood-brain barrier is typically present in metastatic brain cancers, and T1 weighted MRI with contrast is particularly useful in identifying these lesions. However, it might be challenging to distinguish brain metastases from other intracranial illnesses such as infection, radiation necrosis, or original brain tumor.[40] Advanced imaging methods, such as diffusion weighted imaging (DWI) or perfusion weighted imaging (PWI), may provide additional diagnostic information in individuals with vaulted soft areas, who may be more likely to hemorrhage.[41]

A novel approach to diagnosis is the liquid biopsy, which finds circulating tumor DNA (ctDNA) or CTCs in CSF (cerebrospinal fluid) or blood. For the noninvasive identification of brain metastases and treatment response monitoring, liquid biopsy is an alternative.[42] Research has shown that ctDNA can help with treatment decisions by providing information on the mutational profile of brain metastases, even if the field is still in its early stages. Moreover, liquid biopsy can identify specific driver mutations, those affecting EGFR or ALK, and can assist in determining the efficacy of targeted therapy.[43]

The prognosis is dismal for individuals whose lung cancer has spread to their brain, with a median survival of only 3–12 months, depending on the extent of lesions, tumor histology, and accessibility to targeted therapies. Numerous factors, such as the patient's performance status, neurologic symptoms, and tumor molecular features, affect the prognosis. Patients with actionable mutations in ALK or EGFR have better outcomes because targeted medications that can bridge the blood-brain barrier are so successful.[44,45]

Challenges in the Early Detection of Brain Metastases

Brain metastasis continues to be an important challenge in the early diagnosis of disease despite ongoing advancements in imaging and molecular diagnostics. Small, asymptomatic lesions in advanced illness could go undetected until they enlarge or cause neurological symptoms. For many patients, the lack of regular brain imaging in the absence of symptoms frequently causes delays in diagnosis. Furthermore, although clinical use for brain metastases is still in its infancy and further validation is required, liquid biopsy may someday offer non-invasive detection capabilities.[46] In contrast to original lung tumors, which might manifest respiratory symptoms like coughing or dyspnea, brain metastases typically do not exhibit any neurological symptoms right away. Only when the metastasis is large enough to impact crucial brain areas or elevate intracranial pressure may symptoms as headaches, seizures, or motor impairments be observed. Brain metastases are frequently latent, and it is typical for diagnosis to be delayed and to come up after the disease has progressed.[47–49]

MRI is used for detecting brain metastases due to its high sensitivity, but it is not frequently used in asymptomatic lung cancer patients, which can result in undiagnosed early-stage metastases.[50] Additionally, MRI may be limited by

accessibility, cost, and patient intolerance. Emerging diagnostic methods like liquid biopsy, which detect circulating tumor cells (CTCs) or DNA (ctDNA), offer potential for earlier detection, but their effectiveness is limited for brain metastases due to fewer tumor cells being released into circulation.[51]

Theranostics and Its Relevance in Oncology

Theranostics combines diagnostic and therapeutic approaches to personalize cancer treatment based on individual tumor characteristics. This shift from traditional one-size-fits-all methods aims to improve efficacy and minimize side effects. Theranostic technologies enable rapid monitoring of tumor responses and early detection of recurrence, which is crucial for treating metastatic cancers like lung cancer with brain metastasis. Nanotechnology plays a key role in theranostics, with engineered nanoparticles that can deliver drugs directly to tumors and serve as diagnostic tools. These advancements allow for earlier detection and more targeted treatments, improving patient outcomes and offering new possibilities in cancer care.[52]

Role of Nanotechnology in Cancer Diagnostics and Therapeutics

Nanotechnology is advancing oncology by providing innovative strategies for both cancer diagnosis and treatment, categorized into nanodiagnostics and nanotherapeutics.[53] The unique properties of nanoparticles, their small size, surface characteristics, and functionalization capabilities, enable molecular-level interactions with biological systems, offering substantial advantages in precision medicine. Nanodiagnostics utilizes nanomaterials to detect and monitor cancer, particularly at early stages.[54] A significant benefit of nanotechnology is its ability to enhance imaging techniques like MRI, PET, and CT, allowing for the detection of tumors at the microscale often when they are undetectable by conventional methods. For example, magnetic nanoparticles functionalized with tumor-specific ligands can enhance MRI contrast, facilitating the identification of small metastatic lesions.[55] Nanoparticles are also improving liquid biopsy techniques by detecting circulating tumor cells (CTCs) or tumor-derived exosomes in bodily fluids, providing a less invasive alternative to traditional biopsies. Nanoparticle-based sensors enhance the sensitivity of liquid biopsies, enabling earlier detection of metastatic spread and more precise monitoring of therapeutic responses.[56]

Nanotechnology in Cancer Therapeutics

In the treatment of brain metastases resulting from lung cancer, considerable attention must be directed toward nanoparticles capable of crossing the BBB which often restricts the delivery of therapeutic agents, preventing effective treatment of brain tumors. However, nanoparticles have demonstrated the capacity to bypass this barrier, enabling precise delivery of drugs to metastatic brain lesions. Additionally, nanoparticles can be engineered to work synergistically with other therapeutic approaches, such as gene therapy and chemotherapy, thereby enhancing their overall effectiveness.[57]

Ongoing research is increasingly focused on the use of liposomes and dendrimers have shown promise in advancing therapeutic applications. These nanostructures are being evaluated for their ability to optimize drug delivery, increase the concentration of therapeutic agents at metastatic sites, and reduce systemic toxicity. Moreover, gold nanoparticles are emerging as a potential strategy to enhance the efficacy of radiation therapy by concentrating energy specifically within cancerous tissues, thus improving treatment outcomes.[58]

Current Treatment Strategies for Brain Metastasis in Lung Cancer

A multimodal treatment strategy combining surgery, radiation therapy, systemic therapy, and supportive care is used to treat brain metastases from lung cancer. The treatment option is determined by a variety of parameters, the tumor's molecular makeup, the patient's general health, and the size and quantity of metastases.[1,59] These are the primary therapy techniques now in use in the field.

Surgical Resection

Surgical resection is considered in situations with a limited number of brain metastases (usually no more than three lesions) and a few metastases that are medically accessible without an excessive risk of neurological impairment. Surgery is used to treat symptomatic lesions that cause mass consequences, that result in elevated intracranial pressure or

neurological impairments. When paired with other treatments like radiation, total resection of some malignancies can result in enhanced survival and quick symptom alleviation. Advancements in surgical procedures like as neuronavigation, awake craniotomies, and intraoperative MRI have made it possible to precisely remove metastases while preserving essential brain functions. However, certain individuals are not suitable candidates for surgery; these patients include those who have deep-seated lesions, numerous metastases, or poor general health.[60–62]

Radiation Therapy

Radiation therapy is a widely used treatment for brain metastasis alone or in combination with surgery or systemic therapies.[63] Two main types of radiation currently used are WBRT and SRS. Patients receiving whole-brain radiation therapy (WBRT) typically have several brain metastases or severe metastatic disease. Although WBRT can stop tumor development, it is frequently used in conjunction with radiation-induced brain damage (RID) and unfavorable cognitive deterioration.[64] There have been attempts to limit the use of these medications due to their negative effects, particularly in patients who may benefit from more specialized therapies or who are expected to survive longer. SRS, or stereotactic radiosurgery is being used more and more to treat patients with limited brain metastases because to its accuracy and minimal adverse effect profile. CyberKnife and Gamma Knife use high radiation dosages to the tumor while causing the least amount of harm to the surrounding healthy tissue. SRS is particularly useful for well-defined, tiny lesions and is frequently applied to patients with fewer than four brain.[65]

Targeted Therapies and Immunotherapy

The development of immunotherapy and targeted medicines has particularly changed the paradigm for treating patients with actionable mutations of EGFR, ALK, or ROS1 when it comes to brain metastases. The treatments are designed to target certain molecular alterations present in cancer cells, which enable the cells to spread to other parts of the brain and breach the blood-brain barrier.[66] Targeted therapies have been effective in treating brain metastases because they allow the medications osimertinib (for EGFR mutations) and alectinib (for ALK mutations) to permeate the BBB and decrease tumor development.[67] Compared to traditional chemotherapy, these medicines offer substantially higher progression-free and overall survival rates. Immunotherapy (immune checkpoint inhibitors, nivolumab and pembrolizumab), which work by broadening the ability of the immune system to recognize and kill tumor cells by targeting the PD-1/PD-L1. These agents have had limited efficacy for brain metastasis because of the brain's immune privileged status. However, recent research indicates that better results for individuals with brain metastases can result from combining immunotherapy with additional therapies like radiotherapy.[68]

Chemotherapy, Palliative Care and Supportive Therapy

Due to the difficulty of drugs crossing the blood-brain barrier, brain metastases generally respond less favorably to chemotherapy than extracranial metastases. In an effort to improve drug delivery to the brain, more advanced therapies and combination treatments are being developed. Temozolomide, for instance, has been investigated in combination with other treatments, radiation, to improve outcomes for patients with lung cancer brain metastases.[69] Chemotherapy is typically reserved for patients who are not candidates for other treatment modalities, primarily due to its limited efficacy. Palliative care plays a crucial role in managing symptoms and improving the quality of life for patients with brain metastases, particularly when combined with curative treatments.[70] Corticosteroids are commonly used to reduce cerebral edema and alleviate related symptoms headaches and neurocognitive impairments. Additionally, anticonvulsants are prescribed for patients experiencing seizures, and pain management remains an essential component of care.[71]

Limitations of Conventional Diagnostic and Therapeutic Approaches

As previously discussed, routine brain screening is not conducted throughout the course of the disease, and early brain metastases are often asymptomatic, leading to delayed diagnoses. While advanced imaging techniques like MRI are highly effective, their widespread use is limited, especially in asymptomatic individuals. Furthermore, liquid biopsy, although still in experimental stages and not yet sufficiently sensitive for detecting early brain metastases, holds potential as a noninvasive diagnostic tool. The BBB poses significant challenges for both diagnosis and treatment. Most systemic

therapies are unable to effectively cross the BBB, and brain metastases often exhibit resistance to conventional chemotherapy. While immunotherapies and targeted treatments have shown promise in more effectively penetrating cancer cells, their efficacy remains variable, and resistance mechanisms may develop over time.[72]

Whole-brain radiation therapy is one of the most commonly used treatments for brain metastases, although it is associated with considerable neurological and cognitive side effects. Radiation-induced brain injury can lead to long-term impairments in memory, quality of life, and executive function, particularly in patients undergoing WBRT. Efforts have been made to mitigate these effects, such as hippocampus-sparing WBRT, but the risks remain significant. Tumor heterogeneity further complicates both diagnosis and treatment.[73] According to Hoshino et al, brain metastases may exhibit a genetic and molecular profile distinct from that of the primary lung tumor, necessitating a tailored therapeutic approach. Additionally, brain metastases can develop novel resistance mechanisms, rendering them less responsive to immunotherapies and targeted treatments.[74]

Nanotechnology in Oncology

Nano-oncology involves the use of nanotechnology to enhance cancer detection, treatment, and monitoring by manipulating materials at the nanoscale (1–100 nanometers).[75] Nanomaterials exhibit unique properties, such as increased surface area-to-volume ratio, enhanced reactivity, and altered optical, electrical, and magnetic behaviors, which can be harnessed for targeted drug delivery, controlled release, and improved imaging. These materials can be functionalized with ligands (antibodies, peptides, small molecules) to selectively bind to cancer cell receptors, ensuring precise drug delivery and minimizing damage to healthy tissues.[53,76] Nanoparticles, as liposomes, polymeric micelles, and quantum dots, are used for encapsulating anticancer drugs, enhancing solubility, and enabling controlled release, while also serving as contrast agents in imaging modalities like MRI, CT, and PET. Moreover, nanoparticles can deliver RNA interference (RNAi) agents or small-molecule inhibitors to target molecular pathways crucial for tumor progression. While nano-oncology shows promise in improving treatment specificity and reducing toxicity, challenges remain in optimizing nanoparticle design for stability, biocompatibility, and long-term safety.[75,77]

Types of Nanomaterials Used in Cancer Theranostics

Liposomes are spherical vesicles made of lipid bilayers that can hold both hydrophilic and hydrophobic medications. In oncology, liposomal formulations are utilized to decrease the toxicity and boost the absorption of chemotherapy drugs.[78,79] Liposomes can be selectively directed to tumor cells through the addition of targeting moieties, which allow for the release of their payload in response to specific environmental cues, such as changes in temperature or pH. One notable example of liposomal formulations is liposome-encapsulated doxorubicin (Doxil), which is used in the treatment of various cancers, including ovarian and breast cancer. This formulation of doxorubicin has been shown to reduce cardiotoxicity and improve tolerability without compromising its anticancer efficacy.[80]

Nanoparticles such as gold, silver, and quantum dots are increasingly utilized in cancer diagnosis and treatment due to their distinctive optical and chemical properties. Gold nanoparticles, in particular, have been widely studied for enhancing imaging techniques like CT and for improving drug delivery. These nanoparticles are easily synthesized and can be made tumor-specific through functionalization with targeting ligands. In addition to serving as drug delivery agents, gold nanoparticles exhibit surface plasmon resonance, making them suitable for photothermal therapy, a technique that uses light to generate heat and selectively destroy tumor cells. Silver nanoparticles, known for their antimicrobial properties, may also have potential in inhibiting cancer cell growth.[81] However, their clinical application has been limited by concerns regarding cytotoxicity and long-term safety.[82] Quantum dots are semiconductor nanocrystals with unique optical features, size-dependent fluorescence. They offer features that make them ideal for cancer imaging applications that need real-time observation of tumors and metastases.[83]

Carbon nanoparticles based on carbon, such as carbon nanotubes and graphene oxide, are gaining popularity as nanomaterials for cancer treatment. CNT is a cylindrical carbon structure with exceptional mechanical strength and electrical conductivity, making it ideal for medication administration and photothermal treatment. This allows CNTs to be functionalized with a wide range of medicines and targeting ligands, enabling site-specific drug delivery. They have a particular structure that allows them to efficiently transfer therapeutic materials across biological membranes.[84] CNTs will preferentially eliminate tumor cells in photothermal treatment by absorbing near infrared (NIR) light and converting it to heat.

Graphene oxide (GO), a derivative of graphene with a huge surface area, can be functionalized with pharmaceuticals and biological molecules to treat cancer. Indeed, GO has been found to have potential in imaging applications due to its strong optical absorption and production of reactive oxygen species (ROS) capable of killing cancer cells.[85]

Polymeric nanoparticles may be manufactured from artificial or natural polymers, and their pharmacological cargo can be released in response to physical triggers. Dendrimers are extremely branching, tree-like polymers that can encapsulate pharmaceuticals or conjugate drugs to their surfaces. Their well-defined design allows for exact control over drug release and targeting capabilities. In the presence of water, amphiphilic block copolymers self-assemble into polymeric micelles. With a hydrophobic core and a hydrophilic shell, they can encapsulate poorly soluble pharmaceuticals while remaining stable in biological fluids. Polymeric micelles are effective in delivering chemotherapeutics such paclitaxel.[86,87]

Iron oxide or ferrite magnetic nanoparticles (MNPs) are utilized in cancer detection and treatment because they may be controlled by an external magnetic field Figure 2. With advancements in bioimaging techniques, they can be used as MRI probes to track metastatic lymph nodes in cancer patients as they can be preferentially phagocytosed by normal lymphoid cells after injection. Metastatic lymph nodes that do not absorb nanoparticles have high signal intensity on T2*-weighted imaging.[88] These nanoparticles can also be coated with targeting compounds and directed to tumor locations via magnet to release their therapeutic payload. Magnetic nanoparticles are also utilized as contrast material in MRI to increase the visibility of tumors and metastases. Furthermore, magnetic hyperthermia, in which nanoparticles create heat by an alternating magnetic field, is being investigated as a noninvasive cancer therapy.[89]

Advantages of Nanotechnology in Cancer Treatment

Nanotechnology in cancer therapy enhances drug delivery by targeting tumor cells specifically, reducing systemic toxicity and side effects associated with conventional chemotherapy. They can be functionalized with tumor-targeting ligands (antibodies, peptides) for selective drug delivery to cancer cells. Drugs with limited water solubility, paclitaxel, can be encapsulated in

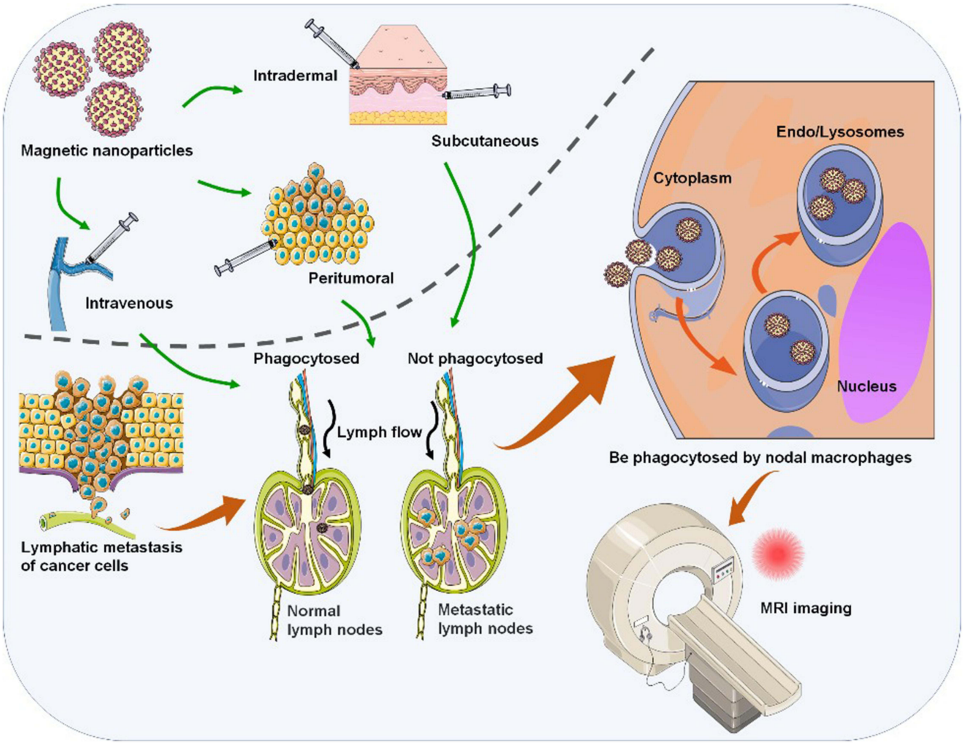

Figure 2 Magnetic nanoparticles (MNPs) are used in cancer detection and treatment due to their ability to be controlled by an external magnetic field. MNPs can also be used as MRI probes to track metastatic lymph nodes in cancer patients due to bioimaging advances. MNPs may be preferentially phagocytosed by normal lymphoid cells after injection, darkening T2*-weighted pictures. Metastatic lymph nodes that do not absorb nanoparticles have high signal intensity on T2*-weighted imaging. Adapted from Yan Y, Liu Y, Li T, et al. Functional roles of magnetic nanoparticles for the identification of metastatic lymph nodes in cancer patients. J Nanobiotechnol. 2023;21(1):337. Under the terms and conditions of Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).[88]

nanoparticles to improve solubility and bioavailability. Nanotechnology also improves imaging contrast in MRI, CT, and fluorescence imaging using agents like quantum dots and gold nanoparticles, enabling early tumor detection and real-time monitoring of therapy. Additionally, nanoparticles facilitate combination therapies by delivering multiple therapeutic agents simultaneously, overcoming drug resistance mechanisms like efflux pumps. This approach ensures effective drug concentrations within the tumor microenvironment. Despite these advancements, challenges remain in addressing nanoparticle toxicity, immune clearance, and scalability for therapeutic applications.[90–92]

Nanotechnological Approaches for Early Detection of Brain Metastasis

Early detection of brain metastases is vital for improving lung cancer outcomes, but current methods lack sufficient sensitivity. Nanoscale technologies enhance diagnostic precision, enabling earlier detection and more effective monitoring.[93] Table 1 provides an overview of both current and investigational nanotechnology applications in lung cancer and brain metastases.

Nanotechnological Tools for Therapeutic Targeting in Brain Metastasis

Brain metastasis may be treated using nanotechnology's transformational solutions, which address the challenges of drug transport, increase therapeutic precision, and battle metastatic cells' resistance mechanisms. The BBB is the primary impediment to treating brain metastases because it prevents most conventional medications from reaching the brain. Nanoparticles have been found to effectively unload the BBB and deliver medicines directly to metastatic brain tissue. Furthermore, these nanotechnological techniques enable the simultaneous administration of chemotherapeutic drugs, radiosensitizers, and immune modulators, increasing therapy effectiveness.[102]

Table 1 Overview of Current and Investigational Nanotechnology Applications in Lung Cancer and Brain Metastases

Application	Nanoparticle Type	Clinical Status	Purpose	Example	References
Drug Delivery for NSCLC	Liposomal Nanoparticles	FDA-approved	Targeted drug delivery to improve efficacy and reduce side effects.	Doxil® (liposomal doxorubicin)	[94]
Theranostics	Multifunctional Nanoparticles	Clinical Trials	Simultaneous diagnosis and therapy for brain metastases.	Ongoing clinical trials for combination therapies.	[95]
Gene Delivery	Polymeric Nanoparticles	Investigational	Targeted delivery of genetic material to tumor cells.	Research in gene therapy for NSCLC and brain metastases.	[96]
Targeted Drug Delivery	Nanocapsules (Polymeric, Lipid-based)	Clinical Trials	Controlled release of chemotherapy drugs to the tumor site.	Nanocapsule delivery of paclitaxel for NSCLC treatment.	[97]
RNA Delivery	Lipid Nanoparticles	Investigational	Delivery of RNA molecules (siRNA, mRNA) to silence tumor genes or provide therapeutic proteins.	Lipid nanoparticles for siRNA delivery in cancer therapy.	[98]
Photothermal Therapy	Gold Nanorods or Nanoparticles	Investigational/ Pre-clinical	Conversion of light to heat to destroy tumor cells.	Research on gold nanorods for photothermal therapy in NSCLC.	[99]
MRI Contrast Enhancement	Iron Oxide Nanoparticles	FDA-approved /Investigational	Improve MRI contrast to identify metastases and track tumor growth.	FDA-approved Feridex® (iron oxide nanoparticles for MRI)	[100]
Targeted Nanobots for Surgery	Nanoscale Robots	Investigational	Deliver drugs directly to cancer cells during surgery or precision therapy.	Research on nanobots for targeted drug release during surgery.	[101]

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Nanoparticles for Drug Delivery to the Brain

Brain metastases present a significant therapeutic challenge due to the BBB, which prevents over 98% of small-molecule drugs from entering the brain. Nanoparticles can be engineered to improve drug permeability across the BBB by modifying their physicochemical properties.[103] These nanoparticles can encapsulate poorly bioavailable drugs, protecting them from degradation while facilitating their delivery to the brain. Surface modifications, such as functionalizing nanoparticles with ligands like transferrin or lactoferrin, enable receptor-mediated transcytosis, allowing nanoparticles to bind to BBB receptors and cross into the brain. Additionally, nanoparticles can exploit the BBB's leaky vasculature in tumor regions to enhance drug delivery to brain metastases.[104]

Passive targeting and active targeting are the two primary ways for delivering nanoparticles to brain metastases, as illustrated in Figure 3. The Enhanced Permeability and Retention (EPR) effect allows nanoparticles to passively target the tumor microenvironment by taking advantage of the tumor's unique vasculature, which enhances nanoparticle retention at metastatic sites.[105] Active targeting further refines this approach by functionalizing nanoparticles with ligands or antibodies that bind to overexpressed receptors on cancer cells, such as integrins or folate receptors. This targeting increases the specificity of drug delivery to metastatic cells, reducing damage to healthy brain tissue. Additionally, combining receptor-mediated transcytosis with active targeting enhances drug penetration across the BBB and ensures precise medication release at the tumor site, minimizing systemic side effects.[106]

Nanocarriers for Chemotherapy and Radiotherapy in Brain Metastasis

Nanocarriers, such as polymeric nanoparticles and liposomes, enhance the delivery of chemotherapy drugs and radiosensitizers to brain metastases by protecting the drugs from premature breakdown, improving solubility, and enabling controlled release at the tumor site, thus increasing drug concentration while minimizing systemic toxicity. Polymeric nanoparticles, made from biodegradable polymers like PLGA, chitosan, and polyethylene glycol (PEG), can encapsulate both hydrophilic and hydrophobic drugs, offering regulated release and protection from enzymatic degradation. Surface modification with targeting ligands allows for selective accumulation at brain metastases, reducing off-target effects on healthy brain tissue. Liposomes, composed of phospholipid bilayers with an aqueous

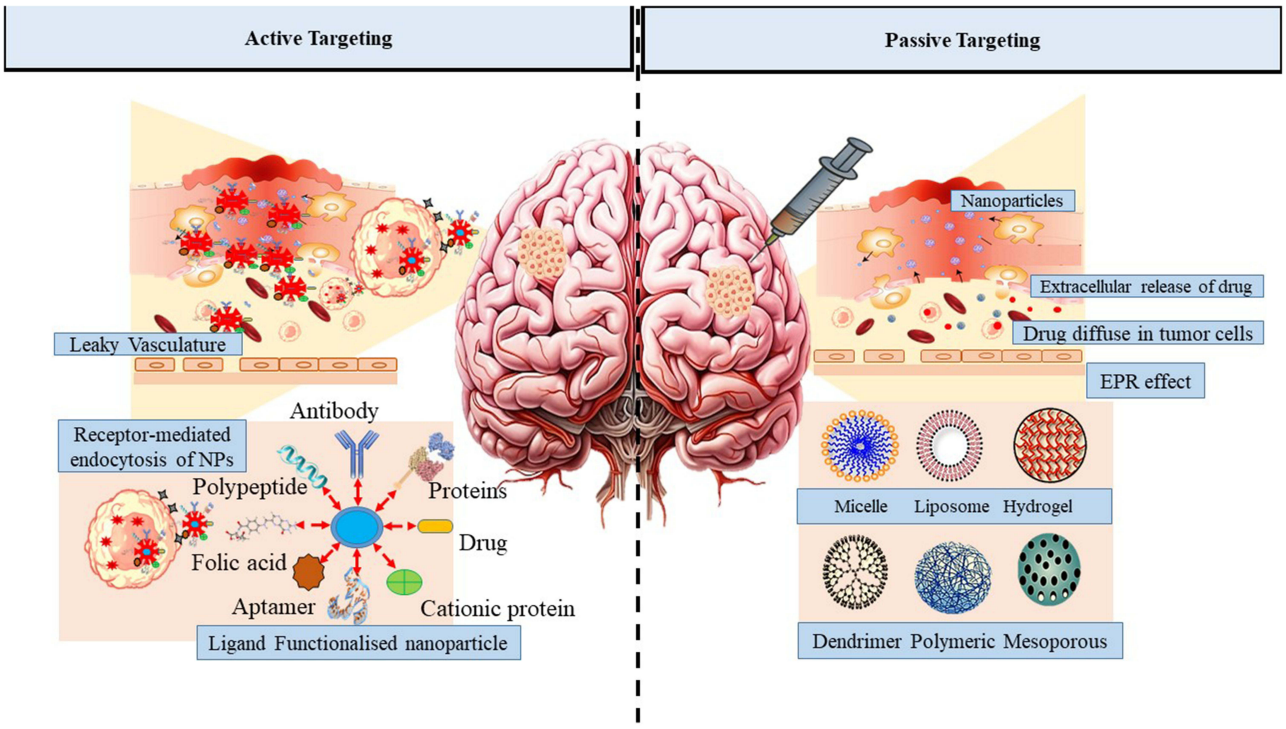

Figure 3 The diagram illustrates the two strategies for Nanotechnological therapeutic targeting in brain metastasis: passive and active targeting.

core, are biocompatible carriers that accommodate both hydrophilic and hydrophobic drugs, enhancing the delivery of chemotherapeutic agents like paclitaxel and doxorubicin. Surface modification with PEG extends circulation time, enabling accumulation in brain metastases via the EPR effect. Liposomal formulations improve treatment outcomes by enhancing drug delivery and minimizing adverse effects, and are being explored for co-delivering drugs and radiosensitizers to increase tumor radiosensitivity.[107,108]

Stimuli-responsive nanocarriers, designed to release drugs in response to specific tumor microenvironment factors (pH, temperature, enzymatic activity), enable targeted, on-demand drug delivery. These carriers release their therapeutic payloads in response to the acidic conditions or elevated temperatures typically found in tumors, reducing damage to healthy tissue while improving the efficacy of chemotherapy and radiation.[109]

Nanotechnology in Immunotherapy for Brain Metastasis

Immunotherapy leverages the body's immune system to target and eliminate tumor cells, including those in brain metastases. Nanotechnology enhances immunotherapy by improving the delivery and efficacy of immune checkpoint inhibitors, nanovaccines, and combination treatments targeting metastatic brain lesions. Immune checkpoint inhibitors (anti-PD1/PDL1 or anti-CTLA4) help overcome immune suppression and enable immune system activation against tumors.[110,111] However, their effectiveness is limited by the BBB. Nanoparticles encapsulating these inhibitors facilitate improved delivery to brain metastases, enhancing drug transport across the BBB and activating the immune response at the tumor site. Nanovaccines, which deliver tumor-associated antigens and adjuvants to antigen-presenting cells such as dendritic cells, are gaining traction in immunotherapy.[112] By conditioning the immune system to recognize and target brain metastasis cells, these nanovaccines have shown potential in preclinical studies to induce significant, long-lasting immune responses and improve long-term survival in metastatic brain cancer.[113]

Nanoparticles in Combination Therapies (Chemo, Radio, and Immuno)

Nanoparticles can provide numerous therapeutic techniques, including as chemotherapy, radiation, and immunotherapy, concurrently in a single treatment strategy for brain metastases. With combination therapy, we achieve a synergistic impact that improves the efficacy of each modality while lowering toxicity. For example, such nanoparticles can be loaded with chemotherapeutic medications and radiosensitizers to increase the susceptibility of brain cells with metastases to radiation, as well as immunotherapy compounds to amplify an already strong immune response. This multipronged method ensures that everything arriving at tumor cells comes from numerous sources, enhancing the treatment's chances of success.[114–116]

Overcoming Multidrug Resistance Using Nanotechnology

Metastatic cancer, in general, and brain metastasis in particular, provide a significant difficulty in the treatment of metastatic cancer due to tumor cells evolving methods to evade the effects of chemotherapy. Drug delivery using atypical techniques that bypass resistance pathways is a unique solution offered by nanotechnology to overcome MDR. For example, we can design nanoparticles that co-deliver silencing of MDR-related genes, restoring a tumor's chemosensitivity. Furthermore, nanosized particles can encapsulate efflux pump blockers, stopping cancer cells from expelling therapeutic drugs, improving medication retention in tumor cells, and contributing to increased treatment effectiveness. These treatments have a high potential for overcoming MDR in brain metastases and provide new hope to patients with resistant malignancies.[117,118]

Theranostic Nanoparticles: Integrated Diagnosis and Therapy

Theranostic nanoparticles provide simultaneous imaging of tumor growth and response to treatment with diagnostic and therapeutic agents, resulting in more tailored and adaptive cancer therapy. These nanoparticles' dual function makes them incredibly effective in resolving the complex problems associated with administering medications across the BBB and tracking the effectiveness of treating brain metastases.[53,119]

Targeted Nanotheranostics in Brain Metastasis

Targeted nanotheranostics offer a promising strategy for the treatment of brain metastases by enabling precise drug delivery and real-time diagnostic monitoring. These systems leverage the unique targeting properties of nanoparticles to overcome the challenges posed by the BBB and selectively deliver therapeutic agents to metastatic lesions, minimizing off-target effects. Nanoparticles functionalized with epidermal growth factor receptor (EGFR) ligands can specifically target lung cancer brain metastases, while antibody-conjugated nanoparticles can direct drugs to immune checkpoint proteins like PD-L1, enhancing treatment precision. By targeting the molecular and genetic signatures of tumors, nanotheranostics allows for personalized therapy, such as EGFR inhibitor-loaded nanoparticles for patients with EGFR mutations or immune checkpoint inhibitor-conjugated nanotherapies for those with PD-L1 expression. Additionally, the incorporation of biomarkers enables real-time monitoring of treatment response, facilitating adaptive strategies that optimize therapeutic outcomes and reduce recurrence risk.[120,121] In a recent study, a hybrid cell membrane-coated indocyanine green liposomes (HM-Lipo-ICG) were developed as biomimetic near-infrared (NIR) fluorescent probes for targeted BBB penetration and to precisely delineate infiltrative glioblastoma (GBM) borders. The HM-Lipo-ICG incorporates ICG within its core and employs a hybrid cell membrane outside, facilitating targeted delivery and improved BBB permeability. Quantitative evaluations upon incubation with bEnd.3 cells and CLSM imaging showed that HM-Lipo-ICG attained 2.8 times higher BBB penetration efficiency compared to traditional ICG liposomes. In addition, the HM-Lipo-ICG facilitated high-contrast NIR-imaging in glioblastoma regions of an orthotopic glioma murine model, and enhanced tumor margins detection accuracy (Figure 4). This study signifies the use and efficacy of hybrid cell membrane-coated liposomal probes in accurately imaging and addressing infiltrative GBM edges.[122]

Challenges in the Clinical Translation of Theranostics

Off-target interactions represent a significant concern, as nanoparticles may unintentionally accumulate in non-target tissues, leading to adverse effects such as immune responses or toxicity. These issues underscore the necessity for precise

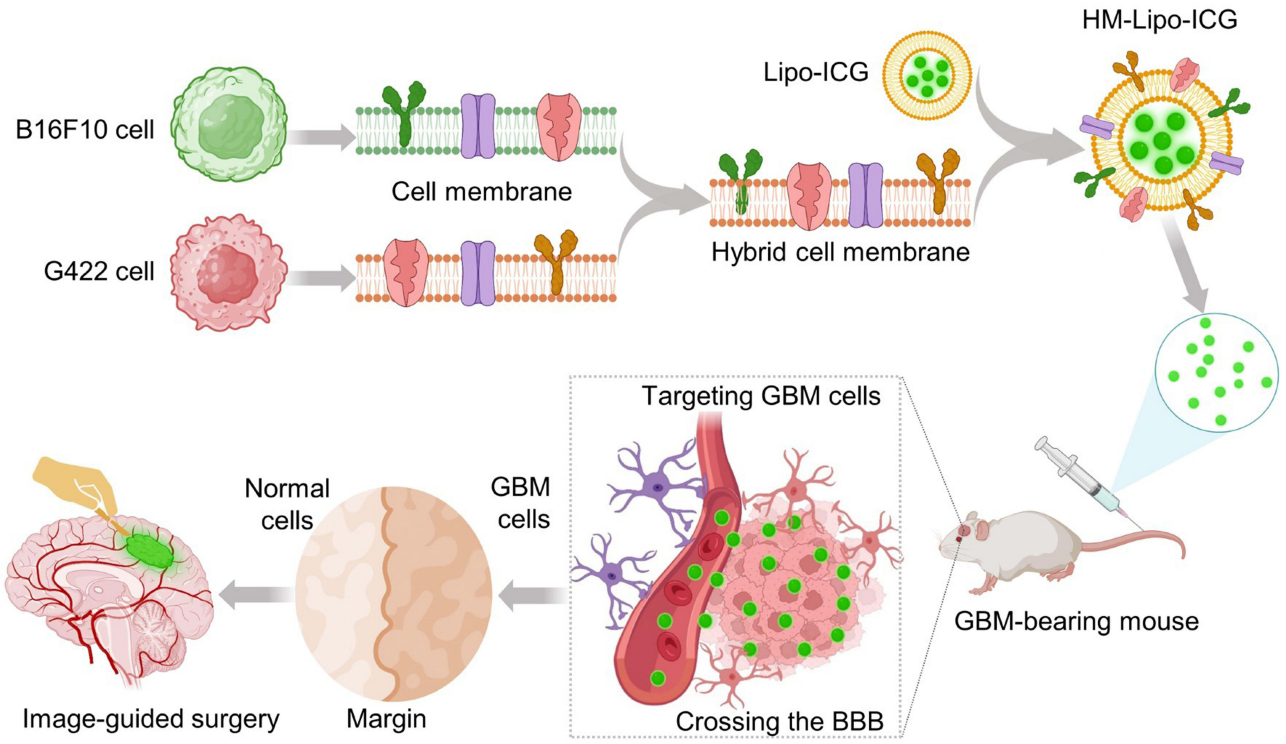

Figure 4 Schematic representation of the preparation for HM-Lipo-ICG and its application in NIR fluorescence imaging of GBM-bearing mice, including tumor margin delineation and surgical resection guidance. The HM-Lipo-ICG facilitated high-contrast NIR-imaging in glioblastoma regions of an orthotopic glioma murine model, and enhanced tumor margins detection accuracy. Adapted from Liu P, Lan S, Gao D, et al. Targeted blood-brain barrier penetration and precise imaging of infiltrative glioblastoma margins using hybrid cell membrane-coated ICG liposomes. J Nanobiotechnol. 2024;22(1):603. Under the terms and conditions of Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (http://creativecommons.org/licenses/by-nc-nd/4.0/).[122]

nanoparticle design, with enhanced targeting mechanisms to minimize unintended interactions.[123] Regulatory challenges arise from the complex approval process for theranostic agents, which must meet the standards for both drugs and medical devices. The current lack of standardized regulatory guidelines further complicates the clinical approval process, limiting the widespread use of theranostic platforms.[52,124]

Nanoparticle clearance remains another critical challenge, as nanoparticles can accumulate in organs such as the liver and spleen, posing potential long-term toxicity risks. Ensuring efficient clearance while maintaining therapeutic efficacy requires careful optimization of nanoparticle characteristics, including size, surface charge, and biocompatibility.[125–127]

Tumor Heterogeneity Tumor cells within the same patient can exhibit significant variability in their molecular and genetic makeup, making it difficult to develop a one-size-fits-all theranostic approach. This heterogeneity can affect the efficacy of both diagnostic and therapeutic components of theranostic agents, complicating their use for personalized medicine.[128]

Manufacturing and Scalability Producing theranostic nanoparticles at a consistent, large-scale level while maintaining their quality, stability, and therapeutic efficacy is a significant challenge. The complexity of nanoparticle formulation, as well as the need for strict quality control, can hinder the scalability of these technologies for widespread clinical use.[129,130] Biocompatibility and Toxicity Despite advances in nanoparticle design, issues related to biocompatibility and potential long-term toxicity remain a concern. Long-term safety data is often limited, which poses a challenge for regulatory approval and clinical adoption.[131]

Immunogenicity Nanoparticles used in theranostics can provoke immune responses, particularly when foreign materials are introduced into the body. This can lead to premature clearance of the nanoparticles, reducing their therapeutic potential. Additionally, immune reactions may result in inflammation or other adverse effects, further complicating the clinical application of theranostic agents.[132]

Targeting Efficiency and Delivery Achieving precise targeting and efficient delivery of theranostic agents to the tumor site remains a challenge. Tumor microenvironments are often characterized by poor vascularization and heterogeneous drug penetration, which can limit the effectiveness of theranostic nanoparticles. Overcoming these delivery barriers is essential to enhance therapeutic outcomes.[133] Cost and Accessibility The development and manufacturing of theranostic agents can be resource-intensive, leading to high production costs. This may limit the accessibility of these technologies in low-resource settings or for patients who cannot afford the advanced treatments, thereby affecting their widespread adoption in clinical practice.[134]

Material and Methods

A thorough literature search was performed using prominent academic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search strategy involved the use of a combination of specific keywords, such as "nanotheranostics", "brain metastases", "lung cancer brain metastasis", "nanoparticles for brain delivery", and "early detection of brain metastases". The search was restricted to articles published within the past decade to include the most current research. The final selection of articles focused on the application of nanotechnology in brain metastasis, particularly in relation to drug delivery systems, early detection methods, and the clinical implementation of nanotheranostic platforms.

Conclusion

Nanotechnology has opened new avenues for the diagnosis and treatment of brain metastases, particularly in lung cancer, offering innovative solutions to persistent challenges such as the blood-brain barrier, multidrug resistance, and early detection. This review highlights the transformative potential of nanoparticles in both diagnostic and therapeutic applications, including site-specific drug delivery, imaging, and monitoring. Theranostic nanoparticles exemplify the synergistic integration of diagnostic and therapeutic functions, paving the way for more personalized and effective treatment strategies in oncology and beyond. Moreover, the application of nanotechnology is advancing the field of precision medicine by enabling the customization of drug type, dosage, and delivery systems tailored to the molecular and pathological characteristics of tumors. Recent developments in smart nanocarriers, immune checkpoint inhibitors, and nanovaccines have further expanded the possibilities for targeted therapies in brain metastases. Importantly, the

integration of artificial intelligence with nanotechnology holds significant promise in optimizing treatment outcomes. AI can assist in refining nanoparticle design, improving the precision of drug delivery, and enhancing real-time monitoring through advanced imaging techniques. Concrete examples include AI algorithms that can predict the behavior of nanoparticles in vivo, improving treatment efficacy and reducing off-target effects, as well as AI-driven systems that enable personalized treatment planning based on patient-specific data. However, several challenges remain, including scalability, safety, and regulatory hurdles, which must be addressed for the successful clinical translation of nanomedicine. Future research efforts should focus on overcoming these barriers, with particular attention to improving early diagnostic capabilities, overcoming MDR, and preventing metastasis. As the convergence of AI and nanotechnology continues to evolve, these innovations have the potential to revolutionize clinical practice, offering a more integrated and precise approach to cancer treatment.

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Disclosure

The Authors declare that they have no competing interests financial or non-financial or any other interests that might be perceived to influence the results and/or discussion reported in this paper.

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