International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Application of Nanotechnology in TACE Treatment of Liver Cancer

Linmei Yao[1,*], Zixuan Gao[1,*], Xin Wei[1,*], Shuojie Wang[1,*], Weihua Cao[1], Wen Deng[1], Xinxin Li[1], Ziyu Zhang[1], Shiyu Wang[1], Yaqin Zhang[1], Ruyu Liu[1–3], Yao Xie[1,2], Minghui Li[1,2]

[1]Department of Hepatology Division 2, Beijing Ditan Hospital, Capital Medical University, Beijing, 100015, People's Republic of China; [2]Department of Hepatology Division 2, Peking University Ditan Teaching Hospital, Beijing, 100015, People's Republic of China; [3]Department of Hepatology Division 3, Beijing Ditan Hospital Xuzhou Hospital (Xuzhou Seventh People's Hospital), Xuzhou, Jiangsu Province, 221000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ruyu Liu; Minghui Li, Email liuruyu28@163.com; wuhm2000@sina.com

Abstract: Liver cancer, particularly hepatocellular carcinoma (HCC), remains a global health challenge with limited therapeutic options for advanced stages. Transarterial chemoembolization (TACE), the first-line treatment for intermediate and advanced-stage HCC, faces limitations such as incomplete tumor embolization and systemic toxicity. This review synthesizes recent advancements in nanotechnology to address these challenges, focusing on nanoparticles (NPs) as embolic agents, drug carriers, and imaging contrast agents. Nanoparticle-based drug delivery systems (eg, gold NPs, liposomes) enable localized drug release in tumors, enhancing chemotherapy efficacy while minimizing systemic side effects. Multimodal imaging NPs (eg, superparamagnetic iron oxide NPs, gadolinium-based NPs) enhance real-time visualization of tumor vasculature during TACE, facilitating precise embolization and treatment monitoring. Additionally, combining NPs with photothermal therapy or anti-angiogenic agents (eg, sorafenib) demonstrates synergistic effects in inhibiting tumor recurrence and metastasis. In conclusion, nanotechnology significantly enhances TACE's precision and efficacy through targeted delivery and multimodal imaging, though challenges in biocompatibility, safety, stability, and large-scale production require urgent attention. Future studies should focus on developing multifunctional nanocarriers and personalized nanomedicine strategies to optimize clinical outcomes for HCC patients.

Keywords: liver cancer, nanoparticles, transarterial chemoembolization, drug delivery carriers, imaging

Introduction

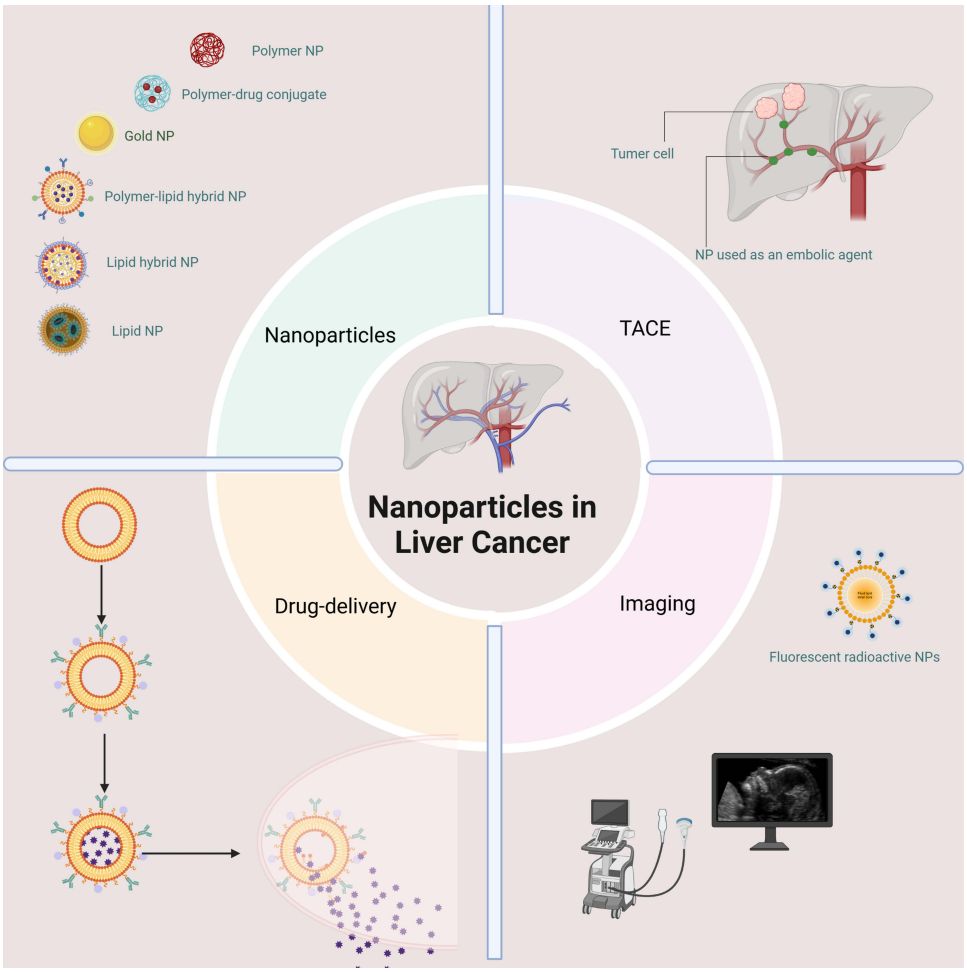
Primary liver cancer remains a severe threat to global health. According to the data revealed by the National Cancer Center of China, in 2022, the incidence rate of primary liver cancer ranked fifth among all cancers, and the number of deaths and mortality of primary liver cancer in the same year ranked second.[1] HCC is the main form of liver cancer, accounting for approximately 90% of primary liver cancers.[2] Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are the most important cause of HCC.[3] The treatment of HCC includes multiple methods,[4] and the most commonly is based on the Barcelona Clinical Liver Cancer (BCLC) staging system[5] to guide the selection of different treatment plans. However, most HCC patients are only diagnosed in the middle to late stages, which limits surgical treatment due to poor liver function.[6]

As the first-line therapy for intermediate and advanced HCC, TACE achieves local tumor control in 15–60% of cases by occluding hepatic artery blood supply and delivering chemotherapy.[7] However, its efficacy is limited by incomplete tumor embolization, systemic toxicity from drug leakage, and hypoxia-driven tumor recurrence mediated by the tumor microenvironment (TME).[8,9] These challenges necessitate innovative approaches to enhance treatment precision.

Nanotechnology offers transformative solutions to address TACE's limitations. NPs, characterized by tunable size (1–100 nm), high surface-area-to-volume ratios, and modifiable surfaces, enable three critical advancements in drug delivery, specific targeting, and imaging applications: (1) targeted drug delivery via NPs[10,11] enhances chemotherapeutic

Received: 11 March 2025
Accepted: 15 July 2025
Published: 4 August 2025

Graphical Abstract



accumulation in HCC lesions by 2–3 fold while minimizing systemic exposure to normal liver tissue, overcoming the nonspecific distribution of traditional embolic agents; (2) multimodal imaging guidance using NPs,[12] such as superparamagnetic iron oxide nanoparticles (SPIONs), achieves capillary-level (<10 μm) vascular visualization. Combined with CT/MRI dual-modal probes, this technology reduces embolization range assessment errors and enables real-time monitoring of treatment efficacy.

This review synthesizes recent advancements in nanotechnology-driven TACE, focusing on NP-based embolic agents, drug carriers, and imaging contrast agents. By integrating materials science with interventional oncology, we aim to provide a comprehensive roadmap for translating nanomedicine into clinical practice for HCC patients (Figure 1 illustrates the core concepts and their main branches of this study, aiding readers in understanding the overall framework of the research).

The Application of TACE in the Treatment of Liver Cancer

The Mechanism of Action of TACE in Treating Liver Cancer

The blood circulation of the liver is unique because it has a dual blood supply. About 80% of the blood supply to normal liver tissue is provided by the portal vein, while over 95% of liver cancer patients are supplied by the hepatic artery.[13] The fundamental principle of TACE involves obstructing the blood supply to solid tumors via the hepatic artery,[14] thereby impeding nutrient acquisition by tumor cells while sparing normal hepatocytes from disruption. Simultaneously

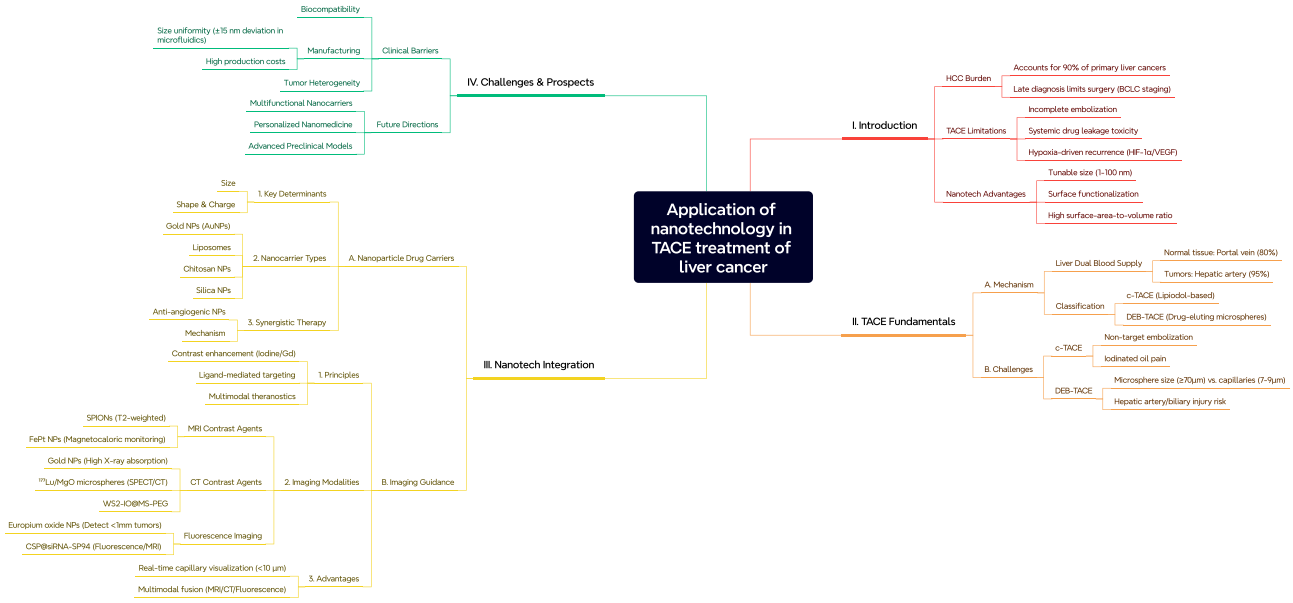


Figure 1 Mind map of the manuscript.

administering chemotherapy drugs to achieve the effects of vascular occlusion and tumor ischemic necrosis.[13] Figure 2 (by figdraw, www.figdraw.com) shows the basic principle diagram of TACE treatment for liver cancer. The classification of liver cancer TACE is based on the different embolic agents, including conventional TACE using lipiodol (c-TACE) and TACE using drug-eluting microspheres.

C-TACE and the Treatment of Liver Cancer

TACE was originally developed for hepatic artery embolization (HAE). c-TACE uses iodinated oil emulsion (lipiodol) and particle embolic agents (such as gelatin sponge particles, blank microspheres, or polyvinyl alcohol particles) to directly deliver cytotoxic drugs (such as doxorubicin, cisplatin, doxorubicin, mitomycin C, or idarubicin) to the tumor

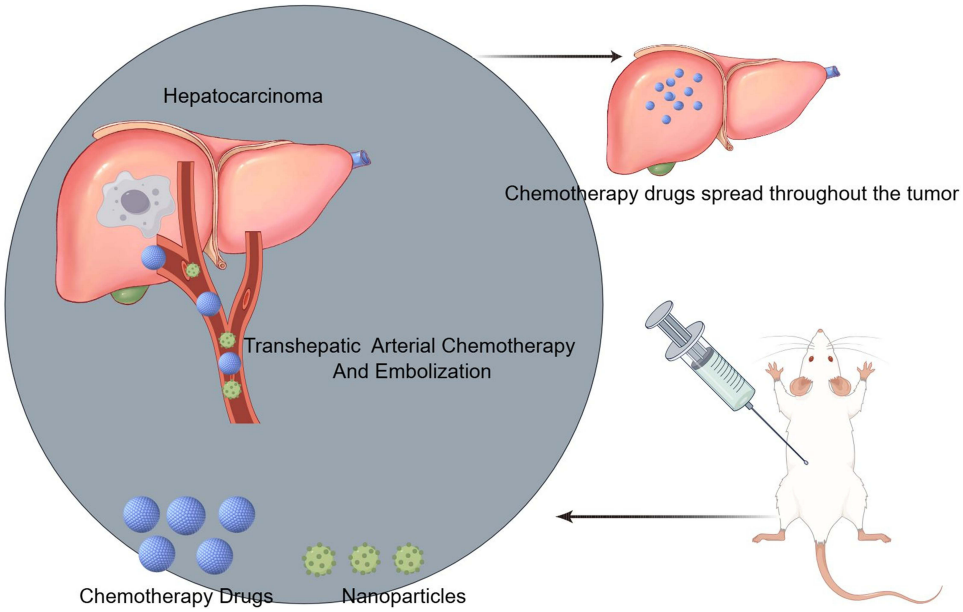


Figure 2 Basic schematic diagram of TACE treatment for liver cancer.

https://doi.org/10.2147/IJN.S527518

itself,[15] rather than causing TME embolization. Due to the easy separation of chemotherapy drugs from target lesions and their entry into the circulatory system, as well as the embolization of normal liver tissue into non target organs, their effectiveness as monotherapy is often limited.[16] Numerous studies have investigated the combination of c-TACE and sorafenib for advanced HCC, demonstrating promising therapeutic outcomes and extending overall survival.[17] In addition, due to significant technical and scheduling deficiencies in c-TACE that have not yet been standardized, as well as the possibility of severe pain in some patients caused by the use of lipiodol,[18] the acceptance of TACE as a standard tumor treatment has been hindered. Therefore, based on this, drug eluting bead transarterial chemoembolization (DEB-TACE) was developed.

DEB-TACE and the Treatment of Liver Cancer

DEB-TACE, also known as drug eluting microsphere transarterial chemoembolization. Since its first launch in 2006, many clinical trials have shown its efficacy in HCC patients and its advantages in overcoming the drawbacks of c-TACE.[19] Compared with patients receiving c-TACE, patients receiving DEB-TACE may have higher complete remission rates, disease control rates, and 3-year survival rates.[20] However, in terms of patient tumor response and safety, the advantages of DEB-TACE over c-TACE have never been proven, and the differences in cost and cost-effectiveness between DEB-TACE and c-TACE are not significant. In addition, c-TACE has been shown to reduce the recurrence of HCC after liver transplantation and improve overall survival after transplantation, especially when the waiting time exceeds 6–12 months.[21] Compared to cTACE, DEB-TACE has a higher risk of hepatic artery and biliary tract injury.[22] In DEB-TACE treatment, drug-eluting beads/microspheres can embolize the tumor blood supply artery, allowing the loaded chemotherapy drugs to achieve more sustained drug release in the local tumor. Maintaining relatively high blood drug concentrations in local tumors results in sustained embolic effects. Simultaneously providing tumor selective drug delivery while preserving healthy liver tissue supplied by the portal vein. Therefore, in addition to c-TACE, DEB-TACE is also used as a first-line treatment in some institutions.[23] The clinical indications and contra-indications of DEB-TACE and c-TACE are very similar. The optimal candidates for DEB-TACE are asymptomatic patients who exhibit preserved hepatic function, favorable Eastern Cooperative Oncology Group (ECOG) performance status, selective and targeted progression of liver disease, and an absence of significant vascular invasion or extrahepatic complications. Many research[24–26] have synthesized the indications, relative contraindications, and absolute contra-indications of DEB-TACE treatment.

While DEB-TACE demonstrates advantages in sustained drug release compared to conventional TACE, its clinical efficacy remains limited by three key challenges: (1) incomplete embolization of capillary-level tumor vasculature (7–9 μm) due to the larger size of drug-eluting microspheres (≥70 μm);[27,28] (2) nonspecific drug distribution leading to systemic toxicity and liver parenchymal injury;[24,29] and (3) hypoxia-driven tumor recurrence mediated by HIF-1α/VEGF upregulation in the post-embolization microenvironment.[30] In order to further improve the therapeutic effect of TACE and reduce complications, nanotechnology, as an emerging technology, is gradually being introduced into the treatment of TACE. Nanotechnology overcomes these limitations via innovative designs: tunable-size NPs (1–100 nm) enable precise tumor microvasculature occlusion. Surface-functionalized NPs (eg, CD147-targeted liposomes) enhance intratumoral drug accumulation by 2–3 fold while protecting normal tissues.[31] Multimodal imaging NPs (eg, SPIONs) improve real-time embolization visualization to reduce errors.[32,33] The following sections elaborate on NP-based embolic agents, drug carriers, and imaging tools, highlighting their potential to transform TACE into a more precise and effective modality for HCC treatment. Figure 3 (by figdraw, www.figdraw.com) shows the application of NPs in TACE.

NPs and TACE

NPs as Drug Delivery Carriers in TACE

The Mechanism of Action Between Drug NPs and TACE

Nanotechnology enables precise manipulation of matter at the 10^{-9} meter scale.[34] NPs (<100 nm) exhibit unique properties governed by shape (spherical/sheet-like/tubular), size, material composition, surface charge, and functional coatings (eg, PEGylation, targeting ligands).[35–38] Their nanoscale diameter (1–100 nm) facilitates penetration of tissue gaps, capillary beds

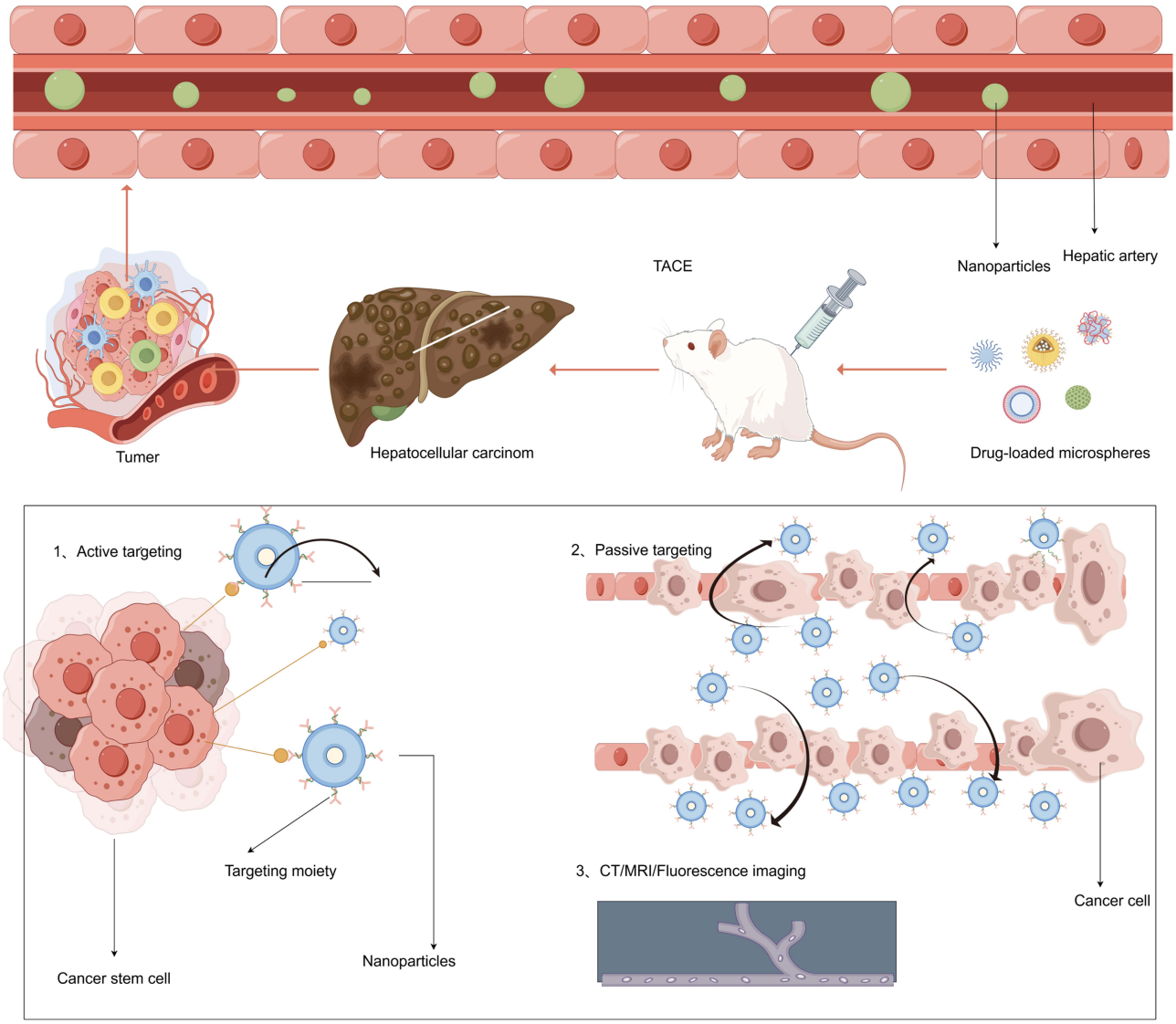


Figure 3 Application of nanoparticles in TACE.

(<10 μm), and even endothelial barriers, enabling tumor-specific accumulation via the enhanced permeability and retention (EPR) effect. As drug carriers, NPs achieve dual goals of targeted delivery (via passive phagocytosis by reticuloendothelial system or active antibody-ligand binding) and controlled release, thereby improving bioavailability while minimizing systemic toxicity.[39] This mechanism underlies the clinical integration of nanotechnology with TACE for HCC treatment.

Factors Affecting NP Efficacy in TACE

Particle Size: Vascular Dynamics and Drug Delivery

The therapeutic efficacy of NPs in TACE is profoundly influenced by their size, which dictates both vascular interaction and drug distribution. Given the typical capillary diameter ranging from 7 to 9 micrometers, conventional drug-eluting beads (DEBs, ≥70 μm) may induce occlusion of branch vessels situated distal to the capillary bed, resulting in downstream thrombus formation.[28,40,41] This obstruction prevents the delivery of anticancer drugs to the finest vessels, which is crucial for optimal transmural transport, and consequently restricts drug penetration to the distal regions of the tumor.[40] Smaller microbeads (eg, 70 μm DEBs) improve tumor edge targeting but face challenges at the nanoscale: submicron or nanometer-sized particles may fail to completely occlude arterial blood supply, risking endothelial cell absorption or tumor penetration through enlarged intercellular gaps.[41]

https://doi.org/10.2147/IJN.S527518

For drug delivery, NP size must balance payload capacity and biological distribution. While NPs >100 nm enhance drug loading, the ideal anticancer NP size (70–200 nm) aligns with tumor endothelial fenestrations (200–780 nm), enabling enhanced permeability and retention (EPR) effect-mediated accumulation.[42] For example, 400–600 nm dextran-coated arsenite NPs[43] demonstrate complete vascular occlusion and sustained drug release in VX2 liver tumor models, though smaller sizes (eg, <50 nm) may induce premature drug burst release due to high surface-area-to-volume ratios. Bergen et al[44] showed that 50 nm lactose modified gold NPs exhibited 2–3 fold greater hepatic accumulation than larger counterparts (80–150 nm), underscoring size-dependent cellular localization efficiency.

Shape and Surface Charge: Modulating Circulation and Targeting

The morphology and surface charge of NPs jointly determine their in vivo distribution efficiency and targeting capability. Non-spherical particles (eg, rods, tubes) reduce macrophage phagocytosis due to their hydrodynamic properties, prolonging blood circulation time.[45] Their irregular shapes enhance intravascular rolling effects, thereby increasing the probability of tumor vessel wall contact via the enhanced permeability and retention (EPR) effect.[46] Meanwhile, surface charge influences clearance rates by regulating interactions with biological interfaces:[47] positively charged particles are readily recognized and internalized by macrophages in organs like the liver, spleen, and lungs, leading to systemic toxicity; neutral or slightly negatively charged modifications (eg, PEGylation) evade immune surveillance and prolong circulation half-life.[48] For instance, negatively charged liposomes persist in the bloodstream longer than positively charged counterparts, while non-spherical neutral particles achieve efficient tumor accumulation by reducing Reticuloendothelial System (RES) capture and enhancing vascular wall adhesion. This synergistic optimization of shape and charge significantly expands the therapeutic window of NPs in TACE, balancing targeting precision with systemic safety.[49]

Application of Various NPs as Traditional Chinese Medicine Delivery Carriers in TACE

Due to the ability of nanocarriers to image disease tissues, diagnose conditions, detect cancer cells at an early stage, and simultaneously treat diseases, nanocarriers are used as tools for drug delivery. It has multiple advantages, such as enhancing the solubility of hydrophobic drugs, maintaining their release, and prolonging their circulation time, achieving excellent drug loading and better biocompatibility,[50] and reducing toxicity associated with anti-tumor agents. In addition, they also have the potential to be transmitted to cells, thereby enhancing the permeability and retention through inflammatory tissue endothelium.[51]

Application of AuNPs in TACE

Gold NPs (AuNPs), commonly known as colloidal gold, are one of the most extensively studied and well-known NPs. Firstly, we can easily synthesize various shapes of AuNPs, such as spherical, rod-shaped, cage shaped, etc. The optical and electrical properties of AuNPs largely depend on their shape and size.[52] Secondly, due to the negative charge on AuNPs, they can be easily functionalized by various biomolecules such as drugs, genes, and targeting ligands.[53] Thirdly, AuNPs have biocompatibility and non toxicity.[54] Fourthly, AuNPs exhibit significant surface effects, ultra small sizes, macroscopic quantum tunneling effects, and the presence of surface plasmon resonance (SPR) bands.[55] All these special properties make AuNPs the most promising materials for various biomedical applications. The main mechanism by which AuNPs exert their anti-cancer properties:[56] AuNPs are absorbed by cells through endocytosis, and vesicles are distributed in the cytoplasm and nucleus, producing toxic effects that lead to cell apoptosis or programmed cell death. Recent research has revealed that AuNPs specifically target cancer cells, triggering the effective expression of caspase-9, the initiating caspase in the apoptotic pathway. Additionally, another study has demonstrated that AuNPs targeting the nucleus induce cell cycle arrest, inhibit cytoplasmic division, ultimately driving the cells towards apoptosis. In many cases, AuNPs are used as delivery systems or combined with therapeutic molecules or even genes to provide significantly better anti-cancer cytotoxicity.[42,54]

In TACE therapy, AuNPs can serve as carriers for chemotherapy drugs, delivering them directly to the tumor site. It can significantly increase the concentration of drugs in tumor tissues while reducing damage to normal tissues. Through reasonable surface modification, AuNPs can achieve active drug targeting and improve therapeutic efficacy. Secondly, they also have excellent photothermal effects, which can generate heat under specific wavelength laser irradiation, thereby destroying tumor

cells.[57–60] The use of AuNPs as carriers for chemotherapy drugs can achieve the combined application of chemotherapy and photothermal therapy. This combination therapy not only increases the local concentration of drugs, but also enhances the sensitivity of tumor cells through photothermal effects, achieving better therapeutic effects.[61,62] Thirdly, AuNPs also have radiosensitizing properties,[63,64] which can enhance the killing effect of radiation on tumor cells during radiotherapy. When AuNPs are injected into tumor tissue, they can absorb more radiation energy during radiation therapy and convert it into forms such as thermal energy or free radicals, thereby disrupting the structure and function of tumor cells. In summary, AuNPs have shown great potential for application in TACE, but due to the incomplete understanding of their distribution and metabolic mechanisms, further research is needed on their safety and effectiveness.

Application of Liposomes in TACE

Liposomes, spherical vesicles composed of phospholipid bilayers and cholesterol, represent a versatile nanoplatform for drug delivery in TACE. Their biocompatibility, biodegradability, and non immunogenicity make them ideal for enhancing therapeutic efficacy while minimizing systemic toxicity. Liposomes can encapsulate both hydrophilic and hydrophobic drugs within their aqueous cores or lipid bilayers, respectively, enabling controlled release and improved tumor accumulation through the enhanced EPR effect.[65] Key design parameters, including phospholipid type, bilayer rigidity, particle size (typically 50–200 nm), and surface charge, dictate their circulation half-life, tissue distribution, and cellular uptake.[66,67] For instance, negatively charged liposomes exhibit reduced phagocytosis by the reticuloendothelial system, prolonging blood circulation, while cationic formulations enhance interaction with negatively charged tumor cell membranes.[68]

A notable advantage of liposomes is their adaptability for active targeting. Wang et al developed CD147-targeted liposomes conjugated with doxorubicin, demonstrating enhanced cytotoxicity against Huh-7 and HepG2 HCC cells compared to non-targeted counterparts.[52,69] The CD147 antibody decoration improved tumor-specific binding, leveraging overexpression of this receptor on HCC cell surfaces. Similarly, Persico et al evaluated chitosan-coated liposomes loaded with butyric acid (BA) in HepG2 cell lines, showing that surface modification with chitosan enhanced cellular uptake and anticancer efficacy compared to uncoated liposomes or free BA.[31,70] These findings highlight how surface engineering can optimize liposomal delivery for TACE, ensuring preferential accumulation in tumor tissues while sparing healthy hepatocytes. Lipid-based nanocarriers also offer flexibility in multi-drug co-delivery. Zhao et al developed dual-drug liposomes encapsulating doxorubicin and curcumin, demonstrating high encapsulation efficiency and sustained release profiles in a murine HCC model.[71] The combination of chemotherapeutic and natural anti-tumor agents within a single carrier enhanced synergistic cytotoxicity and tumor growth inhibition. Such systems address the limitations of monotherapy by integrating multiple mechanisms of action, the advantages of which include reducing the dosage of each drug and the likelihood of drug resistance.

Despite these advancements, liposomes face technical challenges in TACE translation. For example, instability in the acidic TME and variability in lipid composition can lead to premature drug leakage or inconsistent embolization efficacy.[72] Additionally, large-scale production of monodisperse liposomes with uniform size and charge remains a bottleneck for clinical scalability. Future research should focus on developing pH-responsive lipid formulations and microfluidic-based manufacturing techniques to improve consistency and therapeutic precision.

Application of Chitosan NPs in TACE

Chitosan is a biodegradable cationic polysaccharide polymer. It is mainly produced through two processes: ordinary process and fermentation process. The ordinary process includes demineralization, deproteinization, and decolorization to separate chitin, and then deacetylation to convert chitin into chitosan.[73] The main characteristics of chitosan biopolymers are their molecular weight and degree of deacetylation, which are crucial for controlling the properties of chitosan, including solubility, polycation, antimicrobial activity, biocompatibility, and biological adhesion. Therefore, the different shapes and physical forms of chitosan determine its various uses in different fields,[73,74] including their implementation in drug delivery.

Due to the very low loading efficiency of chitosan itself, the creation of various chitosan derivatives, especially in the form of NPs, has been proven to be effective. Many researchers have studied chitosan NPs for drug delivery in liver cancer for therapeutic purposes. The main advantages of chitosan NPs in controlled release systems include: (i) improving drug stability, (ii) reducing drug side effects,[75] (iii) reducing dosage, (iv) increasing convenience, (v) improving drug efficacy, (vi) increasing

drug bioavailability, (vii) reducing overall costs, and (vii) improving patient compliance.[76] Loutfy et al (2016)[77] synthesized chitosan NPs for evaluating an in vitro human liver cancer cell model (HepG2). Their study demonstrated the cytotoxicity of chitosan NPs toward liver cancer cells, confirming suitability for hepatic oncotherapy drug delivery.[78] Badawy et al[78] demonstrated the anti-HCC efficacy of chitosan coated iron oxide nanocomposites (Fe3O4/Cs) in a rat model. The results have shown that Fe3O4/Cs could induce apoptosis of liver cancer cells by increasing the expression of cleaved caspase-3 and induce immune suppression of cytokines, demonstrating good anti-tumor effects.

Application of Silica NPs in TACE

Silicon dioxide has a tetrahedral framework structure, formed by covalent bonds between one silicon atom and four oxygen atoms. Mesoporous silica NPs (MSN) are a type of porous material with a pore size distribution of 2–50 nm and are a promising nanoscale carrier. It is easy to synthesize, has a uniform structure, adjustable size (50–200 nm), large pore volume (0.6–1.4 cm3/g), high specific surface area (700–1000 m2/g), high drug loading capacity,[79] as well as adjustable pore size, controllable morphology and high mechanical/thermal stability, good biocompatibility and biodegradability, making it an excellent substrate material for constructing various nanocomposites.[80]

In general, MSN is usually produced by surfactant template sol-gel method. Their structure and morphology are influenced by different factors. Among them, surfactants as structure directing agents play a crucial role in determining the mesoporous structure of MSN, because they can induce micellization of foam in the reaction process.[81] Silica NPs, especially amorphous silica NPs, are widely used in medical applications such as chemotherapy drug delivery and multimodal imaging. The performance of MSN mainly depends on the composition, particle size, and dispersion of the inorganic phase.[82]

Introducing MSNs into polyester can greatly improve the crystallization, mechanical, and other properties of nanocomposites. In addition, the excellent optical transparency of MSNs can be used to obtain fluorescent PET, further expanding the application potential of MSNs.[83] In an in vitro and in vivo study reporting mesoporous and drum shaped silica nanospheres as drug carriers,[84] silica nanocolumns were developed for the first time as drug delivery systems for in vitro and in vivo liver cancer treatment. Loading docetaxel into PEGylated silica nanospheres (SN-PEG) resulted in lower systemic toxicity and stronger anti-tumor activity.[85] Tang et al[85] systematically reviewed the advancements in mesoporous silica NPs and their multifunctional carriers for drug delivery systems, demonstrating silica NPs' potential as promising drug carrier candidates. Their study further indicated that polymer nanocarriers might represent the most effective approach for controlled and sustained delivery of anticancer targeted drugs. It can overcome the limitations of liposomes because they are more stable in vivo, with longer drug circulation times, higher drug loading capacity, more uniform size distribution, and the ability, and can produce more controlled and targeted drug release curves at extended time periods and different predetermined rates,[86] while also avoiding renal rejection reactions. Table 1 summarizes the applications of several common nanocarriers.

Synergistic Integration of NPs and Anti-Angiogenic Agents in TACE

Most embolization procedures cause ischemic damage to tumors, thereby creating a deep hypoxic TME that leads to upregulation of hypoxia inducible factor-1α (HIF-1α). Upregulation of HIF-1 α can lead to overexpression of the pro angiogenic vascular endothelial growth factor (VEGF) gene, followed by a systemic increase in VEGF.[30,94] To counteract this adaptive response, integrating anti-angiogenic agents with NPs in TACE has emerged as a promising strategy to enhance therapeutic efficacy. Anti-angiogenic drugs such as sorafenib, sunitinib, and vandetanib have shown synergistic effects when delivered via NPs.[95] For instance, sorafenib-loaded drug-eluting microspheres in DEB-TACE demonstrate prolonged local retention and reduced systemic exposure compared to free drug formulations.[96,97] Clinically, combinations of TACE and sorafenib have shown survival benefits for unresectable HCC patients, particularly those with tumor recurrence.[26,97] Nanostructured lipid carriers (NLCs) further exemplify this synergistic approach. Bondì et al (2015) developed NLCs for controlled sorafenib release, demonstrating enhanced anticancer activity compared to free drugs in vitro.[98] The lipid-based carriers exhibit biocompatibility and sustained drug release, characteristics that optimize tumor-targeted delivery while sparing healthy liver tissue supplied by the portal vein. Similarly, sunitinib- and vandetanib-loaded magnetic beads have been validated for effective embolization and anti-angiogenic therapy, leveraging nanoparticle surface modifications to enhance drug retention.[99,100]

Table 1 Application of Several Common Nanocarriers

Nano-Carrier	Drug	Mechanism	Cell Line	Consequence	References
Gold nanoparticle	Doxorubicin	Chemical photothermal combined therapy	BEL-7402 tumor-bearing nude mice	DHTP Au nanocarriers mediated integrative therapy significantly delayed tumor growth.	[87]
Polymer nanoparticle	Various anticancer agents	Targeted drug delivery	HepG2	TPGS-b-PCL NPs loaded with SFB was more effective in inhibiting HepG2 cell growth and delaying tumor growth.	[88]
Lipid nanoparticles	Adriamycin and curcumin	Increase the accumulation of drugs at the tumor site, improve permeability and retention	HepG2	It has a synergistic effect on HCC apoptosis, proliferation and angiogenesis.	[89]
Silica nanoparticles	Doxorubicin	Tissue and nucleus specific targeting	H22 tumor bearing mouse model	TLS11a-LB@TATp-MSN/DOX reduces systemic side effects while enhancing anti-tumor effects.	[90]
Micelle	Sorafenib	Peg-poly(ε-caprolactone) micelles can increase the concentration of sorafenib in tumor tissues	Tumor bearing mouse model	Showed higher tumor growth inhibition in vivo.	[91]
Chitosan coated multi-walled carbon nanotubes	Doxorubicin		HepG2, mice with H22 tumors	O-CNTs-LCH-DOX showed higher antitumor activity and stronger fluorescence intensity in tumor tissues.	[92]
Graphene oxide	Protocatechuic acid	Conjugation and surface adsorption	Human hepatocytes, HepG2	GAGP Au has significant cytotoxicity to human hepatocellular carcinoma line (HepG2).	[93]

Abbreviations: DHTP Au nanocarriers, A system that can load doxorubicin, consisting of hyaluronic acid-grafted and A54 peptide-targeted PEGylated AuNCs; HepG2, Human Hepatocellular Carcinoma cell line G2; TPGS-b-PCL, d-α-Tocopheryl Polyethylene Glycol Succinate-b-Poly(ε-caprolactone)("b" means block); TLS11a - LB@TATp - MSN/DOX, A nanodrug carrier system for tumor - targeted therapy; CNTs-LCH-DOX, A galactosylated chitosan-grafted oxidized carbon nanotube system for pH-dependent sustained release and hepatic tumor-targeted delivery of doxorubicin; GAGPAu, Nanocomposite derived from conjugating Gd with PA (forming GAGPA) and subsequent coating with AuNPs.

https://doi.org/10.2147/IJN.S527518

Some traditional Chinese medicine (TCM) components such as berberine, curcumin, and ginsenoside Rg3 have also been demonstrated to possess potential anti-angiogenic effects. Numerous studies[101,102] have confirmed that co-delivery carriers composed of these components and NPs may be effective for treating human HCC. Zhang et al prepared the pH-sensitive NPs, composed by d-α-tocopheryl polyethylene glycol 1000-block-poly(β-amino ester) (TPGS-PAE) polymers for co-delivery of doxorubicin and curcumin. This system promotes apoptosis and anti-angiogenesis, enhancing anti-tumor efficacy while reducing systemic toxicity.[103] Huang et al developed novel galactosylated chitosan (GC)-modified NPs (GC@NPs) based on poly(ethylene glycol) methyl ether block-poly(lactide-co-glycolide) (PEG-PLGA). These NPs can target the asialoglycoprotein receptor (ASGPR) expressed on HCC cells, release curcumin for chemotherapy, achieve higher drug accumulation at the tumor site, and enhance antitumor therapy.[104] Yue et al prepared disulfide bond (S-S)-bridged mesoporous silica NPs (SS-MON), which promote berberine release by breaking the disulfide bonds in SS-MON and exhibit excellent isotype targeting ability, selectively killing cancer cells without harming normal cells.[105] The document introduces a nanohybrid synthetic nanomedicine that combines ginsenosides with self-targeting and enhanced MRI contrast and applies it to liver cancer treatment, demonstrating good antitumor effects.[106]

This integrative strategy addresses both the physical occlusion of tumor blood supply and the molecular drivers of angiogenesis, offering a dual-pronged approach to suppress tumor progression. By leveraging NPs as delivery platforms for anti-angiogenic agents, TACE protocols can achieve more durable local control and mitigate the risk of treatment resistance associated with TME.

NPs for Image Guidance in TACE

Images play an important role in TACE surgery, helping doctors determine the branches of the hepatic artery and the location of tumors, thus facilitating better embolization. In addition, imaging can also help doctors evaluate the effectiveness of embolization and the prognosis of patients. Due to the multiple branches of the hepatic artery, traditional TACE treatment may inject into the wrong blood vessel branches, resulting in unnecessary damage. Secondly, embolic agents may not be able to completely block the blood supply to tumors, resulting in poor treatment outcomes. Radiation and MRI visible microspheres and NPs are embolic agents that can be visualized on imaging, and their appearance has brought important progress to TACE therapy. In addition, these microspheres and NPs can be detected to evaluate the effectiveness of embolization and the prognosis of patients, and adjust treatment plans in a timely manner. Secondly, radioactive microspheres and NPs can release radioactive substances, thereby killing cancer cells and enhancing therapeutic efficacy.[107] At present, commonly used radioactive microspheres and NPs include yttrium (90Y) microspheres[108–110] and iodine (131I) microspheres.[111] These microspheres can be accurately located through imaging examination after embolization, thereby achieving better therapeutic effects. The visible microspheres and NPs in MRI include ferrite (Fe3O4) NPs,[112–114] gadolinium (Gd) NPs,[115] etc. Researchers are exploring the combination of radioactive and MRI visible microspheres and NPs with other therapeutic methods, such as immunotherapy and targeted therapy, to improve treatment efficacy and reduce side effects.

The Application Principle of NPs in Image Guidance

Image guided technology refers to the use of imaging techniques to accurately locate target areas and monitor changes in real-time during the treatment process, in order to improve the accuracy and effectiveness of treatment. The application of NPs in image guidance is mainly based on their characteristics in the following aspects: (1) Enhancing imaging contrast.[116] NPs can significantly improve imaging contrast by adsorbing or encapsulating specific contrast agents, such as iodine, gadolinium, etc. Especially in imaging techniques such as MRI (magnetic resonance imaging) and CT (computed tomography), NPs as contrast agents can more clearly display the lesion area and provide accurate diagnostic information for doctors. (2) Targeting.[117,118] The surface of NPs can be modified with specific ligands (such as antibodies, peptides, small molecules, etc.) to enable them to specifically bind to target cells or tissues. This targeting ability enables NPs to accurately locate the lesion area in image guidance, improving the specificity and sensitivity of imaging. (3) Multifunctionality.[119] NPs can integrate multiple functions such as imaging, therapy, and diagnosis together to form a multimodal imaging probes. This multifunctionality not only improves the accuracy of diagnosis but also provides the possibility for achieving precise treatment.

Application of NPs as Contrast Agents

NPs can be used as contrast agents for vascular imaging during TACE process.[120–122] By injecting contrast agents containing NPs, doctors can clearly observe the morphology, distribution, and blood flow of blood vessels, providing accurate evidence for subsequent embolization treatment.

MRI Imaging

MRI is a non-invasive imaging diagnostic technique widely used in clinical diagnosis and treatment. However, MRI still faces difficulties in detecting small lesions or early-stage diseases. NPs have become powerful tools for improving MRI resolution and accuracy due to their unique magnetic and imaging enhancing abilities. By adjusting the size, shape, and surface modification of NPs, their magnetism and stability can be optimized to achieve high contrast imaging of specific tissues or lesions. In the past few decades, T2 weighted contrast agents based on iron oxide NPs have been used in clinical trials,[123,124] and iron platinum NPs (FePt NPs) can also be used for precise MRI detection, characterized by the generation of magnetocaloric energy for cancer-related applications.

Recently, SPIONs are widely utilized contrast agents in liver magnetic resonance imaging. Lihong et al[125] evaluated SPION with different coatings (SMG and SHP) and core sizes (10 nm and 30 nm) for liver MR imaging and found that SHP-30 is an effective contrast agent for liver MR imaging, with the best contrast and highest macrophage uptake, and may be an improved alternative to Felide liver imaging. Wei et al[126] developed magnetic embolic microspheres based on SPION with low Curie temperature. Under the action of an alternating magnetic field, the embolic microspheres can automatically adjust the thermal therapy temperature to around 50°C, and the drugs loaded in the microspheres can be released in a controllable manner. Embolic microspheres can also be detected by CT and MR. These characteristics enable microspheres to simultaneously achieve self regulating temperature hyperthermia, on-demand drug release, embolization, and CT/MR imaging.[127] Moghadam[127] systematically reviewed the diagnostic applications of SPIONs as contrast agents for MRI.

CT Imaging

CT technology can provide high-resolution three-dimensional tomographic images, but there are limitations in detecting low contrast lesions.[128] NPs as CT contrast agents can effectively improve the contrast of images. Compared with traditional iodine contrast agents, NPs have higher atomic numbers and densities, which can better absorb X-rays and produce stronger contrast effects.

Currently, gold is the most commonly used material in the research of magnetic NPs (MNPs) as a CT imaging component. Tseng et al[129] used multiple gold NPs to bind to the surface of MNPs. In this study, multiple extremely small IONPs with a diameter of about 2nm were adsorbed on the surface of worm like mesoporous SiO2 NPs through electrostatic interactions. Then, a layer of mesoporous SiO2 shell was coated on the outer surface, and AuNPs were anchored outside the silicon shell through boronic ester bonds, thus constructing a nano drug delivery system with T1W-MRI/CT dual-mode imaging function.

Yang et al[130] self-assembled two-dimensional nanomaterials WS2 and IONPs, coated them with mesoporous silica, and surface modified them with PEG to construct an MRI/CT dual-mode imaging system WS2-IO@MS-PEG A multifunctional nano drug delivery platform, in which WS2 can absorb X-rays for CT imaging and near-infrared lasers for photothermal therapy. Liu et al[131] developed polymer composite microspheres capable of simultaneously loading 177Lu and MgO NPs, demonstrating ideal in vivo stability. This microsphere is used for interventional radioembolization therapy of liver cancer and allows for real-time SPECT/CT imaging for up to 8 weeks.

Fluorescence Imaging

NPs can also be used for fluorescence imaging, by introducing fluorescent labels on their surfaces to achieve detection and imaging of specific regions. This method not only improves the accuracy and sensitivity of imaging but also has real-time and non-invasive capabilities, providing important support for clinical diagnosis and treatment. Hanchen et al[132] developed a therapeutic diagnostic nanoplatform CSP for targeted gene therapy of HCC/TPE@siRNA-SP94 by testing its dual imaging modalities (fluorescence and MRI), enhanced imaging characteristics were demonstrated, and in vivo anti-

Table 2 Several Common Contrast Agents for Imaging Diagnosis and Treatment of HCC

Contrast Agent Type	Nanoparticles	Cell Model	Advantage/Application	References
Gadolinium contrast agent	PEG-Gd_2O_3NPs	BALB/c nude mouse	PEG-Gd2O3NPs as MRI nano-contrast agent has high relaxation and enhanced imaging effect.	[134]
Manganese contrast agent	CTN-MnO_2-PEG	Nude mice with HeLa tumor	CNT-MnO_2 -PEG can be used to target tumor ablation and real-time disease tracking.	[135]
	HMS	HCC, NEC and ADC nude mice bearing the tumor	It has low systemic toxicity and can release Mn2+ as a liver-specific MR contrast agent in liver tumor models under physiologically acidic conditions.	[136]
	DMNF	MCF-7 tumor-bearing BALB/c nude mice	DMNF shows high tumor-specific MRI and enhanced T1-weighted imaging effects as well as high spatial resolution imaging of the liver.	[137]
	Mn_3O_4 nano-cluster	Nude mice bearing the tumor	It has high biosafety and colloidal stability, and can be used as T1 magnetic resonance contrast agent for accurate diagnosis of tumors.	[138]
Iron oxide contrast agent	Fe (3) O (4)/MnO hybrid nanocrystals	BALB/c nude mice	It can be used as double contrast agent to obtain double contrast enhanced MR Images.	[139]
	atta@Fe_3O_4@Ru nanocarrier		It has fluorescence and magnetic properties as well as significant magnetic resonance properties, further improving the visibility of liver cancer tissue and normal liver tissue.	[140]

Abbreviations: PEG-Gd_2O_3NPs, Pegylated gadolinium oxide nanoparticles; CTN-MnO2—PEG, Therapeutic diagnostic nanoplatform related to tumor microenvironment; HMS, Hollow manganese silicate nanoparticles; NEC, Neuroendocrine Carcinoma; ADC, Adenocarcinoma; DMNF, DNA-Mn hybrid nanoflower; MCF-7, Human Mammary Carcinoma Cell Line 7.

https://doi.org/10.2147/IJN.S527518

tumor studies also showed significant anti-tumor properties. A new type of europium oxide NP[133] can mediate fluorescence imaging from emitting drugs and even detect ultra small tumors below 1 millimeter. These can all be used for fluorescence imaging during TACE process to improve the efficacy of TACE. Table 2 summarizes several common contrast agents that can be used for imaging diagnosis and treatment of HCC.

Imaging Advantages of NPs in TACE

Improve Visualization Effect

NPs, due to their extremely small size and unique physicochemical properties, can significantly improve imaging resolution and contrast. For example, superparamagnetic iron oxide SPIONs can clearly display the distribution and dynamic changes of NPs in vivo under MRI, thereby monitoring the therapeutic effect of TACE in real time.[141] PVA microspheres loaded with Lipiodol[142] and CT imaging detection improved visualization effects and provided three-dimensional spatial distribution of embolic materials in target organs, which can provide real-time intraoperative feedback for interventional radiologists.

Multimodal Imaging Capability

Some NPs possess multimodal imaging capabilities, such as SPIONs,[143–145] which not only play a role in MRI, but can also be combined with other imaging techniques such as ultrasound imaging, X-ray, CT, etc. to achieve multimodal and multi angle imaging. The reason why SPIONs can be used for tumor imaging:[146] (1) They have a unique imaging mechanism, SPIONs can shorten T2 and cause image darkening; (2) Having the characteristics of NPs, intravenous injection can be cleared by macrophages in the liver, spleen, lymph nodes, and bone marrow, and can be highly taken up; (3) It can be transmitted to tumors through EPR effects. Drug carriers loaded with SPIONs, such as liposomes, micelles, and NPs, can target drug delivery under external magnetic field conditions and observe drug delivery in real-time under MRI. This multimodal imaging capability helps doctors to more comprehensively understand the state of tumors and develop more accurate treatment plans,[127] which has become a research hotspot recently.[147]

Chunxia et al[148] combined the unique advantages of upconversion NPs and mesoporous silica to construct a multifunctional anti-cancer drug nanocarrier, which absorbed doxorubicin into the nanospheres without increasing cytotoxicity. T1 weighted MRI measured in aqueous solution showed that contrast enhancement increased with the concentration of Gd 3+component. Dong Hyun et al[149] used the microfluidic gel process to prepare MRI/CT visible drug eluting nanocomposite microspheres containing multimodal imaging contrast agents (magnetic clusters and gold nanorods), and evaluated their drug release curves and imaging characteristics in vivo and in vitro for the first time, and found that they had the potential of MRI/CT detection. Dawei et al[150] prepared Fe@EGaIn/CA microspheres integrate CT/MR dual-mode imaging and Fe@EGa in the photothermal/photodynamic functions of NP core and the embolization and drug loading functions of CA microspheres are utilized to achieve intelligent chemoembolization.

Summary and Prospect

HCC is a malignant tumor of the digestive tract that poses a serious threat to human health. Early diagnosis and effective treatment have always been the focus of research. This review highlights that nanotechnology enhances TACE for HCC by enabling targeted drug delivery and multimodal imaging guidance. Drug-eluting nanospheres facilitate sustained chemotherapy release, while imaging NPs enable real-time visualization of tumor vasculature during interventions, enhancing treatment precision.

In precise drug delivery, nanocarriers enhance chemotherapeutic accumulation in tumor tissues by 2–3 times while reducing systemic exposure through active targeting modification (eg, CD147 antibody-conjugated liposomes) and intelligent release mechanisms (eg, pH-responsive mesoporous silica). Such designs break through the drug release limitations of traditional embolic agents, significantly reducing damage to normal liver tissue through a “precision blasting” model. These innovations address critical TACE limitations, such as incomplete tumor embolization and systemic toxicity, by improving intratumoral drug accumulation and minimizing off-target effects. The innovation in multimodal imaging guidance represents a key breakthrough where nanotechnology empowers TACE. SPIONs have improved intraoperative vascular imaging precision to the capillary level (diameter <10 μm). Combined with CT/MRI

dual-modal nanoprobes (eg, gold nanorod-magnetic bead complexes), they can significantly reduce embolization range assessment errors. Real-time visualization not only optimizes intraoperative decision-making but also reduces post-operative recurrence rates through dynamic monitoring of tumor blood supply changes. Regarding synergistic therapy, NPs address treatment resistance by integrating anti-angiogenic, photothermal, and other multiple mechanisms.

Despite the promising prospects, clinical translation of nanotechnology faces significant challenges: (1) Insufficient long-term biocompatibility data for nanocarriers; (2) Control of particle size uniformity in industrial production (current microfluidic technology has a deviation of ±15 nm, requiring further optimization); (3) Variability in targeting efficiency due to tumor heterogeneity (approximately 30% of HCC patients exhibit low antigen expression affecting antibody targeting efficacy). Additionally, complex manufacturing processes and high costs limit clinical scalability and so on. Future research should prioritize developing multifunctional nanocarriers that integrate drug delivery, imaging, and responsive release mechanisms to tackle tumor complexity. Personalized nanomedicine strategies—tailoring nanoparticle properties (eg, size, surface charge) to individual tumor characteristics—and optimizing preclinical models to mimic human HCC microenvironments are also essential to advance translational outcomes for nanotechnology-based TACE.

In summary, nanotechnology is driving a paradigm shift in TACE from "empirical treatment" to "precision medicine" through targeted delivery, imaging innovation, and mechanistic synergy. With the deep integration of materials science and interventional technology, NPs are poised to become a core breakthrough for survival benefits in advanced HCC patients, with their clinical translation prospects warranting close attention.

Abbreviations

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; NPs, nanoparticles; HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinical Liver Cancer; TME, tumor microenvironment; SPIONs, superparamagnetic iron oxide nanoparticles; DEB-TACE, drug eluting bead transarterial chemoembolization; HAE, hepatic artery embolization; ECOG, Eastern Cooperative Oncology Group; DEBs, drug-eluting beads; EPR, enhanced permeability and retention effect; RES, reticuloendothelial system; SPR, surface plasmon resonance; AuNPs, gold NPs; MSN, mesoporous silica NPs; SN-PEG, PEGylated silica nanospheres; HIF-1α, hypoxia inducible factor-1α; VEGF, vascular endothelial growth factor; NLCs, nanostructured lipid carriers; TCM, traditional Chinese medicine; GC@NPs, galactosylated chitosan (GC)-modified NPs; ASGPR, asialoglycoprotein receptor; PEG-PLGA, poly(ethylene glycol) methyl ether-block-poly(lactide-co-glycolide); SS-MONs, disulfide (S-S)-bridged mesoporous organosilica nanoparticles; MRI, magnetic resonance imaging; CT, computed tomography; MNPs, magnetic NPs; IONP, iron oxide nanoparticle.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by The National Key Research and Development Program (2022YFC2603500, 2022YFC2603505). The Capital Health Research and Development of Special Public Health Project (2022-1-2172). Beijing Municipal Health Commission High-Level Public Health Technical Personnel Construction Project, discipline leader-03-26. The Digestive Medical Coordinated Development Center of Beijing Hospitals Authority (XXZ0302). Beijing Hospitals Authority Clinical Medicine Development of Special Funding Support (XMLX 202127). Major Special Projects during the 14th Five Year Plan (2023YFC2306901, 2023YFC2308105).

Disclosure

The authors declare no conflicts of interest.

References

1. Zheng RS, Chen R, Han BF, et al. [Cancer incidence and mortality in China, 2022]. *Zhonghua Zhong Liu Za Zhi*. 2024;46(3):221–231. doi:10.3760/cma.j.cn112152-20240119-00035
2. Kim E, Viatour P. Hepatocellular carcinoma: old friends and new tricks. *Exp Mol Med*. 2020;52(12):1898–1907. doi:10.1038/s12276-020-00527-1
3. Shi JF, Cao M, Wang Y, et al. Is it possible to halve the incidence of liver cancer in China by 2050? *Int J Cancer*. 2021;148(5):1051–1065. doi:10.1002/ijc.33313
4. Balogh J, Victor D, Asham EH, et al. Hepatocellular carcinoma: a review. *J Hepatocell Carcinoma*. 2016;3:41–53. doi:10.2147/JHC.S61146
5. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76(3):681–693. doi:10.1016/j.jhep.2021.11.018
6. Belghiti J, Kianmanesh R. Surgical treatment of hepatocellular carcinoma. *HPB*. 2005;7(1):42–49. doi:10.1080/13651820410024067
7. Vogl TJ, Zangos S, Balzer JO, et al. [Transarterial chemoembolization (TACE) in hepatocellular carcinoma: technique, indication and results]. *RoFo: Fortschritte Auf Dem Gebiete Der Rontgenstrahlen Und Der Nuklearmedizin*. 2007;179(11):1113–1126. doi:10.1055/s-2007-963285
8. Zou JH, Zhang L, Ren ZG, et al. Efficacy and safety of cTACE versus DEB-TACE in patients with hepatocellular carcinoma: a meta-analysis. *J Digestive Dis*. 2016;17(8):510–517. doi:10.1111/1751-2980.12380
9. Petrillo M, Patella F, Pesapane F, et al. Hypoxia and tumor angiogenesis in the era of hepatocellular carcinoma transarterial loco-regional treatments. *Future Oncol*. 2018;14(28):2957–2967. doi:10.2217/fon-2017-0739
10. Ren Z, Chen X, Hong L, et al. Nanoparticle conjugation of ginsenoside Rg3 inhibits hepatocellular carcinoma development and metastasis. *Small*. 2020;16(2):e1905233. doi:10.1002/smll.201905233
11. Kang T, Zhu Q, Wei D, et al. Nanoparticles coated with neutrophil membranes can effectively treat cancer metastasis. *ACS nano*. 2017;11(2):1397–1411. doi:10.1021/acsnano.6b06477
12. Chen J, White SB, Harris KR, et al. Poly(lactide-co-glycolide) microspheres for MRI-monitored delivery of sorafenib in a rabbit VX2 model. *Biomaterials*. 2015;61:299–306. doi:10.1016/j.biomaterials.2015.05.010
13. Ghanaati H, Mohammadifard M, Mohammadifard M. A review of applying transarterial chemoembolization (TACE) method for management of hepatocellular carcinoma. *J Family Med Primary Care*. 2021;10(10):3553. doi:10.4103/jfmpc.jfmpc_2347_20
14. Osman A, Patel S, Gonsalves M, et al. Vascular interventions in oncology. *Clin Oncol*. 2024;36(8):473–483. doi:10.1016/j.clon.2023.09.005
15. Chen YP, Zhang JL, Zou Y, Wu YL. Recent advances on polymeric beads or hydrogels as embolization agents for improved transcatheter arterial chemoembolization (TACE). *Front Chem*. 2019;7:408. doi:10.3389/fchem.2019.00408
16. Chang Y, Jeong SW, Young Jang J, Jae Kim Y. Recent updates of transarterial chemoembololization in hepatocellular carcinoma. *Int J Mol Sci*. 2020;21(21):8165. doi:10.3390/ijms21218165
17. Liu S, Han Y, Zhang Z, et al. Effectiveness of c-TACE combined with sorafenib versus c-TACE monotherapy in advanced hepatocellular carcinoma: a retrospective study. Clinical medicine insights. *Oncology*. 2023;17:11795549221146648. doi:10.1177/11795549221146648
18. Nouri YM, Kim JH, Yoon HK, et al. Update on transarterial chemoembolization with drug-eluting microspheres for hepatocellular carcinoma. *Korean J Radiol*. 2019;20(1):34–49. doi:10.3348/kjr.2018.0088
19. Song MJ, Chun HJ, Song DS, et al. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. *J Hepatol*. 2012;57(6):1244–1250. doi:10.1016/j.jhep.2012.07.017
20. Han T, Yang X, Zhang Y, et al. The clinical safety and efficacy of conventional transcatheter arterial chemoembolization and drug-eluting beads-transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: a meta-analysis. *Biosci Trends*. 2019;13(5):374–381. doi:10.5582/bst.2019.01153
21. Pompili M, Francica G, Ponziani FR, et al. Bridging and downstaging treatments for hepatocellular carcinoma in patients on the waiting list for liver transplantation. *World J Gastroenterol*. 2013;19(43):7515–7530. doi:10.3748/wjg.v19.i43.7515
22. Monier A, Guiu B, Duran R, et al. Liver and biliary damages following transarterial chemoembolization of hepatocellular carcinoma: comparison between drug-eluting beads and lipiodol emulsion. *Eur Radiol*. 2017;27(4):1431–1439. doi:10.1007/s00330-016-4488-y
23. Lanza C, Ascenti V, Amato GV, et al. All you need to know about TACE: a comprehensive review of indications, techniques, efficacy, limits, and technical advancement. *J Clin Med*. 2025;14(2):314. doi:10.3390/jcm14020314
24. Lencioni R, Petruzzi P, Crocetti L. Chemoembolization of hepatocellular carcinoma. *Semin Intervent Radiol*. 2013;30(1):3–11. doi:10.1055/s-0033-1333648
25. Pesapane F, Nezami N, Patella F, et al. New concepts in embolotherapy of HCC. *Med Oncol*. 2017;34(4):58. doi:10.1007/s12032-017-0917-2
26. Varghese J, Kedarisetty C, Venkataraman J, et al. Combination of TACE and sorafenib improves outcomes in BCLC stages B/C of hepatocellular carcinoma: a single centre experience. *Ann Hepatol*. 2017;16(2):247–254. doi:10.5604/16652681.1231583
27. Wang Q, Zhu L, Sheng Q. Clinical research progress of callisperes® of drug-loaded microsphere arterial chemoembolisation in the treatment of solid tumors. *Discov Oncol*. 2024;15(1):161. doi:10.1007/s12672-024-01030-z
28. Bekaroğlu MG, Nurili F, Caymaz İ, et al. Novel magnetic embolic MRI imageable particles with anticancer drug release for transcatheter arterial embolization and magnetic ablation. *Med Phys*. 2023;50(4):1990–1998. doi:10.1002/mp.16052
29. Sieghart W, Hucke F, Peck-Radosavljevic M. Transarterial chemoembolization: modalities, indication, and patient selection. *J Hepatol*. 2015;62(5):1187–1195. doi:10.1016/j.jhep.2015.02.010
30. Feng JK, Liu ZH, Fu ZG, et al. Efficacy and safety of transarterial chemoembolization plus antiangiogenic- targeted therapy and immune checkpoint inhibitors for unresectable hepatocellular carcinoma with portal vein tumor thrombus in the real world. *Front Oncol*. 2022;12:954203. doi:10.3389/fonc.2022.954203
31. Hu CMJ, Aryal S, Zhang L. Nanoparticle-assisted combination therapies for effective cancer treatment. *Therap Delivery*. 2010;1(2):323–334. doi:10.4155/tde.10.13
32. Wang M, Liang Y, Jiang X, et al. α-Fe2O3@Au-PEG-Ce6-Gd nanoparticles as acidic H2O2-driven oxygenators for multimodal imaging and synergistic tumor therapy. *Langmuir*. 2023;39(15):5333–5341. doi:10.1021/acs.langmuir.2c03388
33. Chen J, Nguyen VP, Jaiswal S, et al. Thin layer-protected gold nanoparticles for targeted multimodal imaging with photoacoustic and CT. *Pharmaceuticals*. 2021;14(11):1075. doi:10.3390/ph14111075

34. Mintz KJ, Leblanc RM. The use of nanotechnology to combat liver cancer: progress and perspectives. *Biochim Biophys Acta Rev Cancer*. 2021;1876(2):188621. doi:10.1016/j.bbcan.2021.188621
35. Baranov MV, Kumar M, Sacanna S, et al. Modulation of immune responses by particle size and shape. *Front Immunol*. 2020;11:607945. doi:10.3389/fimmu.2020.607945
36. Truong NP, Whittaker MR, Mak CW, et al. The importance of nanoparticle shape in cancer drug delivery. *Expert Opin Drug Delivery*. 2015;12 (1):129–142. doi:10.1517/17425247.2014.950564
37. Ke X, Howard GP, Tang H, et al. Physical and chemical profiles of nanoparticles for lymphatic targeting. *Adv Drug Delivery Rev*. 2019;151–152:72–93. doi:10.1016/j.addr.2019.09.005
38. He Y, Wang Y, Wang L, et al. Understanding nanoparticle-liver interactions in nanomedicine. *Expert Opin Drug Delivery*. 2024;21(6):829–843. doi:10.1080/17425247.2024.2375400
39. Najahi-Missaoui W, Arnold RD, Cummings BS. Safe nanoparticles: are we there yet? *Int J Mol Sci*. 2020;22(1):385. doi:10.3390/ijms22010385
40. Hoshyar N, Gray S, Han H, et al. The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction. *Nanomedicine*. 2016;11 (6):673–692. doi:10.2217/nnm.16.5
41. Patra JK, Das G, Fraceto LF, et al. Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnol*. 2018;16 (1):71. doi:10.1186/s12951-018-0392-8
42. Chugh H, Sood D, Chandra I, et al. Role of gold and silver nanoparticles in cancer nano-medicine. *Artif Cells Nanomed Biotechnol*. 2018;46 (sup1):1210–1220. doi:10.1080/21691401.2018.1449118
43. Zhao J, Li YS, Liu ZX, et al. Nanosized drug-eluting bead for transcatheter arterial chemoembolization (ND-TACE). *J Mat Chem B*. 2020;8 (37):8684–8694. doi:10.1039/d0tb01295e
44. Bergen JM, Von Recum HA, Goodman TT, et al. Gold nanoparticles as a versatile platform for optimizing physicochemical parameters for targeted drug delivery. *Macromol biosci*. 2006;6(7):506–516. doi:10.1002/mabi.200600075
45. Geng Y, Dalhaimer P, Cai S, et al. Shape effects of filaments versus spherical particles in flow and drug delivery. *Nature Nanotechnol*. 2007;2 (4):249–255. doi:10.1038/nnano.2007.70
46. Prabhakar U, Maeda H, Jain RK, et al. Challenges and key considerations of the enhanced permeability and retention effect for nanomedicine drug delivery in oncology. *Cancer Res*. 2013;73(8):2412–2417. doi:10.1158/0008-5472.CAN-12-4561
47. Arvizo RR, Miranda OR, Thompson MA, et al. Effect of nanoparticle surface charge at the plasma membrane and beyond. *Nano Lett*. 2010;10 (7):2543–2548. doi:10.1021/nl101140t
48. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature Biotechnol*. 2015;33 (9):941–951. doi:10.1038/nbt.3330
49. Albanese A, Tang PS, Chan WCW. The effect of nanoparticle size, shape, and surface chemistry on biological systems. *Ann Rev Biomed Eng*. 2012;14:1–16. doi:10.1146/annurev-bioeng-071811-150124
50. Sarkar S, Osama K, Jamal QMS, et al. Advances and implications in nanotechnology for lung cancer management. *Curr Drug Metabolism*. 2017;18(1):30–38. doi:10.2174/1389200218666161114142646
51. Yousefi Rizi HA, Hoon Shin D, Yousefi Rizi S. Polymeric nanoparticles in cancer chemotherapy: a narrative review. *Iran J Public Health*. 2022;51(2):226–239. doi:10.18502/ijph.v51i2.8677
52. Verissimo TV, Santos NT, Silva JR, et al. In vitro cytotoxicity and phototoxicity of surface-modified gold nanoparticles associated with neutral red as a potential drug delivery system in phototherapy. *Mater Sci Eng C Mater Biol Appl*. 2016;65:199–204. doi:10.1016/j.msec.2016.04.030
53. Akhter S, Ahmad MZ, Ahmad FJ, et al. Gold nanoparticles in theranostic oncology: current state-of-the-art. *Expert Opin Drug Delivery*. 2012;9 (10):1225–1243. doi:10.1517/17425247.2012.716824
54. Hainfeld JF, Slatkin DN, Focella TM, et al. Gold nanoparticles: a new X-ray contrast agent. *Br J Radiol*. 2006;79(939):248–253. doi:10.1259/bjr/13169882
55. Kumar A, Zhang X, Liang XJ. Gold nanoparticles: emerging paradigm for targeted drug delivery system. *Biotechnol Adv*. 2013;31(5):593–606. doi:10.1016/j.biotechadv.2012.10.002
56. Qiu Y, Wu Z, Chen Y, et al. Nano ultrasound contrast agent for synergistic chemo-photothermal therapy and enhanced immunotherapy against liver cancer and metastasis. *Adv Sci*. 2023;10(21):e2300878. doi:10.1002/advs.202300878
57. Gupta N, Malviya R. Understanding and advancement in gold nanoparticle targeted photothermal therapy of cancer. *Biochim Biophys Acta Rev Cancer*. 2021;1875(2):188532. doi:10.1016/j.bbcan.2021.188532
58. Riley RS, Day ES. Gold nanoparticle-mediated photothermal therapy: applications and opportunities for multimodal cancer treatment. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2017;9(4). doi:10.1002/wnan.1449
59. Hwang S, Nam J, Jung S, et al. Gold nanoparticle-mediated photothermal therapy: current status and future perspective. *Nanomedicine*. 2014;9 (13):2003–2022. doi:10.2217/nnm.14.147
60. Turkmen Koc SN, Rezaei Benam S, Aral IP, et al. Gold nanoparticles-mediated photothermal and photodynamic therapies for cancer. *Int J Pharm*. 2024;655:124057. doi:10.1016/j.ijpharm.2024.124057
61. Cao K, Zhou Y, Shen Y, et al. Combined photothermal therapy and cancer immunotherapy by immunogenic hollow mesoporous silicon-shelled gold nanorods. *J Pharmaceut Sci*. 2024;113(8):2232–2244. doi:10.1016/j.xphs.2024.03.007
62. Zhou R, Zhang M, Xi J, et al. Gold nanorods-based photothermal therapy: interactions between biostructure, nanomaterial, and near-infrared irradiation. *Nanoscale Res Lett*. 2022;17(1):68. doi:10.1186/s11671-022-03706-3
63. Jeremic B, Aguerri AR, Filipovic N. Radiosensitization by gold nanoparticles. *Clin Transl Oncol*. 2013;15(8):593–601. doi:10.1007/s12094-013-1003-7
64. Xie J, Gong L, Zhu S, et al. Emerging strategies of nanomaterial-mediated tumor radiosensitization. *Adv Mater*. 2019;31(3):e1802244. doi:10.1002/adma.201802244
65. Huang D, Sun L, Huang L, Chen Y. Nanodrug delivery systems modulate tumor vessels to increase the enhanced permeability and retention effect. *J Personal Med*. 2021;11(2):124. doi:10.3390/jpm11020124
66. Euliss LE, Dupont JA, Gratton S, et al. Imparting size, shape, and composition control of materials for nanomedicine. *Chem Soc Rev*. 2006;35 (11):1095–1104. doi:10.1039/b600913c

67. Karn PR, Cho W, Hwang SJ. Liposomal drug products and recent advances in the synthesis of supercritical fluid-mediated liposomes. *Nanomedicine*. 2013;8(9):1529–1548. doi:10.2217/nnm.13.131
68. Guimarães D, Cavaco-Paulo A, Nogueira E. Design of liposomes as drug delivery system for therapeutic applications. *Int J Pharm*. 2021;601:120571. doi:10.1016/j.ijpharm.2021.120571
69. Sarfraz M, Afzal A, Raza SM, et al. Liposomal co-delivered oleanolic acid attenuates doxorubicin-induced multi-organ toxicity in hepatocellular carcinoma. *Oncotarget*. 2017;8(29):47136–47153. doi:10.18632/oncotarget.17559
70. Quagliariello V, Masarone M, Armenia E, et al. Chitosan-coated liposomes loaded with butyric acid demonstrate anticancer and anti-inflammatory activity in human hepatoma HepG2 cells. *Oncol Rep*. 2019;41(3):1476–1486. doi:10.3892/or.2018.6932
71. Wang J, Wu Z, Pan G, et al. Enhanced doxorubicin delivery to hepatocellular carcinoma cells via CD147 antibody-conjugated immunoliposomes. *Nanomed Nanotechnol Biol Med*. 2018;14(6):1949–1961. doi:10.1016/j.nano.2017.09.012
72. Fan Y, Marioli M, Zhang K. Analytical characterization of liposomes and other lipid nanoparticles for drug delivery. *J Pharm Biomed Analysis*. 2021;192:113642. doi:10.1016/j.jpba.2020.113642
73. Giraldo JD, García Y, Vera M, et al. Alternative processes to produce chitin, chitosan, and their oligomers. *Carbohydr Polym*. 2024;332:121924. doi:10.1016/j.carbpol.2024.121924
74. Jafernik K, Ładniak A, Blicharska E, et al. Chitosan-based nanoparticles as effective drug delivery systems–A review. *Molecules*. 2023;28(4):1963. doi:10.3390/molecules28041963
75. Song X, Wang J, Xu Y, et al. Surface-modified PLGA nanoparticles with PEG/LA-chitosan for targeted delivery of arsenic trioxide for liver cancer treatment: inhibition effects enhanced and side effects reduced. *Colloids Surf B*. 2019;180:110–117. doi:10.1016/j.colsurfb.2019.04.036
76. Mikušová V, Mikuš P. Advances in chitosan-based nanoparticles for drug delivery. *Int J Mol Sci*. 2021;22(17):9652. doi:10.3390/ijms22179652
77. Ye BL, Zheng R, Ruan XJ, et al. Chitosan-coated doxorubicin nano-particles drug delivery system inhibits cell growth of liver cancer via p53/PRC1 pathway. *Biochem Biophys Res Commun*. 2018;495(1):414–420. doi:10.1016/j.bbrc.2017.10.156
78. Badawy MMM, Abdel-Hamid GR, Mohamed HE. Antitumor activity of chitosan-coated iron oxide nanocomposite against hepatocellular carcinoma in animal models. *Biol Trace Elem Res*. 2023;201(3):1274–1285. doi:10.1007/s12011-022-03221-7
79. Kovtareva S, Kusepova L, Tazhkenova G, et al. Surface modification of mesoporous silica nanoparticles for application in targeted delivery systems of antitumour drugs. *Polymers*. 2024;16(8):1105. doi:10.3390/polym16081105
80. Xu B, Li S, Shi R, et al. Multifunctional mesoporous silica nanoparticles for biomedical applications. *Signal Transduct Target Ther*. 2023;8(1):435. doi:10.1038/s41392-023-01654-7
81. Gonçalves MC. Sol-gel silica nanoparticles in medicine: a natural choice. Design, synthesis and products. *Molecules*. 2018;23(8):2021. doi:10.3390/molecules23082021
82. Mohammed BS, Awang AB, Wong SS, et al. Properties of nano silica modified rubbercrete. *J Cleaner Prod*. 2016;119:66–75. doi:10.1016/j.jclepro.2016.02.007
83. Hao T, Wang Y, Liu Z, et al. Emerging applications of silica nanoparticles as multifunctional modifiers for high performance polyester composites. *Nanomaterials*. 2021;11(11):2810. doi:10.3390/nano11112810
84. Li L, Tang F, Liu H, et al. In vivo delivery of silica nanorattle encapsulated docetaxel for liver cancer therapy with low toxicity and high efficacy. *ACS nano*. 2010;4(11):6874–6882. doi:10.1021/nn100918a
85. Tang F, Li L, Chen D. Mesoporous silica nanoparticles: synthesis, biocompatibility and drug delivery. *Adv Mater*. 2012;24(12):1504–1534. doi:10.1002/adma.201104763
86. Chen F, Hableel G, Zhao ER, et al. Multifunctional nanomedicine with silica: role of silica in nanoparticles for theranostic, imaging, and drug monitoring. *J Colloid Interface Sci*. 2018;521:261–279. doi:10.1016/j.jcis.2018.02.053
87. Huang S, Li C, Wang W, et al. A54 peptide-mediated functionalized gold nanocages for targeted delivery of DOX as a combinational photothermal-chemotherapy for liver cancer. *Int J Nanomed*. 2017;12:5163–5176. doi:10.2147/IJN.S131089
88. Masood F. Polymeric nanoparticles for targeted drug delivery system for cancer therapy. *Mater Sci Eng C Mater Biol Appl*. 2016;60:569–578. doi:10.1016/j.msec.2015.11.067
89. Zhao X, Chen Q, Li Y, et al. Doxorubicin and curcumin co-delivery by lipid nanoparticles for enhanced treatment of diethylnitrosamine-induced hepatocellular carcinoma in mice. *Eur J Pharm Biopharm*. 2015;93:27–36. doi:10.1016/j.ejpb.2015.03.003
90. Ding Z, Wang D, Shi W, et al. In vivo targeting of liver cancer with tissue- and nuclei-specific mesoporous silica nanoparticle-based nanocarriers in mice. *Int J Nanomed*. 2020;15:8383–8400. doi:10.2147/IJN.S272495
91. Su Y, Wang K, Li Y, et al. Sorafenib-loaded polymeric micelles as passive targeting therapeutic agents for hepatocellular carcinoma therapy. *Nanomedicine*. 2018;13(9):1009–1023. doi:10.2217/nnm-2018-0046
92. Qi X, Rui Y, Fan Y, et al. Galactosylated chitosan-grafted multiwall carbon nanotubes for pH-dependent sustained release and hepatic tumor-targeted delivery of doxorubicin in vivo. *Colloids Surf B*. 2015;133:314–322. doi:10.1016/j.colsurfb.2015.06.003
93. Usman MS, Hussein MZ, Kura AU, et al. Graphene oxide as a nanocarrier for a theranostics delivery system of protocatechuic acid and gadolinium/gold nanoparticles. *Molecules*. 2018;23(2):500. doi:10.3390/molecules23020500
94. Kim KM, Kim JH, Park IS, et al. Reappraisal of repeated transarterial chemoembolization in the treatment of hepatocellular carcinoma with portal vein invasion. *J Gastroenterol Hepatol*. 2009;24(5):806–814. doi:10.1111/j.1440-1746.2008.05728.x
95. Abdalla AME, Xiao L, Ullah MW, et al. Current challenges of cancer anti-angiogenic therapy and the promise of nanotherapeutics. *Theranostics*. 2018;8(2):533–548. doi:10.7150/thno.21674
96. Park W, Cho S, Ji J, et al. Development and validation of sorafenib-eluting microspheres to enhance therapeutic efficacy of transcatheter arterial chemoembolization in a rat model of hepatocellular carcinoma. *Radiol Imaging Cancer*. 2021;3(1):e200006. doi:10.1148/rycan.2021200006
97. Wan X, Zhai X, Yan Z, et al. Retrospective analysis of transarterial chemoembolization and sorafenib in Chinese patients with unresectable and recurrent hepatocellular carcinoma. *Oncotarget*. 2016;7(50):83806–83816. doi:10.18632/oncotarget.11514
98. Bondì ML, Botto C, Amore E, et al. Lipid nanocarriers containing sorafenib inhibit colonies formation in human hepatocarcinoma cells. *Int J Pharm*. 2015;493(1–2):75–85. doi:10.1016/j.ijpharm.2015.07.055
99. Pokuri VK, Tomaszewski GM, Ait-Oudhia S, et al. Efficacy, safety, and potential biomarkers of sunitinib and transarterial chemoembolization (TACE) combination in advanced hepatocellular carcinoma (HCC): phase II trial. *Am J Clin Oncol*. 2018;41(4):332–338. doi:10.1097/COC.0000000000000286

100. Beaton L, Tregidgo HFJ, Znati SA, et al. VEROnA protocol: a pilot, open-label, single-arm, phase 0, window-of-opportunity study of vandetanib-eluting radiopaque embolic beads (BTG-002814) in patients with resectable liver malignancies. *JMIR Res Protocols*. 2019;8(10): e13696. doi:10.2196/13696
101. Luo H, Vong CT, Chen H, et al. Naturally occurring anti-cancer compounds: shining from Chinese herbal medicine. *ChinMed*. 2019;14:48. doi:10.1186/s13020-019-0270-9
102. Sun L, Lan J, Li Z, et al. Transforming cancer treatment with nanotechnology: the role of berberine as a star natural compound. *Int J Nanomed*. 2024;19:8621–8640. doi:10.2147/IJN.S469350
103. Zhang J, Li J, Shi Z, et al. pH-sensitive polymeric nanoparticles for co-delivery of doxorubicin and curcumin to treat cancer via enhanced pro-apoptotic and anti-angiogenic activities. *Acta Biomater*. 2017;58:349–364. doi:10.1016/j.actbio.2017.04.029
104. Huang M, Liu J, Fan Y, et al. Development of curcumin-loaded galactosylated chitosan-coated nanoparticles for targeted delivery of hepatocellular carcinoma. *Int J Biol Macromol*. 2023;253(Pt 6):127219. doi:10.1016/j.ijbiomac.2023.127219
105. Yue J, Wang Z, Shao D, et al. Cancer cell membrane-modified biodegradable mesoporous silica nanocarriers for berberine therapy of liver cancer. *RSC Adv*. 2018;8(70):40288–40297. doi:10.1039/c8ra07574c
106. Zhao X, Wang J, Song Y, et al. Synthesis of nanomedicines by nanohybrids conjugating ginsenosides with auto-targeting and enhanced MRI contrast for liver cancer therapy. *Drug Dev Ind Pharm*. 2018;44(8):1307–1316. doi:10.1080/03639045.2018.1449853
107. Mondini M, Levy A, Meziani L, et al. Radiotherapy-immunotherapy combinations - perspectives and challenges. *Mol Oncol*. 2020;14(7):1529–1537. doi:10.1002/1878-0261.12658
108. Dhondt E, Lambert B, Hermie L, et al. 90Y radioembolization versus drug-eluting bead chemoembolization for unresectable hepatocellular carcinoma: results from the TRACE phase II randomized controlled trial. *Radiology*. 2022;303(3):699–710. doi:10.1148/radiol.211806
109. El Fouly A, Ertle J, El Dorry A, et al. In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? *Liver Int*. 2015;35(2):627–635. doi:10.1111/liv.12637
110. Ludwig JM, Zhang D, Xing M, Kim HS. Meta-analysis: adjusted indirect comparison of drug-eluting bead transarterial chemoembolization versus 90Y-radioembolization for hepatocellular carcinoma. *Eur Radiol*. 2017;27(5):2031–2041. doi:10.1007/s00330-016-4548-3
111. Fan W, Wu Y, Lu M, et al. A meta-analysis of the efficacy and safety of iodine [131I] metuximab infusion combined with TACE for treatment of hepatocellular carcinoma. *Clin Res Hepatol Gastroenterol*. 2019;43(4):451–459. doi:10.1016/j.clinre.2018.09.006
112. Zheng M, Ma X, Hu J, et al. Novel recyclable BiOBr/Fe3O4/RGO composites with remarkable visible-light photocatalytic activity. *RSC Adv*. 2020;10(34):19961–19973. doi:10.1039/d0ra01668c
113. Barick KC, Singh S, Bahadur D, et al. Carboxyl decorated Fe3O4 nanoparticles for MRI diagnosis and localized hyperthermia. *J Colloid Interface Sci*. 2014;418:120–125. doi:10.1016/j.jcis.2013.11.076
114. Nowak-Jary J, Machnicka B. In vivo biodistribution and clearance of magnetic iron oxide nanoparticles for medical applications. *Int J Nanomed*. 2023;18:4067–4100. doi:10.2147/IJN.S415063
115. Van Elk M, Ozbakir B, Barten-Rijbroek AD, et al. Alginate microspheres containing temperature sensitive liposomes (TSL) for MR-guided embolization and triggered release of doxorubicin. *PLoS One*. 2015;10(11):e0141626. doi:10.1371/journal.pone.0141626
116. Felton C, Karmakar A, Gartia Y, et al. Magnetic nanoparticles as contrast agents in biomedical imaging: recent advances in iron- and manganese-based magnetic nanoparticles. *Drug Metab Rev*. 2014;46(2):142–154. doi:10.3109/03602532.2013.876429
117. Chen M, Shu G, Lv X, et al. HIF-2α-targeted interventional chemoembolization multifunctional microspheres for effective elimination of hepatocellular carcinoma. *Biomaterials*. 2022;284:121512. doi:10.1016/j.biomaterials.2022.121512
118. Liu T, Liu L, Li L, et al. Exploiting targeted nanomedicine for surveillance, diagnosis, and treatment of hepatocellular carcinoma. *Mater Today Bio*. 2023;22:100766. doi:10.1016/j.mtbio.2023.100766
119. Sharma KV, Dreher MR, Tang Y, et al. Development of "imageable" beads for transcatheter embolotherapy. *J Vasc Interv Radiol*. 2010;21 (6):865–876. doi:10.1016/j.jvir.2010.02.031
120. Kang KA, Nguyen MD. Gold nanoparticle-based fluorescent contrast agent with enhanced sensitivity. *Adv Exp Med Biol*. 2017;977:399–407. doi:10.1007/978-3-319-55231-6_52
121. Cole LE, Ross RD, Tilley JM, et al. Gold nanoparticles as contrast agents in x-ray imaging and computed tomography. *Nanomedicine*. 2015;10 (2):321–341. doi:10.2217/nnm.14.171
122. Taupin F, Flaender M, Delorme R, et al. Gadolinium nanoparticles and contrast agent as radiation sensitizers. *Phys Med Biol*. 2015;60 (11):4449–4464. doi:10.1088/0031-9155/60/11/4449
123. Yang J, Feng J, Yang S, et al. Exceedingly small magnetic iron oxide nanoparticles for T1 -weighted magnetic resonance imaging and imaging-guided therapy of tumors. *Small*. 2023;19(49):e2302856. doi:10.1002/smll.202302856
124. Castaneda RT, Khurana A, Khan R, et al. Labeling stem cells with ferumoxytol, an FDA-approved iron oxide nanoparticle. *J Visualized Exp*. 2011;(57):e3482. doi:10.3791/3482
125. Bu L, Xie J, Chen K, et al. Assessment and comparison of magnetic nanoparticles as MRI contrast agents in a rodent model of human hepatocellular carcinoma. *Contrast Media Mol Imaging*. 2012;7(4):363–372. doi:10.1002/cmmi.494
126. Wei C, Wu C, Jin X, et al. CT/MR detectable magnetic microspheres for self-regulating temperature hyperthermia and transcatheter arterial chemoembolization. *Acta Biomater*. 2022;153:453–464. doi:10.1016/j.actbio.2022.09.054
127. Moghadam FF. Using nanoparticles in medicine for liver cancer imaging. *Oman Med Journal*. 2017;32(4):269–274. doi:10.5001/omj.2017.54
128. Cazzato RL, Garnon J, Shaygi B, et al. PET/CT-guided interventions: indications, advantages, disadvantages and the state of the art. Minimally invasive therapy & allied technologies: MITAT. *Official J Soc Mini Invasive Ther*. 2018;27(1):27–32. doi:10.1080/13645706.2017.1399280
129. Tseng YJ, Chou SW, Shyue JJ, et al. A versatile theranostic delivery platform integrating magnetic resonance imaging/computed tomography, pH/cis-diol controlled release, and targeted therapy. *ACS nano*. 2016;10(6):5809–5822. doi:10.1021/acsnano.5b08130
130. Yang G, Gong H, Liu T, et al. Two-dimensional magnetic WS2@Fe3O4 nanocomposite with mesoporous silica coating for drug delivery and imaging-guided therapy of cancer. *Biomaterials*. 2015;60:62–71. doi:10.1016/j.biomaterials.2015.04.053
131. Xiao L, Li Y, Geng R, et al. Polymer composite microspheres loading 177Lu radionuclide for interventional radioembolization therapy and real-time SPECT imaging of hepatic cancer. *Biomater Res*. 2023;27(1):110. doi:10.1186/s40824-023-00455-x
132. Zhang H, Deng L, Liu H, et al. Enhanced fluorescence/magnetic resonance dual imaging and gene therapy of liver cancer using cationized amylose nanoprobe. *Mater Today Bio*. 2022;13:100220. doi:10.1016/j.mtbio.2022.100220

133. Dai YW, Zhu LX, Zhang Y, et al. Au@SiO2@CuInS2-ZnS/Anti-AFP fluorescent probe improves HCC cell labeling. Hepatobiliary & pancreatic diseases international. *HBPD INT*. 2019;18(3):266–272. doi:10.1016/j.hbpd.2019.03.001
134. Dai Y, Wu C, Wang S, et al. Comparative study on in vivo behavior of PEGylated gadolinium oxide nanoparticles and Magnevist as MRI contrast agent. *Nanomed Nanotechnol Biol Med*. 2018;14(2):547–555. doi:10.1016/j.nano.2017.12.005
135. Wang D, Zhang N, Jing X, et al. A tumor-microenvironment fully responsive nano-platform for MRI-guided photodynamic and photothermal synergistic therapy. *J Mat Chem B*. 2020;8(36):8271–8281. doi:10.1039/d0tb01373k
136. Kim JG, Jang MS, Kumari N, et al. Differential characterization of hepatic tumors in MR imaging by burst-released Mn2+-ions from hollow manganese-silicate nanoparticles in the liver. *Biomaterials*. 2020;230:119600. doi:10.1016/j.biomaterials.2019.119600
137. Zhao H, Lv J, Li F, et al. Enzymatical biomineralization of DNA nanoflowers mediated by manganese ions for tumor site activated magnetic resonance imaging. *Biomaterials*. 2021;268:120591. doi:10.1016/j.biomaterials.2020.120591
138. Wang P, Wang Y, Xiao J, et al. Study of preparation of a Mn3O4 nanocluster magnetic resonance contrast agent with pH response and its imaging performance. *BMU J*. 2023;46(2):133–139. doi:10.19739/j.cnki.issn1001-9510.2023.02.011
139. Im GH, Kim SM, Lee DG, et al. Fe(3)O(4)/MnO hybrid nanocrystals as a dual contrast agent for both T(1)- and T(2)-weighted liver MRI. *Biomaterials*. 2013;34(8):2069–2076. doi:10.1016/j.biomaterials.2012.11.054
140. Zhu T, Ma X, Chen R, et al. Using fluorescently-labeled magnetic nanocomposites as a dual contrast agent for optical and magnetic resonance imaging. *Biomater Sci*. 2017;5(6):1090–1100. doi:10.1039/c7bm00031f
141. Hendrick RE, Haacke EM. Basic physics of MR contrast agents and maximization of image contrast. *J Magn Reson Imaging*. 1993;3(1):137–148. doi:10.1002/jmri.1880030126
142. Tacher V, Duran R, Lin M, et al. Multimodality imaging of ethiodized oil-loaded radiopaque microspheres during transarterial embolization of rabbits with VX2 liver tumors. *Radiology*. 2016;279(3):741–753. doi:10.1148/radiol.2015141624
143. Wang YX, Xuan S, Port M, Idee JM. Recent advances in superparamagnetic iron oxide nanoparticles for cellular imaging and targeted therapy research. *Curr Pharm Des*. 2013;19(37):6575–6593. doi:10.2174/1381612811319370003
144. Thorek DLJ, Chen AK, Czupryna J, et al. Superparamagnetic iron oxide nanoparticle probes for molecular imaging. *Ann Biomed Eng*. 2006;34(1):23–38. doi:10.1007/s10439-005-9002-7
145. Lee KH, Liapi E, Vossen JA, et al. Distribution of iron oxide-containing Embosphere particles after transcatheter arterial embolization in an animal model of liver cancer: evaluation with MR imaging and implication for therapy. *J Vasc Interv Radiol*. 2008;19(10):1490–1496. doi:10.1016/j.jvir.2008.06.008
146. Hu Y, Mignani S, Majoral JP, Shen M, Shi X. Construction of iron oxide nanoparticle-based hybrid platforms for tumor imaging and therapy. *Chem Soc Rev*. 2018;47(5):1874–1900. doi:10.1039/c7cs00657h
147. Jia G, Van Valkenburgh J, Chen AZ, et al. Recent advances and applications of microspheres and nanoparticles in transarterial chemoembolization for hepatocellular carcinoma. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2022;14(2):e1749. doi:10.1002/wnan.1749
148. Li C, Yang D, Ma P, et al. Multifunctional upconversion mesoporous silica nanostructures for dual modal imaging and in vivo drug delivery. *Small*. 2013;9(24):4150–4159. doi:10.1002/smll.201301093
149. Kim DH, Li W, Chen J, et al. Multimodal imaging of nanocomposite microspheres for transcatheter intra-arterial drug delivery to liver tumors. *Sci Rep*. 2016;6:29653. doi:10.1038/srep29653
150. Wang D, Wu Q, Guo R, et al. Magnetic liquid metal loaded nano-in-micro spheres as fully flexible theranostic agents for SMART embolization. *Nanoscale*. 2021;13(19):8817–8836. doi:10.1039/d1nr01268a