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Hepatocellular Carcinoma in Focus: A Comprehensive Review of Its Epidemiology, Diagnostic Advances, and Evolving Therapeutic Strategies

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Abstract: Hepatocellular carcinoma (HCC) is the most widely recognized primary liver malignancy. It is also a major cause of cancer deaths worldwide. The prognosis remains poor due to a late diagnosis and lack of effective therapy options, despite improvements in surveillance and therapy. This review aims to describe the epidemiology and diagnostic and therapeutic approaches to the condition at various stages, as well as the increasing role of gene therapy in HCC. A literature review was performed according to PRISMA guidelines. A total of peer-reviewed studies was accessed from PubMed, Scopus, and Web of Science from the year 2000 to 2024. Research involving diagnostics for HCC clinical transarterial experimental gene protocols were the focus of attention. The latest developments in diagnostic practices for HCC focus on imaging (CTs and MRIs), serum biomarkers (AFP and DCP), and molecular profiling (emerging). There are different strategies that are employed for the management of HCC, or hepatocellular carcinoma. The treatment of HCC is based on the BCLC staging system. In the early stages, surgical resection and liver transplantation are used. In the advanced stages, transarterial chemoembolization (TACE), tyrosine kinase inhibitors, and immune checkpoint inhibitors can be used. Another possible approach in parallel is gene therapy. These can deliver a targeted, personalized treatment with the use of CRISPR/Cas9, siRNA, oncolytic viruses, tumor suppressor genes, etc. HCC necessitates a multidisciplinary and stage-specific approach. Gene-based onboarding strategies in clinical care will largely depend on the delivery of methods, clinical validation, and personalization in the future.

Keywords: hepatocellular carcinoma; liver malignancy; serum biomarkers; epidemiology; clinical validation; PRISMA

1. Introduction

Hepatocellular carcinoma (HCC), the most frequent type of primary liver cancer, is a global health problem of considerable significance. According to the World Health Organization, hepatocellular carcinoma is the sixth most diagnosed cancer and the third most lethal [1]. The number of instances is very high in Asia and sub-Saharan Africa, where hepatitis B virus and hepatitis C virus infections occur [2].

Hepatocellular carcinoma develops in the background of chronic liver disease. The major risk factors for liver cancer are hepatitis B and C virus infections, high alcohol consumption, and more and more NAFLD. With the worldwide spike in obesity, type 2 diabetes, and metabolic syndrome, NAFLD is becoming a significant disease contributor to HCC [3].

The asymptomatic manifestation of HCC in the early-stage delays diagnosis of the disease. When curative treatments are limited, many patients present at an advanced stage. Nonetheless, recent development of diagnostic imaging, noninvasive biomarkers, and risk stratification models significantly improved detection possibilities.

The treatment options available for HCC have changed significantly. Locoregional treatment options for hepatocellular carcinoma (HCC) include surgical resection, liver transplantation, radiofrequency ablation (RFA), and transarterial chemoembolization (TACE) [4]. Advanced HCC can be treated using systemic therapies, in particular those that target the use of sorafenib and lenvatinib. Immune checkpoint inhibitors nivolumab and atezolizumab have also shown promise [5].

Though there has been progress, issues relating to managing HCC globally remain. Access to healthcare is not equal, especially in low- and middle-income countries, due to diagnosis delay, low awareness, and high treatment costs, among others [6]. As a result of these issues, patients do not receive therapy on time or at all.

This assessment and review on hepatocellular carcinoma will provide a comprehensive overview. The session will highlight the epidemiology of the disease and new developments in diagnosis and treatment. Through the synthesis of recent evidence, the aim of this paper is to identify knowledge gaps and make recommendations for future research and clinical practice.

2. Methods

2.1. Type of Review

This study is a systematic review performed according to PRISMA guidelines, focused on summarizing recent advancements in the epidemiology, diagnosis, and treatment of hepatocellular carcinoma (HCC). The review aims to consolidate scientific developments, clinical strategies, and evolving therapeutic trends over the past decade (Figure 1).

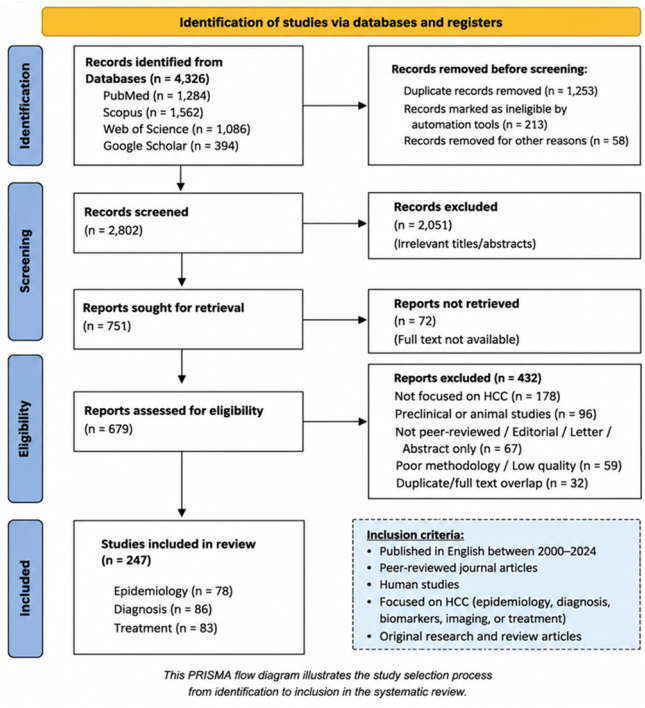

Figure 1. PRISMA flow diagram for the systematic review on the epidemiology, diagnosis, and treatment of hepatocellular carcinoma (HCC). The flowchart illustrates the study selection process, including records identified, screened, assessed for eligibility, and the studies ultimately included in the review.

2.2. Search Strategy

An extensive search of the PubMed, Scopus, Web of Science, and Google Scholar databases during 2000-2024 was undertaken to find the relevant studies. The keywords that were used along with their Boolean combinations (AND/OR): “Hepatocellular carcinoma”, “HCC”, “epidemiology”, “diagnosis”, “biomarkers”, “imaging”, “treatment”, “immunotherapy”, “targeted therapy”, and “liver cancer”. Only human and peer-reviewed studies were included through filters.

2.3. Inclusion Criteria

Studies were included based on the following criteria: (1) published in English between 2000 and 2024, (2) appeared in peer-reviewed journals, (3) focused on human subjects, and (4) addressed HCC-related topics such as global burden, diagnostic methods, or therapeutic options. Both original research and review articles were considered.

2.4. Exclusion Criteria

Studies were excluded if they were (1) preclinical or animal only; (2) not peer reviewed, like letters, opinion pieces, or abstracts without full text; (3) irrelevant, like not related to HCC; or (4) duplicate publications. Moreover, after a quality screening, studies of poor methodology were excluded.

2.5. Data Analysis and Organization

The studies chosen were classified in any of the epidemiology, diagnosis, and treatment categories. All studies were reviewed and synthesized for contributions to clinical practice or scientific understanding. This narrative synthesis is not registered as a formal systematic review but was undertaken in a transparent manner and with a PRISMA-based framework that helps in the selection and interpretation of the studies.

3. Epidemiology of Hepatocellular Carcinoma

According to the latest statistics, hepatocellular carcinoma (HCC) is the sixth most common neoplasm and the third cancer that causes the most deaths. These statistics were reported by Khan et al. [7]. The globally uneven distribution of these infections is characterized by high-burden regions like East Asia and sub-Saharan Africa, where there is a widespread presence of the hepatitis B virus (HBV). In contrast, a growing incidence of HCC has been noted in Western nations—such as the USA, Canada, and certain parts of Europe—architected by non-alcoholic fatty liver disease (NAFLD) and linked to metabolic conditions such as obesity and type-2 diabetes [8,9]. HCV infection is one of the major causes of chronic hepatitis in Japan, Egypt, etc. In addition to viral and metabolic causes, high alcohol consumption (excessive) and exposure to aflatoxin B1 (most common in sub-Saharan Africa and parts of Asia) and genetic liver diseases like hemochromatosis [10]. The epidemiological trends have changed due to extended HBV vaccination and antiviral treatment programs over time. For instance, a national immunization in Taiwan has resulted in a decrease in HCC incidence [11]. The percentage of HCC cases attributed to NAFLD is also increasing, particularly in younger groups in urbanized communities. This shifting landscape of the epidemiology calls for an adaptable surveillance system and region-specific control measures in order to reduce the global burden of HCC.

4. Targeted Inhibition of Oncogenic Signaling Pathways In HCC

The detailed overview of the intracellular signaling in the pathogenesis of HCC and the therapeutic target being investigated or found in the clinics is shown in this figure (Figure 2). On the membrane level, various receptor tyrosine kinases (RTKs), such as VEGFR, EGFR, IGFR, c-MET, PDGFR, FGFR, RET, and c-Kit, get activated by their own growth factors. It further phosphorylates and recruits the downstream adaptor proteins like GRB2, SHC, and SOS. The signals from the interactions of the many growth factors and ligands at the cell surface initiate intracellular cascades mediated primarily through the PI3K/AKT/mTOR and the RAS/RAF/MEK/ERK pathways. In turn, these signals translocate to the nucleus, where transcription factors like c-Myc, CREB, STAT3, etc., regulate genes responsible for cell proliferation, survival, angiogenesis, differentiation, and inflammation [12,13].

Therapeutic agents are emphasized at several tiers in these signaling pathways. Monoclonal antibodies can inhibit growth factors or their receptors extracellularly, for instance, bevacizumab (anti-VEGF), ramucirumab (anti-VEGFR), and cetuximab (anti-EGFR) [12]. Certain small-molecule inhibitors, such as MK-2206 and sirolimus, are used to block intracellular pathways like AKT and mTOR. MEK inhibitors (e.g., trametinib) and BRAF inhibitors (e.g., vemurafenib) disrupt the RAS-RAF-MEK-ERK axis. Multi-kinase inhibitors, which include lenvatinib, sorafenib, cabozantinib, and regorafenib, act at multiple receptor and kinase levels [14].

The figure also shows that inhibition is more complicated than first thought. The blue lines indicate native (natural) inhibition, and the red lines indicate therapeutic (drug) inhibition. A couple of new agents, napabucasin and OPB compounds, were designed to target the transcription factors Stat3 and Stat5 that regulate inflammation and cancer development (oncogenesis) [15]. The full mapping of these pathways highlights the complexity of HCC signaling and lends support to a multi-targeted therapy to overcome resistance and improve efficacy.

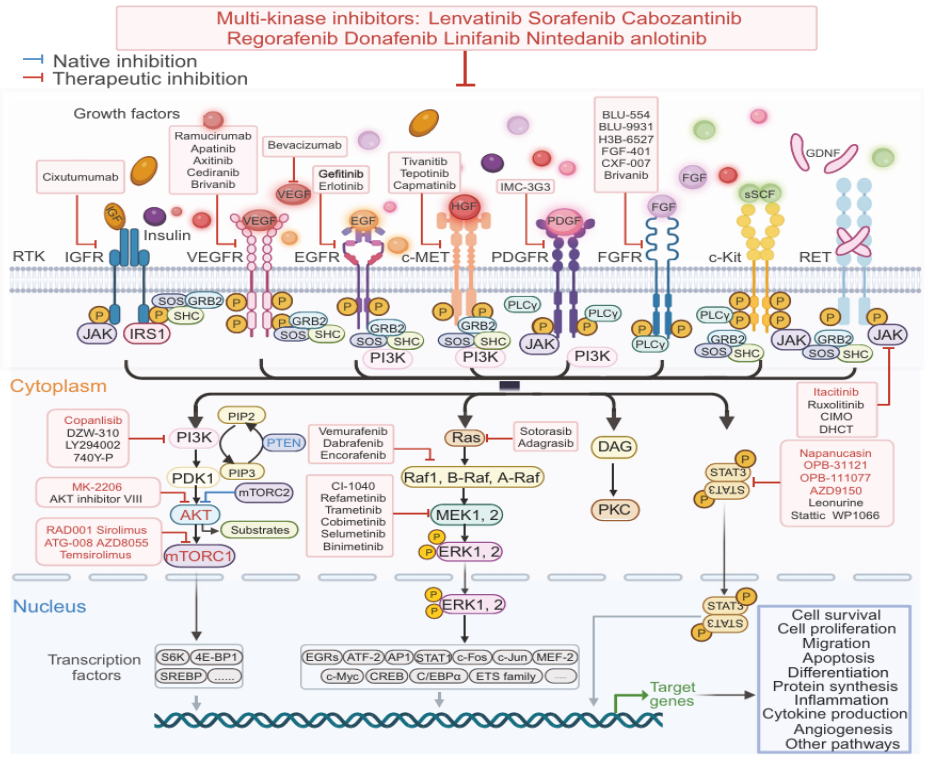

Figure 2. This is a diagram showing the important receptor tyrosine kinases and their intracellular signaling pathways implicated in HCC, such as PI3K/AKT/mTOR or RAS/RAF/MEK/ERK. The points for inhibition, blue being endogenous and red exogenous, are indicated. Drugs directed against extracellular receptors, intracellular kinases, and nuclear transcriptional activity are enumerated, with special reference to multi-kinase inhibitors and pathway-selective modulators [12].

5. Diagnostic Approaches of Hepatocellular Carcinoma

The diagnosis of hepatocellular carcinoma has changed from invasive methods to noninvasive imaging-based approaches based on certain radiologic features. The identification process generally kicks off when a liver nodule is discovered by way of ultrasonography (US) in a routine manner, especially in those at heightened risk, like cirrhotic and chronic hepatitis B/C patients. This begins a staged assessment process with dynamic contrast-enhanced imaging. Most frequently CT or MRI, which are diagnostic mainstays, while Vitamin D deficiency in chronic hepatitis B appears to correlate more with viral activity than with HCC. [16,17].

As per the clinical workflow (Figure 3), enhanced arterial phase and washout in portal or delayed phase nodules are highly indicative of HCC. These characteristic features can help in confidently diagnosing lesions larger than 1 cm without the need for a histological diagnosis in keeping with international recommendations [18].

The size of the tumor is an important variable when no washout is present or enhancement pattern characteristics are atypical. Lesions greater than 1 cm with features that raise suspicion but are not definitive should have optional advanced imaging or biopsy. Nodules that are less than 1.5 cm and do not exhibit characteristic imaging findings should undergo repeat surveillance ultrasound every 3 months. This method aims for early detection while avoiding unnecessary care [19,20]. The paper referenced notes that the non-invasive diagnostic criteria, particularly in cirrhotic livers, have greatly reduced the need for biopsy and, hence, the risks. This also makes improvements to LI-RADS (Liver Imaging Reporting and Data System), which is improving standardization and radiologic interpretation [21,22].

Treatment protocol advises close follow-up when no lesion is seen in CT/MRI and there is a suspicion on the ultrasound so that lesions are detected on time without over-intervention. To sum up, the proposed tiered diagnostic algorithm based on vascular profile and lesion morphology is compliant with a minimally invasive and precision-driven paradigm for HCC.

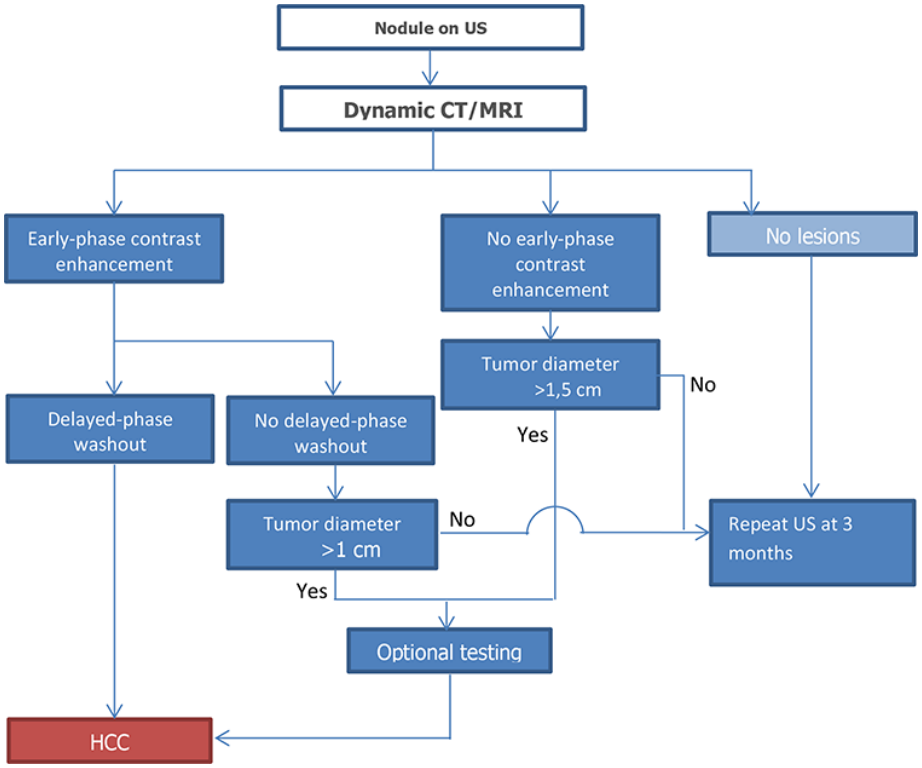

Figure 3. A new algorithm uses imaging features to diagnose Hepatocellular Carcinoma (HCC). The flowchart describes what will happen after a hepatic nodule is found on ultrasound (US). Liver nodules are classified for a diagnosis of HCC, optional assessment, or follow-up based on early arterial-phase enhancement and delayed-phase washout (on dynamic CT or MRI). Larger nodules measuring greater than 1 cm may be diagnosed as HCC based upon the typical arterial enhancement and washout on imaging without biopsy. When an atypical lesion presents or the size is small, refer for observation or further investigations. This text was adapted from current guidelines and imaging criteria for HCC diagnosis [18].

6. Treatment Modalities of Hepatocellular Carcinoma

Today, hepatocellular carcinoma (HCC) treatment is structured phase-wise based on the assessment of the tumor burden, liver functional capacity, and performance status. Generally, the classification of HCC into five stages—very early, early, intermediate, advanced, and terminal—has been done based on the respective treatment options and survival outcomes [23,24]. Early intervention may be beneficial for patients with small tumors and preserved liver function using curative methods such as surgical resection, local ablation, or liver transplantation. When the criteria of patient selection are strictly applied, these approaches can provide a five-year survival outcome [25].

In intermediate-stage HCC as characterized by multinodular disease and adequate liver function, locoregional therapies such as TACE remain the standard of care (Figure 4). In specific cases, other forms of treatment like radioembolization and downstaging could be taken into account to move on to curative treatment [26]. In cases of advanced-stage disease that involves vascular invasion or extrahepatic spread, systemic therapies are utilized to manage the disease. There has been a lot of development in recent years with so many agents like immune checkpoint inhibitors and targeted agents. In randomized trials, combinations of atezolizumab-bevacizumab or durvalumab-tremelimumab showed improved survival.

For patients in the terminal stages of illness and those with poor liver function and poor performance status, generally the best supportive care is recommended. They are unlikely to benefit from aggressive treatments, and they may only affect their quality of life negatively [27]. The treatment stage migration (TSM) has been incorporated into the treatment paradigm. It enables the clinician to adjust the treatment decision on the basis of clinical real-life characteristics, including but not limited to comorbidities, portal hypertension, and patient preference instead of stage limitations [28]. This gives scope for patient characteristics to be included in the treatment options to ameliorate treatment efficacy. A reflection of growing complexity in therapeutic approach is the patient-centered HCC option, which reinforces precision medicine principles [29]. The outcome of HCC patients worldwide will continue to improve with time as research uncovers new biomarkers and imaging and individualized therapy is adopted.

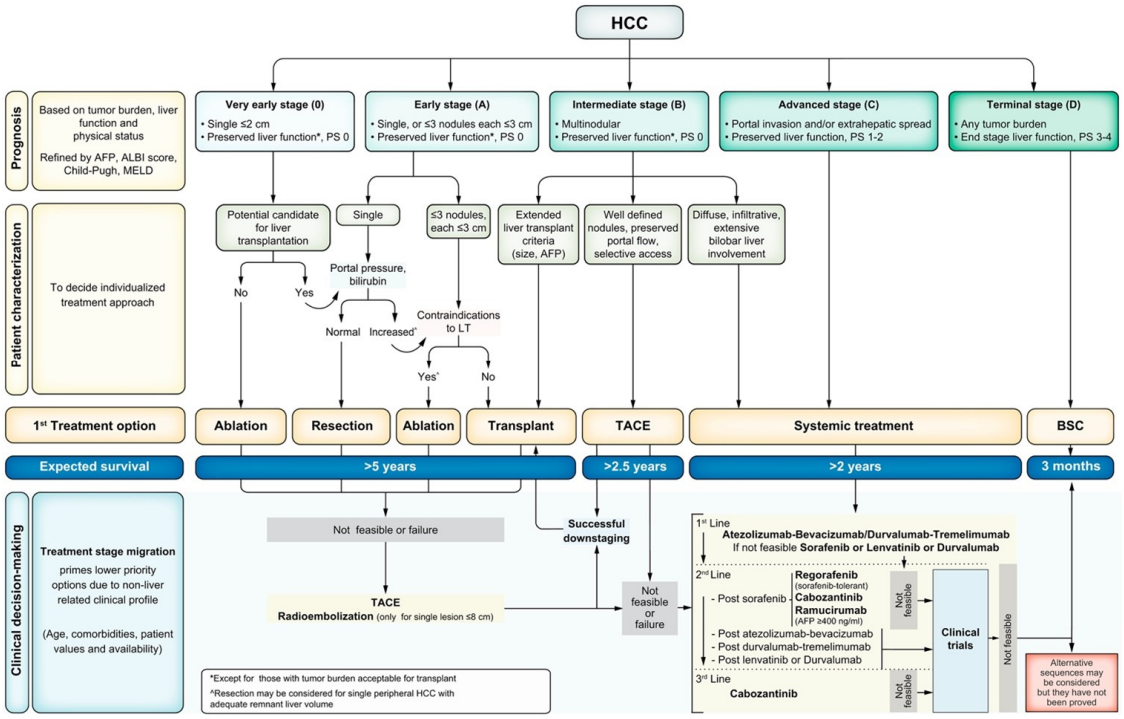

Figure 4. Prognosis and treatment selection in HCC: updated BCLC staging system 2022. The choice of treatment is based on the cancer stage, liver functionality, patient's performance status, curative treatment, and supportive care. TSM stands for treatment stage migration. Other abbreviations include PS (performance status), BSC (best supportive care), and TACE (transarterial chemoembolization) [24].

7. Emerging Therapies and Future Directions in Hepatocellular Carcinoma

The treatment of hepatocellular carcinoma (HCC) is quickly shifting from stage-based treatment to disease biology-driven and patient-personalized treatment with new therapies. Among those, immune checkpoint inhibitors nivolumab, pembrolizumab, and atezolizumab–bevacizumab combinations may have significantly improved survival in advanced HCC, with immunotherapy one of the most promising treatments. Furthermore, therapies guided by biomarkers, such as ramu-cirumab, for instance, in patients with high AFP, are facilitated. Techniques to detect indirect signs of cancer, like circulating tumor DNA (ctDNA) and tumor-derived exosomes, are being studied for use in early diagnosis, monitoring, and therapeutic guidance [30]. Another important direction is the integration of AI and radio-genomics in predictive modelling to identify treatment responders and optimize care pathways. The idea of personalized medicine by genomic profiling (TP53, CTNNB1 mutations) is actively being studied in clinical trials, which exemplifies an emerging paradigm shift in HCC. We shall not only base treatment on the tumor stage but also on the molecular and the immunologic characteristics. One day, these therapies will require the intervention of expert specialists.

8. Precision Treatment in Advanced Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) therapy has seen an uptick in new strategies that favor personalized and biomarker-driven approaches to improve efficacy and reduce toxicity. As shown in the above Figure 5, the new modalities being developed to specifically target tumor cells include proteolysis targeting chimeras, or PROTACs, antibody-drug conjugates, or ADCs, and mRNA-based vaccines. These platforms reflect a major step up from conventional chemotherapies to mechanisms that disrupt tumor-specific molecular pathways [31].

The framework also highlights three complementary directions of precision oncology that are (A) biomarker-based clinical trials with molecularly profiled patient stratification, (B) novel therapeutic techniques with new drug modalities, and (C) functional precision treatments with patient-derived samples (e.g., tumor organoids or biopsies) ex vivo screening to select the most effective therapy. The promising strategies may personalize the treatment of HCC due to its heterogeneity and the underlying complexity of liver disease [32,33].

Incorporating these strategies into hepatocellular carcinoma management could limit the resistance observed with current therapies and allow for artificial tumor biological and patient-specific approaches [34]. Efforts are underway to come up with the ex vivo drug testing platforms, better response prediction, and faster translation from bench to bedside. As functional precision medicine and immuno-oncological platforms mature, their

integration with existing staging and biomarker systems may further enhance treatment decision-making and allow us to probe novel avenues in the management of HCC.

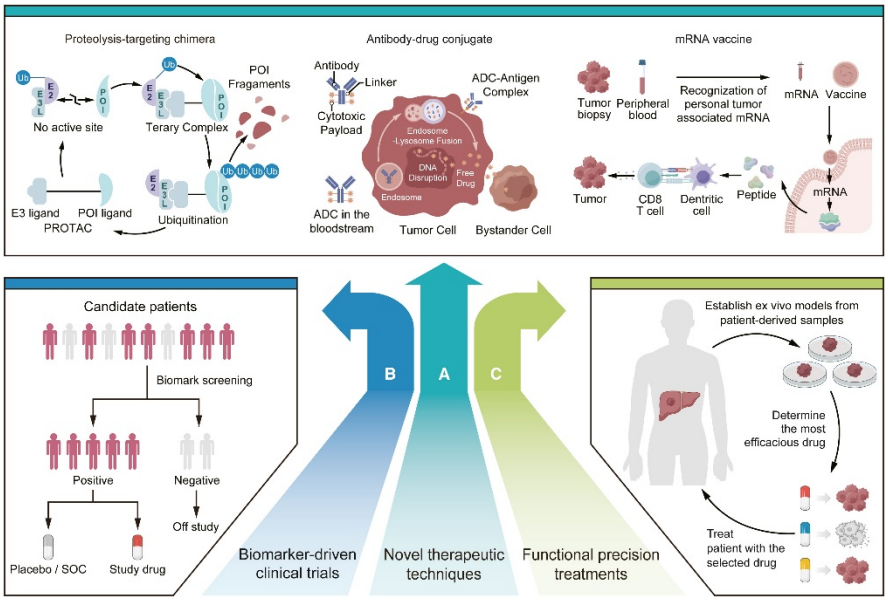

Figure 5. Emerging precision therapies in HCC. Illustration of advanced therapeutic approaches, including PROTACs, antibody-drug conjugates, mRNA vaccines, biomarker-guided trials, and ex vivo drug testing for personalized treatment selection [32].

9. Gene Therapy Strategies for Hepatocellular Carcinoma

Analysis of gene therapy strategies in hepatocellular carcinoma (HCC) has delineated more than 30 approaches either under evaluation or development. The strategies include several techniques such as suicide gene therapy (e.g., HSV-TK), oncolytic viral therapy (e.g., JX-594), gene editing technologies (such as CRISPR/Cas9), RNA interference (siRNA and miRNA), and tumor suppressor gene replacement (e.g., p53, p21).

In Table 1, the development of various immunomodulatory gene therapies is also progressing rapidly, including IL-2, IL-12, GM-CSF, and checkpoint regulation targeting PD-1/PD-L1. Strategies that inhibit tumor blood vessels, like VEGF gene inhibition and endostatin gene therapy, are called anti-angiogenic. In addition, signaling pathways like Wnt/β-catenin and AKT, along with epigenetics, are emerging as important preclinical targets.

Gene transfer systems have evolved with adenoviral and AAV vectors, lipid nanoparticles, plasmid DNA, and hybrid nanocarriers. Most of these therapies are in preclinical or early clinical development. However, several strategies have entered Phase I/II clinical trials and have safety and efficacy data [35–37].

Table 1. Gene therapy strategies for hepatocellular carcinoma–mechanisms, delivery methods, and clinical evidence.

Gene Therapy Strategy	Mechanism of Action	Delivery Method	Preclinical/Clinical Status	Reference
Suicide Gene Therapy	Introduction of a gene (e.g., HSV-TK) that converts prodrug into toxic product	Retroviral vectors, adenoviral vectors	Preclinical and Phase I trials	[35]
Oncolytic Virus Therapy	Viruses replicate selectively in tumor cells	H101, JX-594	Phase II trials	[36]
CRISPR/Cas9 Gene Editing	Knockout of oncogenes or repair of tumor suppressors	AAV or nanoparticle-based	Mostly preclinical	[38]
p53 Gene Replacement	Restores function of mutated tumor suppressor gene	Adenoviral vector	Phase I/II	[37]
miRNA-based Therapy	Regulation of gene expression via microRNAs	Lipid nanoparticle, viral vectors	Preclinical trials	[39]
siRNA Therapy	Gene silencing of oncogenic pathways	Lipid nanoparticle	Preclinical and Phase I	[40]
Cytokine Gene Therapy	Boost immune response via cytokine genes	Plasmid or viral vector	Preclinical	[41]
VEGF Inhibition Gene Therapy	Inhibits angiogenesis	siRNA or plasmid	Preclinical animal studies	[42]
Immune Checkpoint Gene Modulation	Blockade of PD-1/PD-L1 via gene vectors	AAV, lentivirus	Preclinical stage	[43]
TRAIL Gene Therapy	Induces apoptosis in tumor cells	Adenoviral vector	Phase I trials	[44]
Combination Gene-Immunotherapy	Combines immune activation with gene transfer	Nanoparticles, AAV	Ongoing clinical studies	[45]
Gene-directed Enzyme Prodrug Therapy (GDEPT)	Targets prodrug activation at tumor site	Adenovirus or HSV	Phase I/II	[46]

10. Challenges, Future Directions, and Perspectives

Although gene therapy holds enormous promise for the treatment of HCC, there still exist several major challenges. One of the major challenges is the endowment of safe and effective gene delivery systems. Adenovirus or AAV-type viral vectors can trigger off-target immune responses and genome destabilization. Conversely, non-viral vectors tend to exhibit less efficiency for transfection [47]. Moreover, genetic variations within each patient and tumor heterogeneity also limit the effectiveness of gene therapy.

Future directions must aim to advance tailored delivery systems like optimized CRISPR/Cas platforms, smart nanoparticles, and targeted expression systems. Integrating gene therapy with other forms of therapy could improve its effectiveness. By including patient genomic profiling into personalized gene therapies, the treatment could become more effective and individualized.

Moreover, other factors such as clinical regulation, bioethics, cost-effectiveness, and long-term studies will also be relevant [48]. The expanding technological and translational research will make gene therapy an innovative approach for HCC treatment.

11. Evolving Treatment Paradigms Across HCC Progression

The treatment of hepatocellular carcinoma (HCC) has greatly advanced, and therapeutic management of HCC is now stage-specific. In the early stage, the methods that are generally used are surgical resection, liver transplantation, and ablation therapy (Figure 6). As the illness reaches the intermediate stage of its progression, the application of embolization therapy and radiation therapy is more pronounced. This is to control tumor progression and alleviate symptoms. As the disease progresses to its advanced stages, systemic therapies such as chemotherapy, molecular targeted therapy, immunotherapy, and others, and now increasingly gene therapy, come into play. The increasing use of combination therapy, which employs multiple strategies to improve outcomes, is a significant advancement across all levels [49,50].

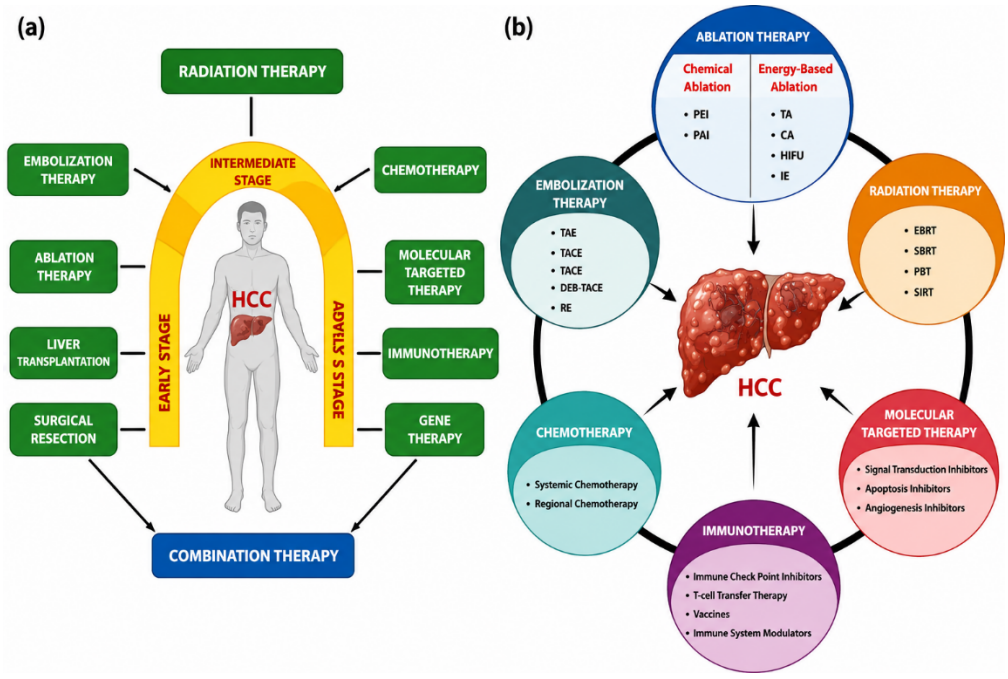

Figure 6. (**a**) Prevention and treatment of different stages of cancer support treatment. Early-stage- surgical and ablative techniques intermediate stage- radiation and embolization and advanced-stage systemic and molecular therapies. Combination therapy for all models. (**b**) This classification of individual therapies includes ablation therapy (chemical versus energy-based), embolization techniques (TAE, TACE, DEB-TACE, RE), chemotherapy (systemic and regional), types of radiation therapy (EBRT, SBRT, PBT, SIRT) and targeted therapies (immunotherapy and molecular inhibitors) [49].

HCC treatments are organized into a number of specific subtypes. According to the ablation therapy, chemical methods such as Percutaneous Ethanol Injection (PEI) and Percutaneous Acetic Acid Injection (PAI) are used along with energy-based methodologies including Thermal Ablation (TA), Cryoablation (CA), High-Intensity Focused Ultrasound (HIFU), and Irreversible Electroporation (IE) [51–53]. Embolization therapy is a

collective term for techniques like trans arterial embolization (TAE), trans arterial chemoembolization (TACE), drug-eluting bead TACE (DEB-TACE) and radioembolization (RE). Radiation therapy options include External Beam Radiation Therapy (EBRT), Stereotactic Body Radiation Therapy (SBRT), Proton Beam Therapy (PBT), and Selective Internal Radiation Therapy (SIRT) [54]. When used in the clinic to treat cancer, research-proven therapeutics such as chemotherapy may be given systemically or regionally. In contrast, molecular targeted therapy works by inhibiting the disordered signal transduction pathway of cancer cells, promoting their apoptosis or blocking angiogenesis. Different kinds of immunotherapies include immune checkpoint inhibitors, T-cell transfer therapies, etc. These treatment regimens highlight the need for a multifaceted approach to tackle different forms of HCC [55].

12. Conclusions

Gene therapy is used in humans to treat high-grade morbidity and mortality diseases. Hepatocellular carcinoma (HCC) is one of the most prevalent liver cancers. This review highlights that different gene therapy approaches, including suicide gene therapy, oncolytic viruses, CRISPR/Cas9 gene editing, RNA interference, and tumor suppressor gene restoration, show strong potential in both preclinical and clinical studies.

By focusing on these cellular activities, investigators have delivered anti-cancer agents to the tumor region and have targeted the important molecules to block HCC development. Improvements associated with the delivery efficiency, immune responses, and long-term efficacy will address the many challenges facing us. In the future, the combination of personalized medicine with gene therapy and multimodal approaches, including the combination with immunotherapies or targeted drugs, may alter HCC management. According to this review, gene therapy has already become clinically relevant and is a burgeoning strategy for the future treatment of HCC.

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