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Nanotheranostics: A powerful next-generation solution to tackle hepatocellular carcinoma

Rusdina Bte Ladju, Zulvikar Syambani Ulhaq, Gita Vita Soraya

Abstract
Hepatocellular carcinoma (HCC) is an epidemic burden and remains highly prevalent worldwide. The significant mortality rates of HCC are largely due to the tendency of late diagnosis and the multifaceted, complex nature of treatment. Meanwhile, current therapeutic modalities such as liver resection and transplantation are only effective for resolving early-stage HCC. Hence, alternative approaches are required to improve detection and enhance the efficacy of current treatment options. Nanotheranostic platforms, which utilize biocompatible nanoparticles to perform both diagnostics and targeted delivery, has been considered a potential approach for cancer management in the past few decades. Advancement of nanomaterials and biomedical engineering techniques has led to rapid expansion of the nanotheranostics field, allowing for more sensitive and specific diagnosis, real-time monitoring of drug delivery, and enhanced treatment efficacies across various malignancies. The focus of this review is on the applications of nanotheranostic modalities as a promising option to address the key challenges present in HCC management.
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Core Tip: Hepatocellular carcinoma (HCC) is a global epidemic burden. The high mortality rate is mostly due to late diagnosis and complexity of treatment. Nanotheranostics is a potential approach for HCC management. We herein discuss the challenges of HCC management, the advancement of nanotheranostics in cancer, and the potential role of nanotheranostics to address the current challenges in HCC management.

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INTRODUCTION

Epidemic burden and risk factors of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and remains the second leading cause of cancer-related deaths worldwide[1,2]. It accounts for around 90% of all primary liver cancer cases worldwide[3], and is an epidemic burden in both developing and developed countries[4]. Whilst certain endemic areas such as East Asia has shown a decreasing trend, regions such as Europe, Africa, and the United States display increasing trends in HCC incidence rate with substantial morbidity and mortality[5,6]. Concerningly, cases have doubled in Europe and America as a result of lifestyle factors such as alcohol abuse, smoking, obesity, and metabolic diseases[7-10]. Variations among age and gender are also interesting epidemiologic features of HCC. Men have a higher prevalence of HCC than women with a ratio of 462.4:185.8 new cases per year in developing countries[11]. Respectively, the risk of HCC significantly increases among those who are older than 40 years of age[12].

The risk factors and etiologies of HCC vary depending on geographic region and lifestyle. Hepatitis B and C infections are major etiological factors that significantly contribute to HCC globally[13-15], accounting for 44% and 21% of HCC cases respectively[16], with the highest number of hepatitis B cases occurring in Asia. Other possible risk factors include the increasing number of nonalcoholic fatty liver disease (NAFLD)[17], alcohol addiction[18,19], and aflatoxin consumption[20]. In Western, Central, and Eastern Europe and North America, a majority of HCC cases were attributed to NAFLD/non-alcoholic steatohepatitis, obesity, and excessive alcohol consumption. In contrast, most HCC cases in Asia and Africa were attributed to hepatitis B virus infection[21,22]. The viral and metabolic etiologies described above not only contributes to HCC occurrence, but also implicates a high risk of de novo recurrence, leading to the development of incurable and advanced stage disease that is resistant towards therapeutic efforts such as complete tumor resection or ablation[6].

Pathological complexity of HCC

Due to the multifactorial nature of HCC, several cellular phenomena can be observed, including hypoxia, inflammation, oxidative stress, and tumor microenvironment. Indeed, the molecular mechanism of liver carcinogenesis involves multiple endogenous and exogenous genetic alterations[23]. Hepatocarcinogenesis is a deliberate and complex multistep process associated with somatic genomic alterations, leading to the production of cellular intermediates that progress into hepatocellular carcinoma[24]. The development of HCC involves a combination of continuous inflammatory damage, necrosis, and fibrotic deposition. The pre-neoplastic stage is a long process that typically requires 10 to 30 years of time. During this stage, phenotypically altered hepatocytes are formed as a result of either DNA methylation alterations, pathogenic agent’s reaction, and point mutation or loss of heterozygosity, which occur in part
through epigenetic mechanisms that lead to the development of dysplastic hepatocytes in foci and nodules. Aberrant and dysplastic hepatocytes are related to the accumulation of permanent structural alteration and changes in genes and chromosomes. Alterations in the malignant phenotype are often distinct, suggesting heterogeneity at the genomic level.

Challenges in HCC diagnosis
Early diagnosis is a major challenge in HCC management, and in most cases, the lack of early diagnostic modalities lead to less than optimal treatment outcomes. In developed countries, 30%-60% of HCC cases can be diagnosed early, enabling higher success rates of curative treatment. Contrastingly, HCC cases in developing countries are mostly diagnosed in late stages, leading to substantially lower likelihood of curative treatment. Diagnosis of HCC is in fact, an important and critical phase that relates directly to the survival and prognosis of the patients.

Complexity of HCC treatment
Treatment of HCC itself is also complex and multifaceted, and outcome depends on the time of diagnosis and the presence of additional comorbidities. Prompt diagnosis of HCC is correlated with better outcomes of curative therapies. This is demonstrated by studies that show higher efficacy of local radiofrequency ablation and surgical intervention (liver transplantation and liver resection) in the very early and early-stage HCC as compared to later stages. However, most HCC patients are excluded from definitive surgical resection due to late diagnosis. In such cases, liver transplantation can be the best treatment for HCC with a low risk of recurrence, though it is suggested as a second line treatment due to the disparity between limited liver donor resources and the increasing number of patients. Based on international guidelines, late stage HCC patients (intermediate and advanced) may receive palliative treatment such as chemoembolization and systemic therapy, while terminal patients can only receive supportive care.

Issues such as tumor recurrence and drug resistance are also major obstacles that frequently complicate HCC management. The 5-year recurrence probability of HCC is around 62% after liver ablation and 80% after liver resection. Palliative treatment often have unexpected and poor outcomes related with high refractoriness to systemic therapy that lead to development of multidrug resistance.

Need for a novel approach in HCC management
The challenges associated with both diagnosis and treatment of HCC has resulted in the high mortality rates across the globe, and calls upon innovative approaches that can improve the prognosis of HCC patients. In the following sections, we describe the rapid advances and implementation of theranostic-based nanomedicine and nanoparticles (nanotheranostic) as a promising option for the improvement of HCC patient outcomes and quality of life.

POTENTIAL OF NANOTHERANOSTICS FOR PRECISION CANCER MEDICINE
Nanotheranostic modalities present a promising solution to the diagnostic and therapeutic challenges encountered in HCC management, through the use of biocompatible nanoparticles that simultaneously performs both diagnostic and therapeutic functions. This approach potentially provides a more personalized and targeted approach to cancer therapy, wherein the nanoparticles can be designed to detect specific biomarkers of the target malignant region, allow real-time monitoring or visualisation of the target, and finally deliver therapeutic modalities in a more precise manner. In recent years, the nanosensor and nanomedicine technologies have experienced major development, and have paved the way for promising means of nanotheranostics implementation in cancer management.

Nanotheranostic is a real-time combination of novel therapeutic and modern diagnostic tool or imaging into a single agent linked and integrated by nanoparticles. Nanoparticles are the key components of the nanotheranostic agent which include aptamer, DNA nanostructure, lactosamine-based nanoparticles, metallic nanoparticles, gold nanoparticle, silver nanoparticle, dendrimer and copolymer-based nanoparticles, lipid-based nanomaterials, magnetic nanoparticles, iron oxide nanoparticle, mesoporous silica nanoparticle and...
Nanotheranostic is an ideal choice for cancer treatment in the era of personalized medicine due to its potential to overcome the diagnostic and therapeutic challenges described prior. Nanotheranostic not only provides the means for early diagnostic tools, nanoimaging-therapeutic integrated medicine, targeted-therapy, and tumor-specific nano-delivery agent, it also holds potential for real-time monitoring of drug response, and reduce side effects and drug toxicity in patients as shown in Figure 2.

Successful demonstration of nanotheranostics for diagnostics and targeted therapy has been shown by Roy et al. in which highly sensitive, polymer-modified gadolinium-doped iron oxide-based T contrast agents were used for successful methotrexate drug delivery. In the second application, nanotheranostics have been utilized for simultaneous imaging and cancer monitoring. An auto-fluorescent platform, constructed from a positively charged amphiphilic polymer polyethyl-eneimine-polylactide, was utilized to simultaneously load the antiangiogenesis agent cobrestratatin together with near-infrared (NIR) dye IR825 and heat-shock protein inhibitors. Altogether, the mechanism represents self-monitoring nanotheranostics, which in a mouse model demonstrated inhibitive properties in the tumour site through anti-angiogenesis and gene silencing enhanced photothermal therapy, while allowing real-time fluorescence monitoring.

The final and most widely developed application of nanotheranostics is for simultaneous imaging and targeted therapy, which has been shown to substantially increase the overall efficacy of therapies. Theranostic platform choice has expanded rapidly in the past decade, and typically combines imaging modalities such as magnetic resonance imaging (MRI), NIR fluorescence, photoacoustic (PA) or ultrasound imaging, with therapeutic modalities such as chemotherapeutic agents, x-rays, hyperthermia, or free radicals.

Depending on the desired diagnostic and therapeutic modality, the nanoparticle of choice may be composed of metals, polymers, carbons and lipids. Each choice provides its own unique characteristics and physicochemical interactions, and also require different fabrication and functionalization procedures. As an example, successful magnetic-based imaging in a nanotheranostic platform is achievable using iron oxide, which is also desired due to its low toxicity and chemical stability. But many platforms prefer the use of multi-functional semiconducting polymers with hydrophobic properties, which simultaneously allow imaging through easy interactions with aromatic chemotherapeutic agents. Nanoparticles can also be engineered to provide multimodal imaging which utilizes modified ultrasmall Ag₂Se nanodots to allow upconversion luminescence, downshifting luminescence, computed tomography and PA imaging techniques.

An increasingly common approach in cancer theranostics is the use of multimodal therapy. To illustrate, the study by Zhang et al. utilized Janus-type γ-Fe₂O₃/SiO₂ nanoparticles to combine the glucose oxidase-mediated cancer starvation strategy with hydroxyl radicals as chemodynamic therapy. Interestingly, nanoparticles can also be designed to become responsive towards environmental stimuli in drug-resistant tumours, meaning that it can be developed specifically towards the pathological profile of the tumor microenvironment as well as the organ-specific tissues and compartments, which contribute to the overall specificity of the drug delivery. For highly complex pathologies such as HCC with drug resistance, this provides a myriad of options for exploration, and becomes an interesting approach for future implementation of HCC-specific nanotheranostics.

Finally, it is also worth noting that metastasis remains a major issue in cancers such as HCC where diagnosis tends to be late. An interesting strategy showed the use of immunotherapy-based theranostics to specifically target metastatic tissue. In said study, magnetic-responsive immunostimulatory nanoagents were added with quantum dots nanoparticle.
superparamagnetic iron oxide nanoparticles and cytosine-phosphate-guanine oligodeoxynucleotides. These engineered components allow for PA and MRI in addition to acting as a therapeutic agent for photothermally triggered immunotherapy.

To illustrate these advancements, we present the current modalities of cancer nanotheranostics in Table 1. In general, cancer nanotheranostics has been used for simultaneous diagnostics and therapeutic[70], real-time monitoring of malignancies [71], guided-imaging[72,73], drug-delivery[74] and multimodal-targeted therapy[75-79].

**Figure 2** Applications of cancer nanotheranostic.

**TACKLING HCC WITH NANOTHERANOSTICS**

The nanotheranostic platform is a promising approach that is urgently needed to overcome the limitations of conventional therapy and diagnosis for more efficient HCC management. Figure 3 illustrates the multimodality of the nanotheranostic platform, which utilizes multipurpose nanoparticles for targeted nano-delivery, continuously controlled release of anticancer agents, guided imaging and early detection, for superior effectivity of transport[80]. Management of HCC requires powerful theranostic-based nanoparticles for early diagnostics and therapeutics with higher sensitivity and specificity, and to surpass the limitation of tissue penetration [81]. Previous studies have demonstrated the promising potential of silica-based nanomaterial as a potent nanotheranostic platform of HCC targeted-therapy nano-delivery[82-86]. In addition, many advances in HCC-specific nanotheranostics platforms are illustrated in Table 2, which demonstrates the multifunctional role of nanotheranostics as a detector to identify the HCC cell and tumor inhibitor by suppressing proliferation, migration and invasion of HCC[87,88].

One of the most remarkable advancements of the nanotheranostic platform is imaging and nano-delivery integration as an innovative resolution for early HCC diagnosis and in situ drug release. In vivo and ex vivo investigations have observed specific nanoplatform activation by the tumor, with minimized toxicity towards non-target cells[89]. Integration of multifunctional nanoparticles with MRI may provide novel perspectives in tumor imaging technology to enhance HCC management and treatment strategy. High precision quantification and sensitivity of nanoimaging technology is needed for tissue penetration issue in early diagnosis of HCC[90].

Aptamer-based nanotheranostic is also a potential tool for HCC management due to its unique characteristics. This oligonucleotide nanomedicine has high specificity and affinity towards various types of target molecules[91]. In HCC clinical application, aptamer-based nanotheranostic development targeting the epithelial cell adhesion molecule demonstrated an improvement of MRI application and drug-delivery with high efficiency of doxorubicin released specifically towards cancer cells[92].

Improvement of therapeutic success is urgently needed for patients with unresectable and advanced HCC. The combination between nanomedicine as a nano-
Table 1 Cancer nanotheranostics

<table>
<thead>
<tr>
<th>Applications</th>
<th>Principle</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Diagnostic and therapeutic</td>
<td>Stimuli responsive nanoparticle and targeted drug delivery</td>
<td>[61]</td>
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<tr>
<td></td>
<td>Activatable nanotheranostic systems diagnosis and therapy of peritoneal metastasis</td>
<td>[70]</td>
</tr>
<tr>
<td>Real-time monitoring and therapeutic</td>
<td>Self-monitoring and triple-collaborative therapy via auto-fluorescence nanoparticles</td>
<td>[62]</td>
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<tr>
<td></td>
<td>Real-time monitoring and tumor targeting via dual-fluorescent hydroxyapatite–doxorubicin</td>
<td>[71]</td>
</tr>
<tr>
<td>Guided-imaging and nanodelivery</td>
<td>Nanoparticle conjugated with antibody for tumor targeting and guided drug delivery</td>
<td>[63]</td>
</tr>
<tr>
<td></td>
<td>A protein-stabilized multifunctional nanoplateform for multimodal imaging and drug-delivery</td>
<td>[64]</td>
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<tr>
<td>Guided-imaging and therapeutic</td>
<td>Dual-targeting nanotheranostic with chemosensitizing agent for MDR chemotherapy</td>
<td>[65]</td>
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<td></td>
<td>Multifunctional nanocarrier for fluorescence imaging guided chemo-phothermal</td>
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<td></td>
<td>Dual-modal imaging and synergistic cancer starvation/chemodynamic therapy</td>
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<td></td>
<td>Tetra-modal imaging guided photothermal therapy</td>
<td>[67]</td>
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<td></td>
<td>Bimodal imaging guided photothermal-triggered immunotherapy</td>
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<td>Hierarchical tumor acidity-responsive magnetic nanobomb photodynamic therapy</td>
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<td>Lipid based nanoparticles nanodelivery-anticancer drug and nanoimaging</td>
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<td>The self-assembly nanoparticles with guided imaging and chemotherapeutic drugs</td>
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<td>Biocompatible nanoparticles as targeted-nanodelivery of chemotherapeutic agent</td>
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<td>Dual-modality mapping guided photothermal ablation for metastatic cancer</td>
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<tr>
<td></td>
<td>Magnetic nanoparticle-doxorubicin for enhancing nanoimaging and targeted therapy</td>
<td>[79]</td>
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MDR: Multidrug resistance.

Table 2 Nanotheranostic development againts hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Applications</th>
<th>Principle</th>
<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td>Diagnostic and therapeutic</td>
<td>Conventional SELEX</td>
<td>[87]</td>
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<td></td>
<td>CE-SELEX</td>
<td>[88]</td>
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<td></td>
<td>Magnetic nanoparticle-aptamer</td>
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<tr>
<td>Enhancing therapeutic</td>
<td>Inducing tumor regression using siRNA-nanoparticle construction</td>
<td>[100]</td>
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<tr>
<td></td>
<td>Enhancing the anticancer efficacy using siRNA-nanoparticle construction</td>
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<tr>
<td></td>
<td>Enhancing chemotherapy using microRNA 375-nanoparticle construction</td>
<td>[102]</td>
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<tr>
<td></td>
<td>Synergistic antitumor effect of microRNA 375-nanoparticle construction</td>
<td>[103]</td>
</tr>
<tr>
<td>Diagnostic and guided-imaging</td>
<td>‘Activatable’ aptamer-based fluorescence probe</td>
<td>[104]</td>
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<tr>
<td></td>
<td>Streptavidin-fluorescent silica nanoparticles combination</td>
<td>[105]</td>
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<tr>
<td></td>
<td>Aptamer- based electrochemical biosensors</td>
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</tr>
<tr>
<td>Gene editing</td>
<td>Next-generation CRISPR/Cas technology</td>
<td>[107]</td>
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</table>

HCC: Hepatocellular carcinoma; SELEX: Systematic Evolution of Ligands by Exponential Enrichment.

delivery system with cancer immunotherapy holds great potential for enhancing the nanotherapeutic outcome for this population. A promising targeted-nano-delivery immunotherapy for advanced HCC that is currently undergoing clinical trial is the 4th generation chimeric antigen receptor (CAR) T cells targeting glypican-3 (GPC3) (ClinicalTrials.gov Identifier: NCT03884751) [93]. This study showed promising phase I results in regard to antitumor activity and safety profile of CAR-GPC3 T-cell immunotherapy. The antitumor activity is positively associated with tumor response with no grade 3/4 neurotoxicity effect in any patients[94]. Several studies have also been done
to achieve said goal by conjugating anticancer drugs with nanoparticles, rendering the treatment safer with more effective systemic administration due to the platform’s capability of controlling and postponing drug release. In the in vivo mouse model, tumor specific uptake of the controlled drug release for several weeks was observed, with minimal toxicity [95].

Molecular-targeted nano-therapies have also been constructed for nano-delivery using a modular design of polymeric nanoparticles for selective accumulation of drug payload within tumor lesions. In in vivo mouse models, the intravenous drug injection was more effective for tumor inhibition than oral administration. This has revolutionized anticancer therapy by enhancing the efficacy and potency of therapeutics through inhibition of the angiogenesis pathway, tumor growth, tube formation and metastasis[96]. Targeted drug delivery using mesoporous silica nanoparticle is also promising. Nanoconstruction of silica nanorattle encapsulated docetaxel exhibited low toxicity with high antitumor activity, making it a prospective candidate for nano-delivery system[97]. Moreover, modified silica nanoparticles targeting low density lipoprotein and loaded with two anticancer drugs for liver cancer chemotherapy showed increased delivery efficiency based on in vitro and in vivo analysis[98].

In addition to anticancer drug nano-delivery for HCC treatment, the nanotheranostic platform is also suitable for targeted nano-delivery of small interfering RNA based therapeutics. This can be used as gene therapy to knock down a specific gene[99-101], and micro RNA for enhancing chemotherapy efficiency[102] to overcome multi-drug resistance in HCC[103].

FUTURE PERSPECTIVES

HCC is an extremely complex and heterogeneous disease with diverse molecular profiles, aetiology and subtypes. Since conventional approaches still fail to overcome limitations in HCC management, nanotheranostic is a promising alternative to overcome the problems. Rapid development in nanotechnology has added a tremendous value on cancer therapy. The future of cancer nanomedicine lies on multimodal nanoplatforms that combine targeting ligands, imaging agents, diagnostic agents and therapeutic components into one unit of functionalized nanoparticles. Thus, multifunctionality is a powerful and unique advantage of nanotheranostic over traditional methods, and evidence has shown its capacity to work efficiently and noninvasively in vivo without systemic toxicity. Development of nanotheranostic in the right direction requires improvement of platforms so that it can be optimized simultaneously for proficient performance as the best clinical outcome in HCC.

CONCLUSION

In summary, nanotheranostic is an emerging and promising approach for HCC diagnosis/imaging and therapy in the future. Nanotheranostic is a powerful, unique, and multifunctional tool that yields positive impact both in the basic research and
clinical application of HCC. We predict that in a near future nanotheranostic platform will continue to exponentially grow and progressively implemented in the development of novel and efficacious diagnostic and therapeutic agents towards cancers, including HCC. Further expansion would be needed to assist clinical translation of the promising preclinical studies in HCC.

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