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Exploiting targeted nanomedicine for surveillance, diagnosis, and treatment of hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the cancers that has the highest morbidity and mortality rates. In clinical practice, there are still many limitations in surveilling, diagnosing, and treating HCC, such as the poor detection of early HCC, the frequent post-surgery recurrence, the low local tumor control rate, the therapy resistance and side effects. Therefore, improved, or innovative modalities are urgently required for early diagnosis as well as refined and effective management. In recent years, nanotechnology research in the field of HCC has received great attention, with various aspects of diagnosis and treatment including biomarkers, ultrasound, diagnostic imaging, intraoperative imaging, ablation, transarterial chemoembolization, radiotherapy, and systemic therapy. Different from previous reviews that discussed from the perspective of nanoparticles' structure, design and function, this review systematically summarizes the methods and limitations of diagnosing and treating HCC in clinical guidelines and practices, as well as nanomedicine applications. Nanomedicine can overcome the limitations to improve diagnosis accuracy and therapeutic effect via enhancement of targeting, biocompatibility, bioavailability, controlled releasing, and combination of different clinical treatment modalities. Through an in-depth understanding of the logic of nanotechnology to conquer clinical limitations, the main research directions of nanotechnology in HCC are sorted out in this review. It is anticipated that nanomedicine will play a significant role in the future clinical practices of HCC.

1. Introduction

Liver cancer is the sixth most common cancer in the world and the third leading cause of cancer death. It was estimated that there were 905,677 new cases and 830,180 deaths worldwide in 2020 [1], and the incidence of liver cancer increased with age [2]. Approximately 80% of liver cancer cases are hepatocellular carcinoma (HCC) [1]. Chronic liver disease is present in the majority of HCC cases, most of which occur on the background of cirrhosis [3]. The surveillance of HCC mainly relies on ultrasound and the level of serum markers such as alpha-fetoprotein (AFP). When there is an abnormality, it is diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI). However, in a few cases, pathological diagnosis is required. Treatment includes surgery, ablation, liver transplantation, transarterial chemoembolization, and systemic therapy [4,5]. HCC is often asymptomatic at the early stage, and less than 20% of patients with liver cirrhosis receive regular screening, therefore, most HCC patients are already in the middle and advanced stage when diagnosed [4]. The five-year survival rate of HCC is only 20% due to factors involving late discovery, rapid progression, poor response to treatment in the advanced stage, and easy recurrence [6]. Hence, there is an urgent need for an improved or innovative diagnostic and therapeutic method.

Recently, there has been a steady increase in biomedical nanotechnology research [7–13]. Consideration has also been given to its

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application in diagnosing and treating HCC [14–16]. The characteristics of nanoparticles provide them with many unique advantages. The appropriate size allows them to easily pass through the tumor's new microvessels and accumulate locally, prolonging circulation clearance. In terms of targeted diagnosis and treatment, nanoparticles have several advantages over other molecular conjugates due to their large specific surface area: 1) they can contain multiple targeting ligands, which can generate higher affinity through multivalent binding to cell surface receptors; 2) they can carry a large number of effector molecules and protect them from degradation; for example, lipiodol-bridged indocyanine green (ICG) nanoemulsion could protect the fluorochrome ICG from degradation for a few days via the shielding effect, while the fluorescence intensity of free ICG solution rapidly declined to zero at the same conditions [17]; 3) they are sufficient to accommodate multiple types of effector molecules; and 4) the release of effector molecules from nanoparticles can be tuned to match the mechanism of action [18]. These advantages enable nanomaterials to improve the detection sensitivity of biomarkers or imaging and facilitate the targeted delivery of drugs, thereby improving the efficacy of diagnosis and treatment while minimizing the side effects of anticancer drugs.

Several analyses have been conducted on the application of nanotechnology to HCC. These articles focused on applying specific characteristics of nanomedicine, such as targeting, self-adaptivity, assembling, the ability of coordination and sensitization [19–23], or used nanomaterials as an entry point to describe their development in HCC or in animal hepatoma models [24–26], or enumerated nanotechnology advancements in various therapeutic approaches [14,16]. There are no review reports on the consensus, limitations, and progression of HCC in clinical practice and how nanotechnology can improve clinical limitations and expand clinical applications. This article provides a systematic overview of the current status of surveillance, diagnosis, and treatment of HCC (Fig. 1). It reviews various nanotechnology-based strategies for overcoming the limitations in HCC clinical practice, such as improving targeting, optimizing the physicochemical properties of effector molecules, combining multiple therapeutic or auxiliary molecules, and others. Through an in-depth understanding of how nanotechnology can be used to achieve optimization and improvement and summarizing the targeted research directions of nanotechnology in HCC, it is beneficial to promote its widespread and promising application in diagnosing and treating HCC.

2. Progress in surveillance and diagnosis of HCC and application of nanotechnology

Regular surveillance for HCC high-risk populations is recommended. According to the guidelines, these populations should undergo ultrasound with or without serum AFP testing every six months. When liver lesions <1 cm are detected, the ultrasound monitoring interval should be shortened to 3–6 months; when liver lesions are ≥1 cm or when AFP is positive (≥20 ng/mL), it is recommended to perform multi-phase CT or dynamic contrast-enhanced MRI for initial diagnosis and determining the management according to LI-RADS category [4,5].

The advancement of nanotechnology has significantly contributed to the development of diagnostic techniques based on molecular markers. In HCC, there are numerous molecules that hold potential as biomarkers, and the surface functionalization of nanocarriers plays a crucial role in targeting these molecules. In biomarker detection, nanoparticles utilize antibodies, aptamers, peptides, etc. as probes to convert the signal of target molecules into electrical, optical, or other signals, enabling sensitive detection [27–29]. On the other hand, in imaging inspection, nanotechnology can enhance the signal-to-noise ratio of imaging by utilizing their unique physiochemical properties and molecular targeting [30,31]. In recent years, numerous studies have actively improved detection strategies through nanotechnology to increase the HCC diagnostic rate (Table 1).

2.1. In vitro diagnosis

Biomarkers play a crucial role in the in vitro diagnosis of HCC, and their applications include clinical diagnosis, progression monitoring, and prognosis assessment. AFP is currently the only widely used HCC serum marker. It is frequently elevated in HCC patients; nonetheless, there are still 30–40% of patients whose AFP will not increase [28]. Moreover, pregnancy, benign liver diseases, malignant gastrointestinal tumors and other physiological or pathological reasons may lead to elevated serum AFP. Therefore, the diagnostic value of AFP alone for HCC is limited, and the sensitivity is only 31–69% [48,49]. At present, AFP is often used in combination with ultrasound for HCC surveillance.

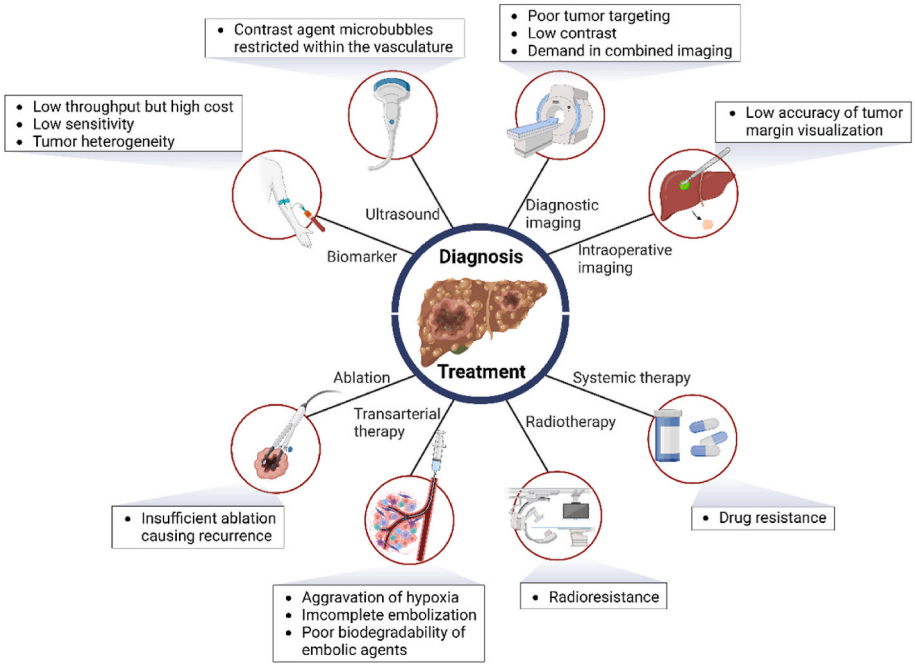

Fig. 1. The clinical limitations of diagnosing and treating HCC.

Table 1
The introduction of diagnostic nanoparticles.

Nanoinducers	Material type	Encapsulation/Conjugation	Functional mechanism	Feature	Hepatic cell lines	Reference
Biomarker						
Nano-gold electrode + PDANPs-Ab_2	Gold nanoparticles (AuNPs) + Polydopamine nanoparticles	Ab_1 + Ab_2	Redox cycling-based charge transfer signal amplification	Improving AFP detection sensitivity	/	Xiang et al. [27]
F-AuNPs + AgMNPs	AuNPs	Three probe-DNA recognizing target miRNAs	SERS-based detection	High sensitivity and multiplex biomarkers detection	/	Wu et al. [28]
GPC3apt/RGO-Hemin/Au NPs/SPE	Reduced graphene oxide-hemin nanocomposites	GPC3 aptamers	GPC3-aptamer conjugation	High affinity and specific binding to GPC3	/	Li et al. [29]
Nanofluidic diode biosensors	Nanopores integrated on microchip	CEA, AFP, HER2 antibodies	Electric charge of the target proteins captured by mAbs	Ultra-sensitive and multiplexed detection	/	Duan et al. [32]
Exo@Au nanozymes	AuNPs	Installing onto the exosomal phospholipid membrane	Nanozyme-assisted immunosorbent assay	Rapid profiling of multiple exosomal proteins	HepG2, LO-2, MCF-7, HeLa	Di et al. [33]
Ultrasound						
FA-NDs	Perfluoropentane nanodroplets	Folate	Phase-transition to microbubbles after low-intensity focused US sonication	Capable of passing through the capillaries allowing effective extravasation into tumor	SKOV3	Liu et al. [30]
HA/CPPs-10-HCPT-NPs		Hyaluronic acid, cell-penetrating peptide, 10-hydroxycamptothecin			SMMC-7721	Zhao et al. [34]
Gas vesicles	Gas vesicles	/	Sound waves are strongly reflected by air-water interfaces	Easy isolation, capable of passing through the capillaries and quantifying phagocytic clearance and lysosomal degradation	RAW264.7, HEK293T /	Ling et al. [35] Wei et al. [36]
Diagnostic imaging						
UAG	USPIO	AFP, GPC3 antibodies	Tumor targeting via ligand-receptor interaction	Actively targeting tumor to improve imaging accuracy	Hepa1-6/ GPC3	Ma et al. [31]
TPP-Bi@PDA@CP	Bismuthine nanosheets	Compound polysaccharide (hepatoma cell targeting), triphenylphosphonium (mitochondrial targeting agent)			Bel-7402	Bai et al. [37]
UMFNPs	Ultrasmall $MnFe_2O_4$ nanoparticles	/	Parameter optimization of contrast agents impacting imaging capability	Improving imaging capability	HepG2	Zhang et al. [38]
MnO nanoparticles	MnO nanoparticles	/			SMMC-7721, H22	Yang et al. [39]
Dual-modal imaging contrast agents	AuNPs	Gd chelator, polyethyleneimine	Combination of different contrast agents onto nanoplatform	CT/MR or PAI/MRI dual mode imaging of tumor	HepG2, HCCLM3	Li et al. [40], Wang et al. [41]
	Fe_3O_4 magnetic nanoparticles	PAI materials such as $FeSe_2$ and semiconductor polymers			HepG2, HUH7, SK-Hep1	He et al. [42], Deng et al. [43]
Intraoperative imaging						
ICG nanoemulsion	Nano-ICG-lipiodol emulsion	/	ICG molecules disperse in lipiodol emulsion	Clearly delineating tumor in surgery and more excellent stability	LO2, Hepa1-6, HepG2	Zhu et al. [17], He et al. [44]
BH–NO_2@BSA	BH–NO_2 + BSA	/	The probe is reduced and activated by the overexpressed nitroreductase in tumor cells	The activatable probe can precisely delineate tumor	HCC-LM3-fLuc	Zeng et al. [45]
ZGC	$ZnGa_2O_4Cr0.00_4$ NIR-emitting persistent luminescent nanoparticles (NPLNPs)	/	Afterglow lasting for several hours after light excitation in vitro to obtain high signal-to-noise ratio and deep penetration in vivo imaging	Excellent long-lasting afterglow properties to accurate delineation of tumor aiding in real-time guided surgery	HepG2, Huh7, LO2	Ai et al. [46]
$F1^{2+}$-ANP-Gal	poly[2-methoxy-5-(2-ethylhexyloxy)-1,4-phenylenevinylene]-based nanoparticles	β-galactose ligands (tumor targeting), EM $F1^{2+}$ (H_2S-responsive chromophore), NIR775	The probe is activated by elevated H_2S in tumor to control afterglow luminescence from MEP-PPV and NIR775	Hepatic-tumor-targeting and activatable afterglow	HepG2	Wu et al. [47]

In recent decades, numerous novel biomarkers have been reported, such as AFP isoform AFP-L3, heat shock protein 70 (HSP70), des-γ-carboxyprothrombin (DCP), glypican-3 (GPC3) [50,51]. They can detect some AFP-negative HCC, nevertheless, few markers have been confirmed by large-scale, multicenter studies to have sufficient diagnostic value in clinical practice. Thus another strategy to improve diagnostic performance and cope with tumor heterogeneity is to combine AFP with other biomarkers or clinical indicators [52,53]. GALAD score, which gained FDA 'Breakthrough Device Designation', combines three tumor markers (AFP, AFP-L3, and DCP) and two demographic risk factors (age and gender). The study found that the performance of the GALAD score in detecting early HCC in patients with nonalcoholic steatohepatitis (NASH) was better than that of any tumor markers alone [54]. A multicenter study in North America revealed that the performance of the GALAD score screening for HCC is better than ultrasound [55]. Moreover, there was the first prospective cohort study

demonstrating the clinical applicability of the GALAD score [56]. The GALAD score is expected to become the routine surveillance program of HCC in the near future. However, it is worth noting that the commonly used detection methods for biomarkers include enzyme-linked immunoassay, fluorescence immunoassay, chemiluminescence, and mass spectrometry. These traditional methods have the disadvantages of being labor-intensive, time-consuming, and expensive to be improved. In addition, several liquid biopsy markers have also been developed in detecting early HCC, such as circulating tumor cells, circulating tumor DNA, exosomes, free microRNA (miRNA) and long non-coding RNA (lncRNA), and others. They can provide much diagnostic information such as carcinogenesis, subtype determination, and tumor burden [57–61]. However, these methods have not yet been commercialized and must be fully evaluated in the five phases of tumor marker discovery and validation.

Nanotechnology primarily enhances in vitro diagnosis through several aspects (Fig. 2A). First, it innovates techniques to achieve HCC detection with high sensitivity, high throughput, rapid response, and cost-effectiveness. Different from the traditional detection approaches, some nanoparticles have unique electrochemical properties. They can be combined with electrochemical technology to implement the detection of biomarkers. Xiang et al. constructed the Ab_1-AFP-Ab_2 sandwich reaction platform on the nano-gold electrode, using polydopamine nanoparticles as the labeling material of Ab_2. The property of polydopamine amplifying the mediator's charge transfer improved the sensor's sensitivity, and the detection limit of AFP was as low as 0.3 pg/mL [27]. Wu et al. utilized the electromagnetic enhancement of gold nanoparticles to implement surface-enhanced Raman scattering, amplifying the collected signal to achieve ultrasensitive detection of biomarkers [28]. The second is to improve the efficacy of target binding. Nanoparticles' high specific surface area and strong adsorption capacity make it possible to combine various ligands to increase the affinity to the target or amplify the detection signal. For example, aptamers are a type of oligonucleotide sequence with a unique three-dimensional conformation with a receptor affinity comparable to antibodies. Moreover, they possess excellent stability, low immunogenicity, and easy preparation and are frequently used as specific target-binding ligands [62]. Li et al. covalently combined reduced graphene oxide-hemin nanoparticles with GPC3 aptamers, immobilizing the complex on the electrode surface, and detected the concentration of GPC3 via the change of electrochemical signal. Under optimal conditions, the linear detection range of GPC3 was 0.001–10.0 μg/mL [29]. Third, using nanoarray microchips for detecting multiplexed biomarkers can potentially overcome tumor heterogeneity [32,33]. Duan et al. integrated nanofluidic diode arrays on microchips and achieved highly selective and ultrasensitive multiple markers (AFP, CEA, HER2) in buffer and unpretreated serum based on antigen-antibody binding and protein charge regulation. The biosensor was less difficult to manufacture and had a fast response, with an ultra-low detection limit, which was expected to be used in the joint detection of multiple markers of HCC in the future [32].

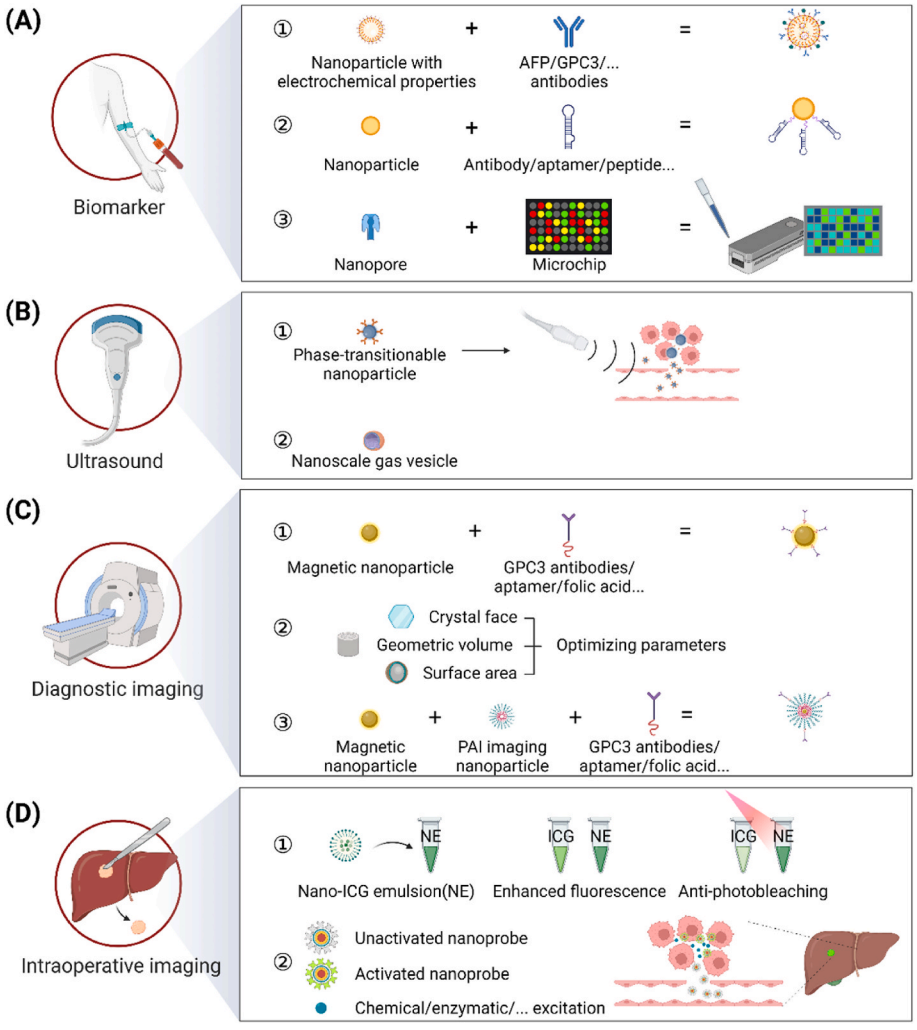

Fig. 2. Nanotechnology application in surveillance and diagnosis of HCC. (A) Nanotechnology enhances in vitro diagnosis via improving detection sensitivity, target binding efficiency, and constructing multiplexed nanoarray microchips. (B) Nanotechnology promotes hypovascular tumor imaging via using nanoscale contrast agents effectively extravasating from vessels. (C) Nanotechnology improves diagnostic imaging via enhancing tumor targeting, improving contrast ratio and developing multi-modal imaging. (D) Nanotechnology improves intraoperative imaging via prolonging ICG retention and improving the signal-to-noise ratio.

2.2. In vivo diagnosis

2.2.1. Ultrasound

Ultrasound is extensively used as a routine screening method because it is simple, flexible, non-invasive and inexpensive. A meta-analysis of 32 studies revealed that the sensitivity of ultrasound to detect HCC at any stage in liver cirrhosis patients was 84%; however, for early HCC (a single nodule <5 cm or 2–3 nodules <3 cm), the sensitivity was only 47% [63]. The development of contrast-enhanced ultrasonography (CEUS) additionally provides hemodynamic characteristics on the basis of ultrasound and improves the accuracy of HCC screening. Randomized controlled trials (RCT) have shown that the HCC nodules detected by the Sonazoid CEUS group based on Kupffer cell-specific uptake were significantly smaller than the B-mode ultrasound group (13.0 ± 4.1 mm vs 16.7 ± 4.1 mm; $p = 0.012$) [64]. The typical HCC CEUS pattern had a high positive predictive value, reaching 98.5% [65]. For nodules of 10–20 mm, the specificity (92.9%) of CEUS in diagnosing HCC was higher than CT (76.8%) and MRI (83.2%). However, its limitation was considerably lower sensitivity than CT/MRI [66], which may be due to the large size of the contrast agent being restricted within the vasculature, resulting in missing hypovascular lesions.

As mentioned above, ultrasound contrast agents are valuable for monitoring HCC; however, the currently used microbubbles (MB) have a large particle size and cannot effectively extravasate from vessels and target tumors, whereas nanoscale contrast agents can solve this problem (Fig. 2B). The researchers developed perfluoropentane-coated lipid nanoparticles with liquid-gas phase-transition properties. Nanoscale MB precursors accumulated in the tumor through passive or active targeting were converted into MB by in situ phase-transition and enhancing tumor imaging capability [30,34]. Besides, gas vesicles (GVs) of certain marine bacteria and archaea have also recently been found to serve as novel nanoscale contrast agents, showing great potential in ultrasound imaging [35,36]. Studies have shown that rugby-shaped GVs from *Halobacteria NRC-1* could generate stable and strong ultrasound contrast signals in mouse liver tumors under optimized parameters and perfuse ischemic tumor regions where MB failed to image, yielding a 6.84 times stronger signal than MB [36]. Ling et al. developed a nanoscale contrast agent made entirely of proteins based on GVs. Hepatic macrophages phagocytized the contrast agent and underwent lysosomal degradation, therefore, its ultrasonic signals could reflect the functions of phagocytosis and lysosomal degradation. Liver dysfunction (such as phagocyte deficiency and nonalcoholic fatty liver disease) leads to changes in the ultrasound signal, which can be used to monitor HCC in the future [35].

2.2.2. Diagnostic imaging

Suspicious lesions detected by ultrasound require further imaging examinations (dynamic contrast-enhanced CT/MRI) to confirm the diagnosis and staging of the tumor. The typical imaging pattern of HCC shows significantly enhanced lesions compared to the surrounding parenchyma in the arterial phase, while in the portal or delayed phase, it is less enhanced than the surrounding. For adult patients with chronic liver disease, the sensitivity and specificity of CT in diagnosing HCC were 77.3 and 91.3% [67], while the sensitivity and specificity of MRI were 84.4 and 93.8%, respectively [68]. The meta-analysis comparing the accuracy of enhanced CT and MRI in detecting HCC revealed that MRI has a higher detection sensitivity, particularly for small nodules <2 cm. However, there was no significant difference in specificity [69,70]. Therefore, MRI is utilized more frequently than CT. In general, MRI has high diagnostic accuracy and is suitable for patients who are allergic to iodine contrast agents, nevertheless, it is expensive, highly sensitive to artifacts, and takes a long time to scan; CT is slightly less accurate, nonetheless, it is cost-effective and applicable to patients who cannot undergo MRI. However, most contrast agents used in clinical diagnostic imaging have issues such as a brief circulation time, lack of tumor targeting, and low sensitivity to small nodules. Therefore, it is necessary to develop new contrast agents and imaging technologies to improve the current diagnostic dilemma of HCC.

Nanotechnology can improve the limitations of HCC diagnosis in numerous ways, such as modifying molecules to improve the targeting of nanoprobes, improving the sensitivity of HCC detection, reducing the dose by optimizing contrast agent parameters, and developing multimodal imaging nanoprobes (Fig. 2C). First, nanotechnology can enhance diagnostic performance by modifying one or more target-docking molecules (antibodies, aptamers, peptides, and others) to endow various contrast agents with active targeting properties [31,40–42]. Ma et al. synthesized ultra-small superparamagnetic iron oxide nanoparticles (USPIO) with or without AFP/GPC3 antibody conjugation and found that AFP and GPC3 antibodies conjugated USPIO had the highest targeting and internalization efficiency to Hepa1-6/GPC3 cells, and minimized MRI T_2 relaxation time, having the potential to overcome biomarker-related tumor heterogeneity [31]. Bai et al. constructed bismuthene-based nanoparticles TPP-Bi@PDA@CP coupled with compound polysaccharide (hepatoma cell targeting agent) and triphenylphosphine (TPP, mitochondrial targeting agent), and its contrast-enhancement efficiency was as high as 51.8 HU mL mg^{-1}, which was 3.16-fold that of iopromide, a commonly used clinical contrast agent. The average HU value in mouse tumor sites was 2.63-fold that of non-targeted particles, which may be used in clinical diagnosis in the future [37].

Second, parameter optimization of specific nanoscale contrast agents can improve the MRI contrast ratio, enabling sensitive liver tumor detection at low doses [38,39]. Yang et al. prepared manganese oxide (MnO) nanoparticles of varying sizes and shapes and investigated the factors affecting T_1-MRI in terms of geometric volume, surface area, crystal plane, and r_2/r_1 ratio. They found that the surface area and occupancy rate of manganese ions positively affected the sensitivity of T_1-MRI, whereas the volume and r_2/r_1 ratio had negative effects. MnO octahedrons exhibited exceptional enhancement in liver T_1 imaging and could detect liver tumors at approximately 1/10 of the clinical dose [39].

In addition, multi-modal imaging has attracted much attention in recent years. It combines various imaging technologies to acquire more detailed images and biological characteristics of tissues, improving inspection and diagnosis efficiency. Nanotechnology can provide a great platform for achieving multi-modal imaging. CT and MRI are the two most common imaging procedures. The former is good at high spatial and density resolution imaging of hard tissues, while the latter provides high-resolution imaging of soft tissues. Therefore, the combination of CT and MRI can provide complementary diagnostic information. For instance, polyethylenimine-based gold nanoparticles have good X-ray attenuation properties, T_1 relaxivity and stability after chelating gadolinium ions, allowing for CT/MRI dual-modal imaging [40,41]. Photoacoustic imaging (PAI) is an emerging hybrid imaging technology with high temporal and spatial resolution real-time imaging capabilities and high optical sensitivity that can deliver diagnostic information at the micron level. Dual-modal PAI/MRI imaging using nanoparticles incorporating PAI materials such as $FeSe_2$ and semiconductor polymers with MRI contrast agent Fe_3O_4 could detect HCC of <1 cm [42,43].

2.2.3. Intraoperative imaging

Surgical resection has the potential to cure patients with early-stage HCC. It has been reported that the five-year survival rate of patients undergoing surgical resection was 47–67% [71–73]. For early-stage HCC <3 cm, the postoperative five-year survival rate was as high as 75% [74]. Previous studies have shown an insignificant difference between surgical resection and radiofrequency ablation (RFA) for treating early-stage HCC [72,74]. However, a meta-analysis of six RCTs showed that for HCC eligible for the Milan criteria (single lesion ≤5 cm or ≤ 3 lesions ≤3 cm each), surgical resection was associated with a higher five-year recurrence-free survival rate [75]; even for early recurrence of HCC, the long-term curative effect of surgical resection was also better than RFA [76]. Therefore, surgery remains the first-line treatment for

resectable HCC. However, the five-year recurrence rate of surgical resection of HCC is more than 70% [49,77]. The lesions missed during surgery are one of the main sources of recurrence [78]. To remove as much cancerous tissue as possible during surgery and reduce the probability of recurrence, intraoperative ICG near-infrared (NIR) fluorescence imaging is used to achieve more accurate visualization of HCC margins and to detect some tiny invisible lesions [79].

Conventional ICG probes have a brief local residence time, are susceptible to photobleaching and degradation, and lack tumor specificity. Therefore, more effective probes are urgently required to acquire stable, tumor-specific fluorescent signals with prolonged intratumoral retention. In addressing these shortcomings, nanotechnology primarily contributes in two ways (Fig. 2D). First, constructing nanoscale ICG-lipiodol emulsion, which is preferentially absorbed by tumor tissue, and its high viscosity makes it resistant to blood flow clearance. ICG molecules dispersed in lipiodol emulsion are stable. According to studies, nano-ICG-lipiodol emulsion exhibited superior imaging properties and greater resistance to photobleaching and degradation than ordinary ICG solution [17,44]. Second, constructing activatable nanoprobes. Inert probes can emit imaging signals at any time. In contrast, the modified activatable nanoprobes can distinguish tumor cells from normal cells based on biological differences, emitting signals only after contacting the target. Activatable nanoprobes can minimize non-specific backgrounds and enhance the detection precision of tumor margins. Zeng et al. developed an activatable nanocomposite BH–NO_2@BSA, which specifically responded to the overexpressed nitroreductase in tumor cells and generated strong NIR-I/II fluorescence and photoacoustic signals. 3D multispectral photoacoustic tomography (MSOT) images could be used for preoperative localization of liver tumors, and NIR-I/II fluorescence images provided intraoperative navigation [45]. However, traditional fluorescence imaging requires in situ light excitation. The inevitable light absorption, scattering, and autofluorescence of biological tissues will limit the penetration depth and result in a low signal-to-noise ratio. Afterglow nanoprobes can overcome this limitation because the probes slowly emit photons after being excited by light, and the afterglow can last for hours [46]. Wu et al. took advantage of the elevation of H_2S in cancer and used the electrochromic material $F1^{2+}$ as the H_2S-responsive chromophore to construct HCC-targeted afterglow nanoparticles. The signal-to-noise ratio of nanoprobe imaging was substantially higher than NIR fluorescence, and it had greater penetrating power, effectively delineating HCC lesions in clinical specimens [47].

2.3. All kinds of surveillant and diagnostic methods

For different diagnostic methods, nanotechnology employs various optimization strategies, which primarily focuses on two aspects.

The first is to utilize the diverse physiochemical properties of nanoparticles, such as electrochemical, magnetic, and optical characteristics, to enhance or innovate biodetection materials and platforms. This enables the achievement of rapid, real-time, highly sensitive, and specific detection. In addition to the electrical nanomaterials, there are many nanoparticles utilized in the detecting techniques. Matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) is a method for determining the mass of biomacromolecules like peptides, proteins, and nucleic acids. It offers advantages such as high throughput and rapid detection. The selection of an appropriate matrix plays a crucial role in obtaining accurate results. Wang et al. employed magnetic SiO_2 nanoparticles as a matrix and connected aptamers and molecularly imprinted polymers (MIPs) through Au–S bonds as substitutes for antibodies. By using this nanoplatform, the signal-to-noise ratio of mass spectrometry in detecting AFP in body fluids was significantly improved compared to direct detection [80]. To detect very early tumor lesions that lack of abundant vasculature, Lei et al. employed positive (tumor vessels) and reverse (tumor parenchyma) contrast-balanced imaging strategy. They developed a gemstone spectral CT/PAI dual-modal imaging nanoprobe PEG-Ta_2O_5@CuS. The CuS outer layer possessed strong PAI capacity at the NIR-II window, enabling sensitive visualization of micron-scale blood vessels in tiny HCC lesions. The nanoprobe could detect 2–4 mm HCC in orthotopic tumor model [81]。

The second is to increase molecular targeting to improve detection accuracy. In the detection of biomarkers, liquid crystal (LC) sensors can transduce and amplify chemical and biological changes into visible light signals. At present, most LC sensors can only detect a single tumor marker, while Qi et al. employed the strategy of LC sensors assisted with target-induced dissociation (TID) of an aptamer to detect multiple tumor markers. In TID, nanomagnetic beads functionalized with aptamer 1 were bound to target proteins, followed by incubation with aptamer 2 and signal DNA duplexes. The combination of the target protein and aptamer 2 released the signal DNA, which was recognized by the LC sensor and formed light signals. The reliability of the detection system was confirmed in the experiments, and it was not affected by hemolysis [82].

3. Progress in treatment of HCC and application of nanotechnology

The therapeutic regimen of HCC is determined by the tumor stage. There are numerous staging systems for liver cancer, including Barcelona Clinic Liver Cancer (BCLC), Tumour, Node, Metastasis (TNM), China Liver Cancer Staging (CNLC), Japan Integrated Staging (JIS), and Hong Kong Liver Cancer (HKLC), among others. The 2018 version of BCLC is currently the most popular staging system for HCC. Based on tumour status, liver reserve function (Child-Pugh score), and physical function status score (ECOG PS), it divides HCC into five stages; surgical resection or RFA for BCLC stage 0; surgical resection, liver transplantation, or ablation according to tumor and liver function conditions for BCLC stage A. BCLC stage B and above should receive transarterial chemoembolization (TACE) or systemic therapy. Supportive treatment is suggested for BCLC stage D [4,5]. Despite various treatment methods, the survival rate of HCC patients is still unsatisfactory due to the limitations of low long-term local tumor control rate, drug resistance, a high recurrence rate, and numerous adverse effects.

With the rapid development of nanomedicine, researchers have used nanotechnology to effectively improve various treatment methods based on clinical needs (Table 2). In these studies, researchers have constructed various highly targeted nanocarriers, loading different effector molecules such as photothermal agents, chemotherapeutic drugs and radioactive particles, and utilized biomimetic materials to increase the bioavailability and stability of drugs. Moreover, they combined diverse regimens containing ablation, TACE, radiotherapy and systemic therapy to improve the treatment effect and to minimize the systemic side effects.

3.1. Ablation

Although surgery is the first choice for treating early-stage HCC, some patients cannot tolerate surgery because most of them have different degrees of liver cirrhosis, and ablation has the advantages of less impact on liver function, less trauma, and a definite curative effect. In some early-stage HCC patients, ablation and surgical resection impacts are similar [74], so ablation is also recommended for HCC patients with lesions $\leq$3 cm. Ablation therapy includes RFA, microwave ablation (MWA), cryoablation (CRA), percutaneous ethanol injection (PEI), and irreversible electroporation (IRE), among which RFA and MWA are the most commonly used. Retrospective studies and RCTs have shown that for HCC patients with small number and size tumor lesions, the efficacy and safety of RFA and MWA are comparable [102,103]. PEI and CRA are less used, and their advantage is causing less damage to surrounding tissues. They are suitable for cancer lesions adjacent to the hilum of the liver and gallbladder, and the risk of vascular complications is extremely

Table 2
The introduction of therapeutic nanoparticles.

Nanoinducers	Nanoparticle material	Encapsulation/Conjugation	Functional mechanism	Feature	Hepatic cell lines	Reference
Ablation						
PCN-ACF-CpG@HA	Metal (H_2TCPP)-organic (zirconium ions) framework-based nanoparticles	ACF (hypoxia inducible factor signaling inhibitor), CpG (immunologic adjuvant), HA (tumor targeting)	Ablation activates liver-cancer-related adaptive immune response which enhanced by CpG and hypoxia is blocked by ACF	Enhancing immune responses to eliminate residue cancer cells and inhibiting hypoxia-induced survival and metastasis	H22	Cai et al. [83]
Transarterial therapy						
CaO_2 NPs	CaO_2 nanoparticles	/	CaO_2 NPs react with water to generate abundant O_2, OH^- and Ca^{2+}	Improving tumor microenvironment by relieving hypoxia, neutralizing acid, and down-regulating the expression of hypoxia-related markers, enhancing the anti-tumor effect of TACE	HepG2	Wang et al. [84]
ATONP/NDEB	Arsenite nanoparticles	/	Arsenite nanoparticles are activated by plasma Pi to sustained release arsenic trioxide	Resulting in more thorough tumor necrosis in TACE	VX2	Fu et al. [85], Zhao et al. [86]
Pickering emulsion	Poly(lactide-*co*-glycolide) (PLGA) nanoparticles	/	The addition of PLGA NPs into the formulation endows the emulsions with biodegradability	No significant toxicity on tumor cells	HepG2, HUVEC	Deschamps et al. [87]
Radiotherapy						
GNP	Iron oxide-gold core-shell nanoparticles	AKG (mitochondrial targeting), 4-HPR (chemotherapeutic drug)	Radiosensitization realized by the accumulation of a large amount of ROS in cancer cells	Increasing treatment efficacy	PLC/PRF/5	Sood et al. [88]
tGd-$GNMs_{siRNA}$	Gd-hybridized gold nanomolecules	VEGF-siRNA, cyclic asparagine-glycine-arginine peptide (tumor targeting)	Radiosensitization realized by increasing local radiation dose deposition and inhibition of tumor revascularization		HepG2, H22, HUVEC	Li et al. [89]
Systemic therapy						
NP(ArtePt)	Polymer nanoparticles	ArtePt (cisplatin + artesunate dual-threat hybrid prodrug)	Polymer fragments deplete GSH via Iodo-Clikc reaction to enhance the efficacy of cisplatin	Relieving drug resistance to improve antitumor effect of cisplatin in HCC	7404	Jin et al. [90]
Gal-SLPs	Galactose-decorated lipopolyplexes	Sorafenib, USP22 shRNA	USP22 shRNA suppresses the expression of multidrug resistance-associated protein 1	Showing increased sorafenib accumulation and enhanced sensitivity to sorafenib	Huh-7, BEL-7402	Xu et al. [91]
usLNPs	Lipid nanoparticles	Sorafenib, MK-siRNA	MK-siRNA increases the sensitivity to sorafenib and ultra-small nanoparticles are easier to penetrate the stroma barrier in tumor	Increasing the chemosensitivity of tumor cells and allowing more drugs to be delivered into tumor	HepG2	Younis et al. [92]
All kinds of therapies						
$Nd_2Fe_{14}B$/Fe_3O_4-PLGA	Fe_3O_4+DSPE-PEG2000-Mal + DPPC + cholesterol nanoparticles	SNF peptide/EpCAM antibody, γ-IFN	Improving therapeutic targeting by modifying tumor target ligands	Hierarchical targeting significantly enhances antitumor effect	Huh7, 97H, 97L, SK-Hep-1, LO2, Hepa1-6	Shi et al. [93]
NP-sfb	PEG-*b*-PLA	Sorafenib	Improving solubility and bioavailability of sorafenib/pterostilbene	Showing significantly improved therapeutic efficacy compared with same dose free-sfb	Hepa1-6, H22, HepG2	Chen et al. [94]
PSN	Eudragit e100	Pterostilbene, polyvinyl alcohol (stabilizer)		Having a better cytocidal effect than raw pterostilbene	HepG2	Tzeng et al. [95]
FCPN	Pluronic F-127	Folic acid-functionalized SMMC-7721 cell membrance, paclitaxel	Improving the biocompatibility and targeting by coating biomimetic materials		SMMC-7721	Shen et al. [96]
(SFN + TPL) @CPLCNPs	Glyceryl monooleate + P507	Huh-7 cell-platelet hybrid membrane, sorafenib, triptolide		Long circulation function and homologous targeting	Huh-7	Li et al. [97]
TBP@DOX	Liposome	P-selectin (tumor targeting), doxorubicin, BML (microwave-sensitizer)	Combining the efficacy of chemotherapy and ablation		HepG2, H22	Xu et al. [98]
UiO-66/Bi_2S_3@DOX	UiO-66/Bi_2S_3 MOF nanoparticle	Doxorubicin	Combining the efficacy of TACE and ablation		N1S1	Liu et al. [99]
BMPMs	SPION	Inhexol, Carrageenan	Combining TACE and MRI	Imageable TACE	HUVECs	Liu et al. [100]
IR820-PEG-MNPs	PEGylated melanin nanoparticle	IR820	Combining PA/MA imaging and ablation	Diagnosis of micro HCC and imaging guided ablation	HepG2, Huh7	Chen et al. [101]

low while ensuring the success rate of ablation [104]. However, insufficient ablation leads to HCC recurrence and may promote its metastasis. Sublethal heat stress may promote tumor cell metastasis by upregulating the expression of the epidermal growth factor receptor [105]. Studies have found that ablation therapy could activate or enhance innate immunity and liver cancer-related adaptive immune response [106,107]; however, the response was weak. Synergistic immunotherapy could enhance the immune response and improve the effect of anti-HCC [108,109], which will solve the above problem.

The therapeutic efficiency can be improved by combining ablation

therapy with various immune adjuvants through nanotechnology (Fig. 3A) [83,110–112]. Synthetic oligodeoxynucleotide with unmethylated cytosine-phosphate-guanine (CpG) is an immune adjuvant that triggers innate and adaptive immunity by stimulating dendritic cells (DC), nevertheless, it requires multiple injections or high doses to stimulate DC maturation. Therefore, Cai et al. designed a metal-organic framework (MOF) nanoparticle formed by photosensitizers and loaded them with CpG and acriflavine (ACF), a hypoxia signaling inhibitor, as an in situ tumor vaccine. The results showed that the nanoparticle promoted local DC maturation, cytokine upregulation, and T-cell infiltration enhancing tumor inhibition [83].

3.2. Transarterial therapy

Transarterial therapy is commonly used for HCC patients who cannot accept curative therapies. Its principle is to deliver a high concentration of chemotherapy drugs to tumor cells and/or to block tumor-feeding arteries. This treatment can minimize the systemic toxicity of chemotherapy. According to different arterial intubation chemotherapy and embolization procedures, it can be divided into TACE, hepatic arterial infusion chemotherapy (HAIC), transarterial embolization (TAE) and transarterial radioembolization (TARE) [113–115]. As the standard treatment for mid-term HCC, TACE consists of conventional TACE (cTACE) and drug-eluting beads TACE (DEB-TACE). The former infuses part of the chemotherapy drugs first and then mixes the other part with lipiodol emulsion for embolization; the latter has the advantage of sustained and stable drug release through drug-eluting beads. Although the randomized trial failed to prove that DEB-TACE is more effective than cTACE, in subgroup analysis, more advanced patients (Child-Pugh B, ECOG 1, bilobal disease, recurrent disease) had a significantly increased objective response rate to DEB-TACE, and the severe liver toxicity of DEB-TACE was less compared with cTACE [116]. Although TACE is the most widely used transarterial therapy in clinical practice, problems still affect the antitumor efficacy, such as aggravating tumor hypoxia, incomplete embolization, and poor degradation of embolic agents. Therefore, nanotechnology is applied to address these problems (Fig. 3B).

TACE will aggravate tumor hypoxia during embolization, which is associated with chemotherapy resistance and recurrence, and can also lead to the invasive phenotype of the tumor, increasing angiogenesis and metastatic activity [117]. Some studies have combined TACE with hypoxia-related protein inhibitors to enhance therapeutic efficacy [118], and nanotechnology can integrate the two. Wang et al. synthesized CaO_2 nanoparticles (CaO_2 NPs) as a synergist for TACE. CaO_2 NPs reacted with water to generate abundant O_2, OH^- and Ca^{2+}, thereby improving the tumor microenvironment by relieving hypoxia, neutralizing acid, and down-regulating hypoxia-related markers' expression, which significantly enhanced the antitumor effect of TACE [84].

Furthermore, TACE is difficult to completely embolize, which may lead to tumor recurrence. DEB-TACE can release drugs stably compared with cTACE; hence researchers exert nanotechnology to optimize DEB-TACE to increase drug loading and enhance sustained release, killing residual cancer cells [85,86]. Zhao et al. synthesizeddextran-coated arsenic trioxide (ATO) nanoparticles as a nanosized drug-eluting bead (NDEB), which was activated by endogenous inorganic phosphate (Pi) to release ATO, while the hydrated dextran layer protected ATO from contacting with the serum to delay the reaction between NDEB and Pi. The therapeutic effect of NDEB-TACE was verified in animal experiments. It was found that compared with cTACE, NDEB-TACE led to the continuous embolization of tumor-feeding vessels and the sustained release of ATO, resulting in more thorough tumor necrosis [86].

In addition, with the widespread use of TACE, the biodegradability of embolic agents is required. Using biodegradable nanomaterials can meet the long retention of embolic agents while making them degrade slowly [87,100,119,120]. Currently, lipiodol emulsion mixed with doxorubicin (DOX) is mainly used clinically for TACE. Adding solid particles to the

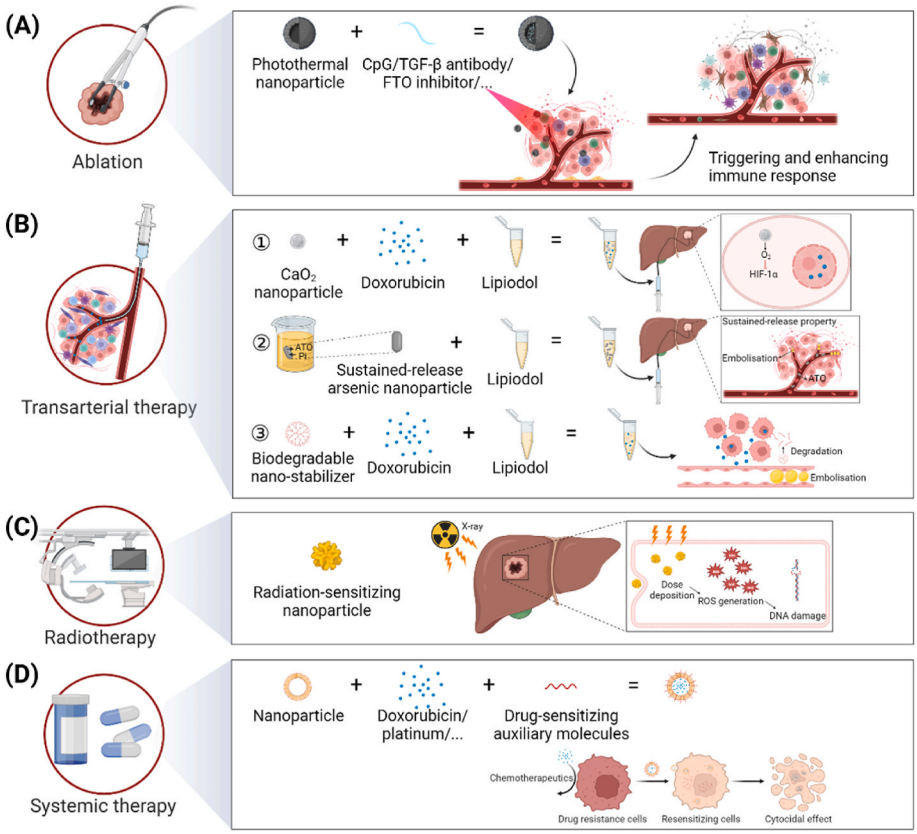

Fig. 3. Nanotechnology application in ablation, transarterial therapy, radiotherapy, and systemic therapy. (A) Nanotechnology enhances post-ablation immune response via combining ablation with immune adjuvants. (B) Nanotechnology improves transarterial therapy via alleviating hypoxia, causing thorough necrosis, and using biodegradable embolic agents. (C) Nanoscale radiosensitizers increase radiation sensitivity. (D) Nanoparticles carrying auxiliary molecules ameliorate drug resistance.

formula can obtain a stable emulsion (i.e. Pickering emulsion). However, organic or inorganic particles are non-degradable and may cause chronic tissue inflammation. Deschamps et al. successfully prepared stable lipiodol emulsion with biodegradable poly(lactide-*co*-glycolide acid) (PLGA) nanoparticles and proposed a new strategy for stabilizing lipiodol emulsion [87]. Liu et al. designed a biodegradable chemoembolic agent composed of carrageenan, iohexol, and superparamagnetic iron oxide nanoparticle (SPION). The porous structure allowed a large amount of loading and controlled DOX release while facilitating the infiltration of various enzymes into its interior. It could be degraded by 20–35% within two months, meeting long embolization duration and biodegradability [100].

3.3. Radiotherapy (RT)

RT for HCC includes stereotactic body radiotherapy (SBRT), proton beam radiotherapy (PBT), and others. Limited studies have found that SBRT was as effective as RFA regarding local tumor control [121,122]. For patients at high risk of portal vein invasion, the local recurrence rate in the SBRT group was lower than RFA [121]. Besides, prospective studies have found that the one-year tumor control rate of SBRT was over 90% [123,124], suggesting that SBRT may be an effective option for liver transplantation bridging therapy. PBT is a novel technique that is theoretically more accurate and efficient. A recent phase III randomized trial found that the efficacy of PBT on postoperative recurrence or residual small HCC lesions was not inferior to that of RFA, proving that this is a promising technique for treating small HCC [125]. However, the drug resistance caused by hypoxia of the tumor is a major problem hindering the effect of RT. Therefore, radiosensitizers have emerged. Commonly used clinical radiosensitizers include radiosensitive compounds such as glycidiazole sodium, sanazole, and oxygen.

In recent years, researchers found that gold nanoparticles have radiation-sensitizing capabilities, which can increase local radiation dose deposition (Fig. 3C). Sood et al. prepared targeted iron oxide-gold core-shell nanoparticle (GNP), and the local tumor ROS levels were significantly increased in the GNP group after radiation exposure [88]. In addition, after radiation exposure, angiogenesis pathways were activated in the tumor and tumor cells became more radioresistant, leading to tumor cell repopulation [126]. Therefore inhibiting angiogenesis pathways is an effective strategy to enhance the radiotherapy response of HCC. Li et al. used targeted gadolinium-hybridized gold nano molecules (tGd-GNMs) as radiosensitizers to increase local radiation dose deposition; meanwhile, effective VEGF siRNA nanocarriers to down-regulate the expression of VEGF, inhibiting tumor revascularization. The tumor inhibition rate increased from 12% of RT alone to 23% [89].

3.4. Systemic therapy

HCC is insensitive to commonly used chemotherapeutic drugs. For HCC patients with liver cirrhosis, the damage of metabolic pathways increases the systemic toxicity of traditional chemotherapeutic drugs; therefore, chemotherapy is not used for the conventional systemic treatment of HCC. Current systemic therapy for advanced HCC consists primarily of targeted therapy [4]. Both sorafenib and lenvatinib are oral multikinase inhibitors that inhibit tumor cell proliferation and angiogenesis. They have been approved as the first-line treatment of advanced HCC after phase III RCTs have confirmed their efficacy [127–129]. Because inhibition of vascular endothelial growth factor (VEGF) signaling has immunomodulatory effects, such as DC maturation, T-cell function, and reversal of immunosuppression, it may result in synergistic antitumor effects when combined with immune checkpoint inhibitors. The recent phase III IMbrave150 trial found that the combination of atezolizumab (anti-PD-L1 antibody) and bevacizumab (anti-VEGF antibody) in patients with advanced HCC who had unreceived prior systemic therapy resulted in a prolonged median survival time and progression-free survival time than the sorafenib group [130,131], which has been approved as the first-line systemic therapy for advanced HCC. Second-line systemic therapies includes regorafenib, cabozantinib and ramucirumab [132–134]. However, drug resistance is one of the most troublesome problems in treating advanced HCC. The mechanism of drug resistance is complicated, involving epigenetics, molecular transport, and tumor microenvironment, and there is still a lack of satisfactory solutions [135].

For the problem of drug resistance, studies have found that some molecules are insufficient to kill HCC, nonetheless can increase the sensitivity of HCC to existing drugs; therefore, nanotechnology can improve drug resistance by carrying different auxiliary molecules (Fig. 3D). Platinum drugs, represented by cisplatin, are the most extensively used chemotherapeutic drugs in clinical practice. However, HCC is insensitive to it, coupled with strong side effects, which greatly limits the application of platinum drugs in HCC. To overcome the acquired drug resistance, Jin et al. designed an iodine-containing polymer nanoparticle loaded with cisplatin to deplete glutathione, which mediates platinum resistance in cancer cells, via an iodine-click reaction and effectively improved the chemotherapeutic effect of cisplatin [90]. This type of research is expected to bring back attention to traditional chemotherapeutic drugs in treating HCC. Additionally, the first-line drug sorafenib, which has been used for many years, is also facing the issue of drug resistance. Studies have found that certain small nucleic acid molecules, such as MK-siRNA, could increase the sensitivity of HCC to sorafenib [136,137]. Xu et al. used nanoparticles to co-deliver sorafenib and USP22 shRNA, which suppresses the expression of multidrug resistance-associated protein 1, demonstrating an increase in sorafenib accumulation and enhanced sensitivity of HCC [91]. However, the tumor microenvironment rich in stroma sometimes hinders the delivery of drugs, so Younis et al. employed microfluidic technology to generate ultra-small lipid nanoparticles of approximately 60 nm, targeted delivering SOF and MK-siRNA, and found that about 70% of sorafenib-resistant HCC growth was inhibited [92].

3.5. All kinds of therapies

According to the preceding, the advantages of nanotechnology are reflected in the methodological improvement of ablation, TACE, RT, and systemic therapy in a targeted and efficient manner. Moreover, nanotechnology can generally optimize the therapies of HCC through several aspects (Fig. 4).

First, improving the therapeutic targeting. The non-specific uptake of drugs can lead to many side effects [127,128], while improving therapeutic targeting by modifying various tumor target ligands on nanoparticles can enhance efficacy and decrease side effects, such as targeting common HCC biomarkers [138,139], coupling with folic acid to target the highly expressed folic acid receptor in solid tumors [140,141], targeting the highly expressed P-selectin in HCC and tumor vascular endothelium to simultaneously target the primary tumor and metastases [98]. Hierarchical targeting is a novel strategy to further improve the accuracy of HCC diagnosis and treatment [37,93]. Shi et al. proposed that tissues (primary targets), cells (secondary targets) and receptors (tertiary targets) should be accurately graded and targeted, and they designed a tertiary targeting nanosystem. The nanosystem was mediated by biomagnetism, and the primary targeting ability to target tissues was improved by a magnetic field in the body. For the secondary targets, the study selected liver cancer stem cells (LCSCs) involved in tumorigenesis, progression, metastasis, recurrence, and drug resistance. Low-intensity focused ultrasound triggers the explosion of nanoparticles around LCSCs, causing physical damage to them. The subsequent release of γ-interferon attained tertiary targeting, which upregulated the major histocompatibility complex (MHC) expression and promoted tumor cell apoptosis after binding to membrane receptors. This nanosystem significantly enhanced the antitumor effect compared with non-tertiary targeting nanoparticles [93].

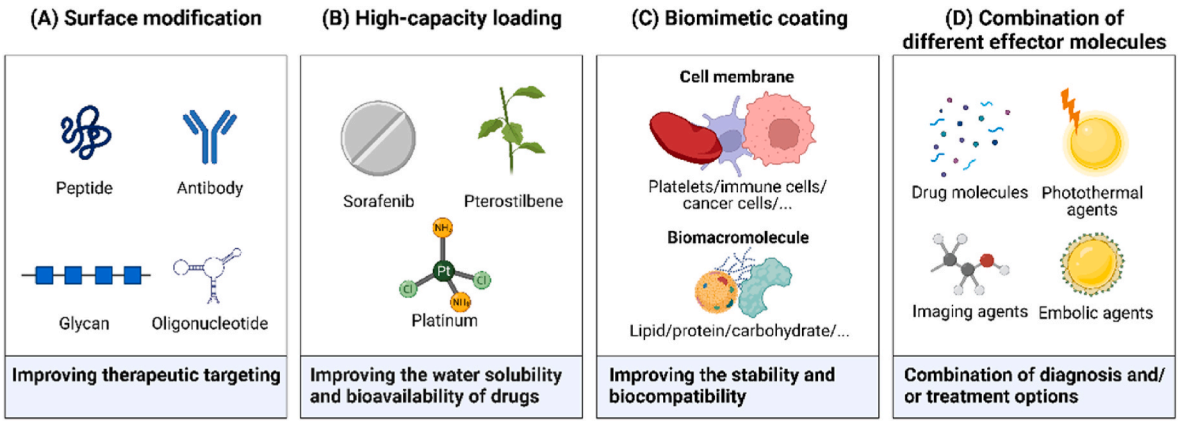

Fig. 4. General application of nanotechnology in treating HCC. (A) Surface modification of nanoparticles improve therapeutic targeting. (B) High loading capacity of nanoparticles improve the water solubility and bioavailability of drugs. (C) Biomimetic coating improves the biocompatibility and stability of nanoparticles. (D) Combination of diagnosis and treatment modalities improves therapeutic efficacy.

Second, improving the physicochemical properties of therapeutic drugs. Some drugs, such as sorafenib, have a tumoricidal effect; however, their clinical application is limited due to poor water solubility, fast metabolism, and low oral bioavailability. The nano-delivery system can improve the water solubility and bioavailability of drugs [94,95,142]. Chen et al. used clinically safe poly(ethylene glycol)-b-poly(lactic acid) as a nanocarrier to deliver sorafenib (NP-sfb), and the inhibition of NP-sfb on tumor growth was significantly stronger than that of free SFB at the same dose, indicating that nanoparticles successfully increased the bioavailability of SFB [94]. The natural chemotherapeutic drug pterostilbene (PTS) is cytotoxic against various tumors, including liver cancer. However, it is insoluble in water, and the solvents commonly used are organic substances with systemic toxicity. The nanoplatform is an ideal substitute. Tzeng et al. increased the solubility of PTS to 604.38 μg/mL by reducing the PTS nanoparticles (PSN) size, adjusting the PTS and excipients ratio, and inducing PSN to undergo amorphous transition [95].

Third, increasing the biocompatibility and stability of the effector molecule. Coating/binding nanoparticles with endogenous substances in the body can improve their biocompatibility and stability, prolong circulation time, reduce the leakage of effector molecules, and facilitate drug absorption. This kind of nanoparticle is called a biomimetic nanoplatform. Currently used biomimetic materials include cell membranes, biomacromolecules, and others [138,143]. Ma et al. coated the target-recognizing CAR-T cell membrane on photothermal agent-loaded mesoporous silica nanoparticles. The results showed that the nanoparticles exhibited excellent biocompatibility in vivo and in vitro [138]. Studies by Shen et al. showed that liver cancer cell membrane-encapsulated paclitaxel nanocrystals (CPN) had longer plasma half-life and higher bioavailability than paclitaxel nanocrystals (PN) [96]. Li et al. found that the phagocytosis of nanoparticles by macrophages was reduced by approximately 10-fold after liver cancer cell-platelet hybrid membrane coating [97].

Fourth, providing a platform for combination therapy. Combining two or more therapies with nanoparticles can enhance the antitumor effect and reduce the probability of recurrence. Previous studies demonstrated that hyperthermia could enhance chemotherapy which in turn can improve ablation efficiency, and the two have synergistic antitumor effects, so many studies have combined the two through nanoplatforms [144–146]. Xu et al. encapsulated DOX and microwave sensitizers in targeted liposome nanoparticles. Under the acidic environment and microwave stimulation, the nanoplatform released more DOX and produced ablation effect. The therapeutic effect on liver cancer was more than 1.5-fold that of nanoparticles without microwave sensitizer, equivalent to 10-fold the dose of free DOX. There were no common side effects of DOX [98]. In addition, since a small part of HCC's blood supply does not originate from the hepatic artery, the clearance of cancer cells by TACE is always incomplete. Combining TACE with ablation therapy can improve the efficiency of TACE. The multifunctional nanoparticles UiO-66/Bi_2O_3@DOX prepared by Liu et al. can achieve low pH triggered DOX release and photothermal ablation, showing stronger tumor inhibitory effect [99].

Fifth, realizing the integration of diagnosis and treatment on nanoplatforms. On the one hand, it can reduce time cost and improve diagnosis and treatment efficiency [93,101,139,141]. Chen et al. coupled PEGylated melanin nanoparticles (PEG-MNPs) with the NIR dye IR820 to construct a highly biocompatible multifunctional nanoplatform IR820-PEG-MNPs with PAI, MRI and photothermal ablation capabilities. Combining the two imaging techniques demonstrated a high sensitivity, high resolution, and deep tissue penetration. After the injection of IR820-PEG-MNPs, the PA/MR signal of the tumor area increased by 4.13-fold and 1.60-fold compared with before injection, capable of detecting tiny orthotopic tumors as small as 1.8 mm; compared with PEG-MNPs, the photothermal conversion efficiency of IR820-PEG-MNPs increased from 18.7 to 40.2% [101]. On the other hand, integrating diagnosis and treatment can realize the monitoring and evaluation of treatment effects and can play the role of precise guidance [100,120]. Liu et al. prepared a DOX-loaded multifunctional porous microsphere, which encapsulated iohexol and SPION at the same time. During TACE, doctors can evaluate the embolism position and scope by digital subtraction angiography (DSA), while SPION can remain for several hours to several days after TACE, therefore, it is convenient to evaluate the degradation degree of BMPM by MRI for follow-up treatment [100].

In short, nanotechnology can enhance efficacy and reduce side effects by improving the targeting of effector molecules, optimizing the properties of effector molecules, and synergizing various therapies. By integrating diagnosis and treatment, it can also improve efficiency as well as achieve real-time assessment.

4. The safety of nanotechnology in HCC

Although the multifunctionality of nanomaterials can overcome some limitations of diagnostic and therapeutic methods, the potential toxicity can't be ignored. The small particle size, special morphology, high specific surface area, complex compositions and surface functions of nanomaterials make them inevitably distribute and accumulate in the normal tissues, eventually leading to body toxicity [147]. The nanomaterials-induced toxicity mechanisms include inflammation, oxidative stress, apoptosis, necrosis, and genetic toxicity, etc [148–150].

The types of materials generally used in nanomedicine include carbon nanotubes, metal nanoparticles, lipid-based nanoparticles, and polymer-based nanoparticles, etc. Nanoparticles can enter the

circulation and then migrate to different organs via skin exposure, airway inhalation, gastrointestinal ingestion, and intravenous injection [151]. As a primary metabolic active organ, liver always becomes the place where nanoparticles in systemic circulation accumulate. It was estimated that 30–99% of nanoparticles in the circulation can accumulate in the liver [152]. Various nanomaterials can lead to elevated liver enzymes, hepatic steatosis, and liver fibrosis [149,153]. According to Zhang et al. exposure of parental mice to multi-walled carbon nanotubes damaged the liver function of offspring mice, resulting in the accumulation of lipid droplets in hepatocytes [154]; Albrahim et al. found that silver nanoparticle poisoning in rat models (80 mg/kg) damaged the liver by interfering with oxidative homeostasis, causing elevated liver enzymes and reduced albumin [155]; while multiple injections of silica nanoparticles (20 mg/kg) induced oxidative damage and apoptosis in mouse hepatocytes, and then activated the TGF-β1/Smad3 pathway to promote liver fibrosis [156]. Although researchers have paid more attention to the nanosafety issues, the current investigation on this aspect are not enough, especially the impacts and mechanisms of long-term accumulation of nanoparticles on the body are not clear. Nanotechnology is a double-edged sword, so translational research needs to be carried out prudently before the assessment norms for the risk of nanomaterials application have been formed.

5. Conclusions and prospects

In recent years, nanotechnology has significantly improved the efficacy of diagnosis and treatment and has become a research hotspot. As described in this article, nanotechnology's high modifiability and loading capacity can improve detection sensitivity, therapeutic targeting, and the properties of effector molecules and the tumor microenvironment to improve the efficacy of diagnosis and treatment. The multifunctional nanoplatform can also facilitate the combination of diagnosis and therapies, further enhancing the efficiency of medicine.

However, there are still some limitations in the research of nanotechnology in HCC: 1) the research evaluation standards are non-uniform, and it is challenging to make comparisons among various analyses. In the future, it will be necessary to develop research evaluation standards for nanotechnology in HCC; 2) several studies blindly combined diagnosis and treatment methods, although they didn't achieve synergism. The combination of therapies should be supported by research on mechanisms in future; 3) certain therapies, such as TARE, have deficiencies; however, there are no improvement strategies and applications of nanotechnology in these fields. Applying bio-nanotechnology in clinical practice will take a long time; however, its prospects are very broad. In addition to the current therapies, nanotechnology can further be applied to the emerging regimens such as surgical nanorobots, immunotherapy, gene therapy, cell therapy and regenerative medicine, etc. Furthermore, it is also expected to play a role in individualized treatment and real-time monitoring of therapy. It can be predicted that nanomedicine will occupy an important position in the future diagnosis and treatment of HCC.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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