SAGE Science Publishing

Hepatocellular Carcinoma: Advances in Early Detection, Surgical Resection, and Targeted Therapeutics

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Abstract

Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer, representing a significant global health challenge due to its high incidence and mortality rates. Early detection, effective surgical interventions, and advancements in targeted therapeutics have significantly improved patient outcomes. The early detection of HCC relies on imaging modalities such as ultrasonography and advanced biomarkers, enabling diagnosis at potentially curable stages. Surgical resection remains a cornerstone of treatment for localized HCC, though patient eligibility is limited by underlying liver function and tumor characteristics. Liver transplantation provides a curative approach for selected patients but is constrained by donor organ availability. Recent advances in targeted therapeutics, including tyrosine kinase inhibitors and immune checkpoint inhibitors, have transformed the management landscape for advanced HCC, offering improved survival and quality of life. However, the high heterogeneity of HCC and the interplay with underlying liver disease complicate therapeutic strategies. This review consolidates the latest progress in early detection, surgical resection, and targeted therapeutics, emphasizing the challenges and future directions in managing HCC.

Keywords: early detection, hepatocellular carcinoma, surgical resection, targeted therapeutics, treatment advances

Introduction

Hepatocellular carcinoma (HCC) is a malignancy of significant global health burden, accounting for approximately 75% of all primary liver cancers and ranking as the sixth most prevalent cancer worldwide. Furthermore, it is the third leading cause of cancer-related mortality, emphasizing its aggressive nature and the ongoing challenges in its management. HCC predominantly arises within the context of chronic liver disease, particularly cirrhosis, with the majority of cases attributed to well-established risk factors such as hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. These viral etiologies are particularly prominent in endemic regions, including East Asia and Sub-Saharan Africa, where the burden of HBV remains significant despite widespread vaccination efforts. Additionally, alcohol-related liver disease and the rapidly increasing prevalence of non-alcoholic fatty liver disease (NAFLD) in Western countries further contribute to the global incidence of HCC. Despite advancements in public health measures, antiviral therapies, and cancer management, the prognosis for HCC remains poor, with a five-year survival rate below 20% in many regions. These statistics underscore the critical need for enhanced strategies in prevention, detection, and treatment to mitigate this significant public health challenge.

One of the defining characteristics of HCC is its asymptomatic presentation in early stages, which significantly limits the efficacy of curative interventions. Many patients are diagnosed at advanced stages when therapeutic options are predominantly palliative rather than curative. Surveillance programs targeting high-risk populations, such as individuals with cirrhosis or chronic HBV and HCV infections, are integral to early detection. These programs rely on a combination of imaging modalities, primarily abdominal ultrasound, and biomarkers like alpha-fetoprotein (AFP). However, the sensitivity and specificity of these traditional tools are suboptimal. Ultrasound, while widely available and cost-effective, is operator-dependent and can miss early-stage lesions, particularly in obese patients or those with nodular cirrhosis. AFP, a glycoprotein biomarker, also has limitations, with elevated levels observed in only a subset of HCC cases. This has spurred extensive research into novel diagnostic modalities, including liquid biopsies that analyze circulating tumor DNA (ctDNA), RNA, or exosomes, as well as advanced imaging technologies such as contrast-enhanced ultrasound and magnetic resonance imaging (MRI) using hepatocyte-specific contrast agents. These innovations hold promise for improving the accuracy and reliability of early HCC detection, which is pivotal for enhancing survival outcomes.

Surgical resection remains the cornerstone of curative therapy for HCC, particularly for patients with localized disease and preserved hepatic function. However, its applicability is limited by several factors, including underlying liver dysfunction, portal hypertension, and the anatomical complexity of the

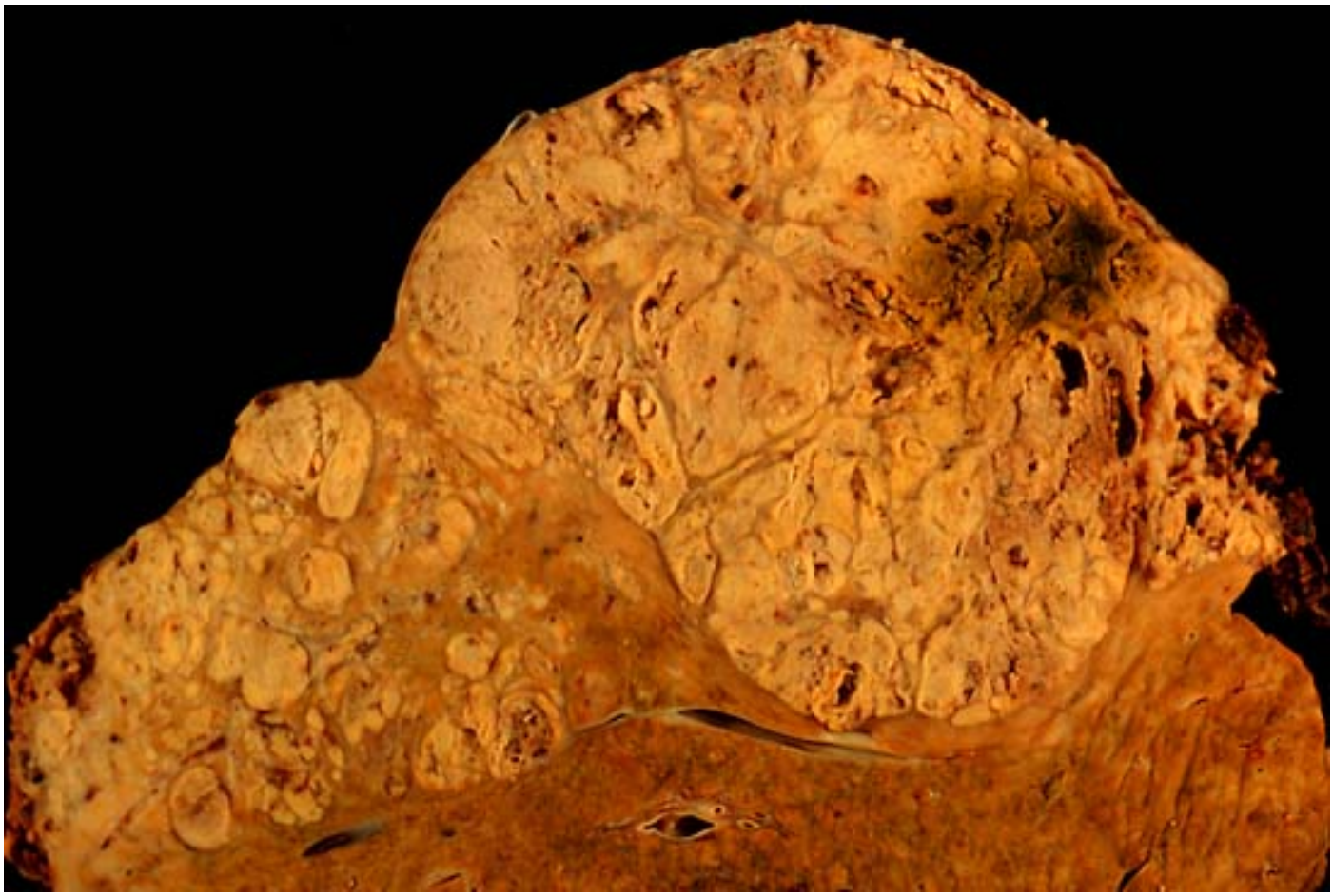

Figure 1 Hepatocellular carcinoma in an individual who was hepatitis C positive. Autopsy specimen.

tumor. The emergence of laparoscopic and robotic-assisted surgical techniques has marked a significant advancement in the field, offering comparable oncologic outcomes to open surgery while reducing perioperative morbidity, postoperative pain, and length of hospital stay. These minimally invasive approaches are particularly beneficial for patients with borderline hepatic reserve, enabling safer resection with faster recovery. Liver transplantation is another curative option, particularly for patients meeting the Milan or UCSF criteria, which define transplant eligibility based on tumor size and number. However, the scarcity of donor organs and long waiting times remain critical limitations, prompting interest in expanding transplantation criteria and exploring living donor liver transplantation as an alternative.

For patients with advanced or unresectable HCC, systemic therapy has undergone a paradigm shift in recent years, driven by the advent of molecularly targeted agents and immune checkpoint inhibitors. Sorafenib, a multi-kinase inhibitor, was the first systemic therapy approved for advanced HCC and demonstrated modest survival benefits. Subsequent agents, such as lenvatinib, regorafenib, and cabozantinib, have expanded the therapeutic landscape, offering incremental improvements in overall survival. The introduction of immune checkpoint inhibitors, particularly the combination of atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF), has revolutionized the treatment of HCC, setting a new standard for first-line therapy in advanced disease. This combination not only prolongs survival but also improves quality of life compared to traditional tyrosine kinase inhibitors. However, therapeutic resistance, immune-related adverse events, and the inherent heterogeneity of HCC present ongoing challenges. The tumor microenvironment, characterized by a highly immunosuppressive milieu, further complicates the efficacy of immunotherapy, necessitating novel strategies to overcome these barriers.

In this review, we provide a comprehensive overview of the current state-of-the-art approaches in the management of HCC, focusing on early detection, surgical resection, and systemic therapies. The aim is to delineate the progress achieved in each domain, highlight the persistent challenges, and propose directions for future research. This multifaceted analysis seeks to inform both clinical practice and translational research, ultimately contributing to improved patient outcomes in this challenging malignancy. The following sections will elaborate on the diagnostic innovations, surgical advancements, and systemic treatment strategies that are reshaping the landscape of HCC management. Table 1 provides a summary of the global burden of HCC, highlighting key regional variations in incidence and mortality rates, while Table 2 outlines the major milestones in the evolution of HCC therapies.

Advances in Early Detection

The early detection of hepatocellular carcinoma (HCC) remains a cornerstone in improving patient outcomes, as curative interventions such as surgical resection, liver transplantation, or

Table 1 Global Burden of Hepatocellular Carcinoma (HCC) by Region

Region	Incidence (per 100,000)	Mortality (per 100,000)
East Asia	35.5	33.8
Sub-Saharan Africa	24.2	23.5
Western Europe	5.7	5.2
North America	6.6	5.9
South America	8.1	7.8
Oceania	6.4	6.0

Table 2 Major Milestones in Hepatocellular Carcinoma (HCC) Treatment

Year	Therapeutic Advancement	Impact on Treatment
2007	Approval of Sorafenib	Established the first systemic therapy for advanced HCC
2018	Atezolizumab-Bevacizumab Combination	Set a new standard for first-line therapy in advanced HCC
2020	Advances in Liquid Biopsies	Enhanced early detection through ctDNA and exosomal analysis
2022	Robotic-Assisted Liver Resection	Improved surgical outcomes with reduced morbidity
2023	Expansion of Liver Transplant Criteria	Broadened eligibility for curative transplantation

ablative therapies are primarily effective during the early stages of the disease. Unfortunately, a majority of cases are diagnosed at an advanced stage, largely due to the asymptomatic nature of early HCC and the limitations of current surveillance methods. Current clinical guidelines, as recommended by major hepatology societies, advocate biannual ultrasonography with or without serum alpha-fetoprotein (AFP) testing in high-risk populations, such as those with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and cirrhosis. While these strategies are widely implemented, they suffer from significant limitations. Ultrasound, though non-invasive and cost-effective, exhibits operator dependence and inconsistent sensitivity, particularly in obese individuals or those with advanced cirrhosis, where the heterogeneous parenchymal architecture complicates lesion visualization. Similarly, AFP, once the cornerstone of HCC biomarkers, demonstrates poor sensitivity and specificity, especially in distinguishing HCC from benign liver conditions or inflammatory activity. These gaps in detection highlight the urgent need for novel and more reliable diagnostic strategies.

A promising area of research involves the identification of new blood-based biomarkers. Des-gamma-carboxy prothrombin (DCP), also known as protein induced by vitamin K absence or antagonist-II (PIVKA-II), has been explored extensively and demonstrates higher specificity than AFP in certain studies. DCP, a prothrombin precursor aberrantly produced in HCC cells due to impaired vitamin K metabolism, offers unique diagnostic potential. Moreover, the study of circulating microRNAs (miRNAs) has opened a new avenue for non-invasive cancer detection. These small, stable RNA molecules, frequently dysregulated in HCC, provide insight into tumor biology and hold promise as both diagnostic and prognostic markers. For instance, miR-122 and miR-21 have been reported as significantly altered in patients with HCC, with potential for stratifying high-risk populations. These advances suggest that a panel of complementary biomarkers, rather than reliance on a single marker, may significantly improve diagnostic accuracy.

The advent of liquid biopsy technologies has further revolutionized the field of early cancer detection. Liquid biopsies enable the analysis of circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and exosomes, providing a window into the molecular landscape of the tumor without requiring invasive procedures. ctDNA, which carries tumor-specific genetic and epigenetic alterations, offers particular promise for detecting early HCC. Emerging evidence indicates that the methylation patterns of ctDNA or specific mutations in genes such as TP53 and CTNNB1 may serve as reliable indicators of malignancy. Similarly, CTC enumeration and characterization allow for the real-time monitoring of tumor burden and may complement existing diagnostic modalities. Exosomes, nanoscale extracellular vesicles enriched with nucleic acids, proteins, and lipids from their cells of origin, are another intriguing diagnostic tool. Specific exosomal RNAs and proteins associated with HCC have been identified, further expanding the potential of liquid biopsy platforms. These non-invasive approaches not only promise earlier detection but also provide insights into tumor dynamics, therapeutic responses, and recurrence risks.

In parallel with biomarker development, imaging technologies have witnessed significant advances. Contrast-enhanced

ultrasound (CEUS) has emerged as a more sophisticated alternative to conventional ultrasonography, offering improved sensitivity and specificity in detecting and characterizing focal liver lesions. By employing contrast agents that enhance vascular imaging, CEUS can differentiate between benign and malignant lesions based on their enhancement patterns during arterial, portal, and late phases. Another breakthrough is magnetic resonance imaging (MRI) with hepatocyte-specific contrast agents such as gadoxetic acid. This technique achieves superior lesion characterization and sensitivity for detecting early-stage HCC compared to traditional computed tomography (CT) or unenhanced MRI. Beyond standard imaging, emerging radiomics and artificial intelligence (AI)-driven analytics are becoming integral to diagnostic workflows. Radiomics, a field that extracts high-dimensional quantitative features from imaging data, allows for the identification of subtle textural or shape-based differences between malignant and benign lesions. Such computational approaches have shown considerable promise in distinguishing early HCC from dysplastic nodules in cirrhotic patients.

AI is rapidly transforming diagnostic paradigms by enhancing the interpretative power of imaging studies. Machine learning (ML) and deep learning (DL) algorithms, when trained on large imaging datasets, can identify subtle patterns and anomalies that elude human radiologists. Several studies have demonstrated that AI-driven models can outperform traditional radiologists in detecting HCC at an earlier stage, particularly in challenging cases involving small or atypical lesions. Additionally, AI systems can integrate data from imaging, laboratory results, and clinical parameters to stratify patients based on their risk of developing HCC, optimizing surveillance and enabling personalized healthcare strategies. These innovations not only improve diagnostic accuracy but also enhance resource allocation by prioritizing high-risk individuals for intensive monitoring.

While progress in biomarker discovery and imaging technologies is encouraging, the inherent heterogeneity of HCC remains a significant obstacle. The molecular landscape of HCC is highly diverse, influenced by a multitude of factors, including the underlying etiology (e.g., HBV, HCV, non-alcoholic fatty liver disease [NAFLD]), environmental exposures, and host genetics. Chronic liver disease, which frequently coexists with HCC, poses additional challenges by creating a pro-inflammatory and fibrotic microenvironment that can obscure early tumor signals. Addressing these issues necessitates a shift towards integrative diagnostic approaches that combine multiple modalities. For instance, the incorporation of multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, could provide a more comprehensive understanding of HCC biology and improve early detection. Integrating these data into robust diagnostic models, potentially enhanced by AI, could pave the way for precision medicine approaches tailored to individual patients.

Table 1 provides a comparative overview of traditional and emerging biomarkers, highlighting their diagnostic utility, while Table 2 summarizes recent advances in imaging modalities and their relative merits in early HCC detection. Together, these advances illustrate the multifaceted approach needed to improve early detection and ultimately reduce the global burden of HCC.

the early detection of HCC is undergoing a transformative phase, driven by advancements in biomarker discovery, liquid biopsy technologies, imaging modalities, and AI integration. While significant hurdles remain, these innovations hold the potential to bridge existing diagnostic gaps and improve outcomes for patients with HCC. A concerted effort to validate these approaches in large, diverse populations and integrate them into clinical practice will be essential for their widespread adoption and success.

Surgical Resection and Liver Transplantation

Surgical resection and liver transplantation represent two of the most effective curative options for hepatocellular carcinoma (HCC), particularly in patients with well-compensated liver function and early-stage disease. Over the past few decades, significant advancements in surgical techniques, perioperative care, and preoperative assessment have dramatically improved the safety and efficacy of these interventions. This section explores the current state of surgical resection and liver transplantation for HCC, highlighting the challenges, recent innovations, and future directions in optimizing outcomes for patients.

Surgical resection remains the treatment of choice for patients with preserved hepatic function and an absence of significant portal hypertension or extrahepatic disease. A cornerstone of successful resection is precise preoperative planning, which relies heavily on high-resolution imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). These tools provide detailed insights into tumor size, location, vascular involvement, and liver parenchymal quality, enabling surgeons to plan the extent of resection while preserving sufficient functional liver remnant. Contrast-enhanced imaging, particularly with multiphasic CT and hepatobiliary-phase MRI, has proven invaluable in delineating tumor margins and assessing the presence of satellite nodules or microvascular invasion. Additionally, advanced imaging techniques such as three-dimensional reconstruction have further enhanced the precision of surgical planning, allowing for more tailored and safer resections.

Minimally invasive surgical techniques, including laparoscopic and robotic-assisted approaches, have revolutionized the field of liver surgery. These techniques offer numerous benefits, including reduced surgical trauma, lower postoperative complication rates, and shorter hospital stays. Oncologic outcomes achieved with minimally invasive approaches are now comparable to those of traditional open surgeries, provided that they are performed by experienced surgical teams. The adoption of robotic systems has added another dimension to minimally invasive liver surgery by improving dexterity, precision, and visualization in complex resections. Despite these advantages, the widespread implementation of such techniques remains limited by the steep learning curve and high costs associated with robotic platforms. Nevertheless, ongoing advancements in training programs and technological innovations are expected to expand the accessibility of minimally invasive liver surgery in the coming years.

Liver transplantation, on the other hand, represents a definitive treatment for patients with HCC and concurrent liver dysfunction, as it addresses both the malignant tumor and the underlying cirrhosis or chronic liver disease. Selection criteria such as the Milan and University of California, San Francisco (UCSF) criteria serve as benchmarks for transplant eligibility, ensuring optimal outcomes by limiting the risk of recurrence. The Milan criteria, which restrict transplantation to patients with a single tumor 5 cm or up to three tumors each 3 cm without vascular invasion or extrahepatic spread, have been widely validated in terms of post-transplant survival and recurrence rates. The UCSF criteria, which slightly expand the size and number of

Table 3 Comparison of Traditional and Emerging Biomarkers for Early HCC Detection

Biomarker Type	Advantages	Limitations
Alpha-Fetoprotein (AFP)	Widely available and cost-effective	Low sensitivity and specificity; influenced by liver inflammation
Des-gamma-carboxy prothrombin (DCP)	Higher specificity than AFP in some studies	Limited sensitivity; not universally available
Circulating Tumor DNA (ctDNA)	High potential for early detection and molecular characterization	High cost; requires standardized protocols
MicroRNAs (e.g., miR-122, miR-21)	Stable in circulation; reflective of tumor biology	Requires further validation in large cohorts
Exosomal RNAs/Proteins	Non-invasive; enriched in tumor-derived material	Technologically demanding; limited clinical adoption

Table 4 Advances in Imaging Modalities for Early HCC Detection

Imaging Modality	Advantages	Limitations
Ultrasonography	Widely available and non-invasive	Operator-dependent; limited sensitivity in advanced cirrhosis
Contrast-Enhanced Ultrasound (CEUS)	Enhanced lesion characterization	Requires specialized expertise and contrast agents
MRI with Hepatocyte-Specific Contrast	Superior sensitivity and lesion characterization	Expensive; limited accessibility in resource-constrained settings
Radiomics	Quantitative analysis of imaging features	Requires extensive computational resources and validation
Artificial Intelligence (AI)-Enhanced Imaging	High diagnostic precision; can integrate multi-modal data	Dependent on quality and size of training datasets

permissible tumors, have also demonstrated comparable results, offering a broader eligibility framework for certain patients.

A major limitation of liver transplantation is the scarcity of donor organs, which has led to prolonged waiting times and significant mortality among patients on the transplant list. To address this challenge, strategies such as living-donor liver transplantation (LDLT) and the use of extended-criteria donors have been explored. LDLT, in particular, offers a viable alternative by utilizing a portion of a healthy donor's liver, thereby alleviating the reliance on deceased donors. Although LDLT is associated with increased surgical complexity and potential donor-related risks, advancements in donor selection and perioperative care have improved its safety profile. Additionally, the use of extended-criteria donors, including older donors or those with mild steatosis, has been proposed to expand the donor pool. However, these approaches require meticulous evaluation to balance the risks of graft dysfunction and tumor recurrence against the benefits of transplantation.

For patients awaiting transplantation, bridging therapies such as transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) play a critical role in maintaining transplant eligibility and reducing tumor progression. TACE, which involves the selective delivery of chemotherapeutic agents and embolic particles to the tumor's feeding arteries, has been shown to achieve significant tumor necrosis and downstaging in a substantial proportion of patients. Similarly, RFA, which uses thermal energy to induce coagulative necrosis, is effective for small, localized tumors. Emerging data suggest that these locoregional therapies not only help to control tumor growth during the waiting period but may also improve post-transplant outcomes by reducing the burden of viable tumor cells, thereby lowering the risk of recurrence.

Despite these advancements, tumor recurrence remains a major challenge following both surgical resection and liver transplantation. Recurrence rates after resection can reach as high as 70% within five years, often due to the development of new primary tumors in the diseased liver or the dissemination of residual microscopic disease. Efforts to mitigate recurrence have focused on adjuvant therapies, such as systemic treatments with tyrosine kinase inhibitors or immune checkpoint inhibitors, as well as locoregional interventions. However, the results of adjuvant therapy studies have been mixed, underscoring the need

for further research to identify effective strategies. Molecular and genetic profiling of tumors has also emerged as a promising avenue for predicting recurrence risk and tailoring treatment strategies. For instance, the identification of specific gene signatures associated with aggressive tumor behavior or resistance to therapy may enable more personalized approaches to postoperative management.

Another promising area of research involves the integration of genetic and molecular data into the selection and stratification of patients for surgery or transplantation. Advances in next-generation sequencing and liquid biopsy technologies have made it possible to detect circulating tumor DNA and other biomarkers, providing real-time insights into tumor biology and treatment response. By incorporating these tools into clinical decision-making, it may be possible to refine patient selection, optimize the timing of interventions, and improve long-term outcomes.

both surgical resection and liver transplantation remain cornerstones of curative therapy for HCC, with significant advancements improving their feasibility and outcomes. While surgical resection is more widely applicable and less resource-intensive, liver transplantation offers the unique benefit of addressing both the tumor and the underlying liver disease. The integration of minimally invasive techniques, expanded donor criteria, and bridging therapies has further enhanced the therapeutic landscape for HCC. Nevertheless, high recurrence rates and limited organ availability highlight the need for continued innovation in patient selection, perioperative management, and adjuvant therapies. As personalized medicine and molecular diagnostics continue to evolve, they are poised to play an increasingly central role in guiding the management of HCC in the future.

Targeted Therapeutics and Immunotherapy

The management of advanced or unresectable hepatocellular carcinoma (HCC) has undergone a paradigm shift with the advent of targeted therapies and immunotherapy. These approaches have significantly enhanced survival outcomes, particularly in patients who were previously limited to palliative care or liver transplantation in the absence of effective systemic therapies. Sorafenib, a multikinase inhibitor that targets vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), and RAF kinases, was the first agent approved for advanced HCC following its demonstration of modest but statistically significant survival benefits in the pivotal SHARP trial. This marked a watershed moment in HCC management, as it provided a systemic therapy option where none existed before. Since the approval of sorafenib, the therapeutic landscape for HCC has expanded with the development of additional multikinase inhibitors, including lenvatinib, regorafenib, and cabozantinib. Each of these agents has contributed to diversifying the treatment armamentarium, particularly for patients who exhibit resistance to sorafenib or are unable to tolerate its associated toxicities.

Targeted therapies for HCC are designed to disrupt molecular pathways critical to tumor progression, such as those regulating angiogenesis, cell proliferation, and apoptosis. Angiogenesis, a hallmark of HCC driven by the overexpression of vascular endothelial growth factor (VEGF) and its receptors, has been a primary focus of targeted interventions. Lenvatinib, for instance, demonstrated non-inferiority to sorafenib in terms of overall survival while achieving superior outcomes in progression-free survival and objective response rates, making it a viable first-line treatment alternative. More recently, the combination of bevacizumab, an anti-VEGF monoclonal antibody, with atezolizumab, an immune checkpoint inhibitor targeting programmed death-ligand 1 (PD-L1), has shown remarkable efficacy in clinical trials. This regimen not only outperformed sorafenib in overall survival and progression-free survival but also highlighted the synergistic potential of combining anti-angiogenic therapy with immunotherapy. Consequently, the bevacizumab-atezolizumab combination has been established as a first-line treatment option for advanced HCC, signaling a new era in systemic therapy.

Immunotherapy, another cornerstone in the contemporary management of HCC, aims to harness the host immune system to identify and destroy malignant cells. Immune checkpoint inhibitors (ICIs), which block inhibitory receptors such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), have garnered significant attention in this regard. Nivolumab, a PD-1 inhibitor, and pembrolizumab, another agent in the same class, have demonstrated durable responses in a subset of HCC patients, leading to accelerated approval by regulatory authorities for second-line treatment. Despite their promise, the overall response rates to ICIs remain modest, underscoring the need for predictive biomarkers to stratify patients who are most likely to benefit from immunotherapy. Efforts to identify such biomarkers are ongoing, with particular focus on tumor mutational burden, PD-L1 expression levels, and immune-related gene signatures.

The integration of ICIs with targeted agents or locoregional therapies represents a burgeoning area of research. Preclinical studies suggest that combining immune checkpoint blockade with agents targeting angiogenesis or oncogenic signaling pathways may yield additive or synergistic antitumor effects. The rationale behind such combinations lies in their ability to modulate the tumor microenvironment, enhancing immune cell infiltration and overcoming mechanisms of immune evasion. For instance, ongoing trials are evaluating the efficacy of combining ICIs with tyrosine kinase inhibitors (TKIs) such as lenvatinib or regorafenib, as well as with locoregional treatments like transarterial chemoembolization (TACE) or radiofrequency ablation (RFA). Preliminary results from these studies are promising, indicating improved response rates and prolonged survival compared to monotherapy.

Table 7 summarizes the key targeted therapies currently approved for HCC management, highlighting their molecular targets, clinical indications, and notable outcomes from pivotal trials.

Despite these advancements, the clinical management of HCC continues to be fraught with challenges, particularly with respect to therapeutic resistance and adverse effects. Resistance to targeted therapies may arise due to secondary mutations in target genes, activation of compensatory pathways, or alterations in the tumor microenvironment that enable immune evasion. For instance, acquired resistance to sorafenib has been attributed to upregulation of fibroblast growth factor receptor (FGFR) signaling, among other mechanisms. Similarly, intrinsic resistance to immunotherapy remains a significant barrier, with many HCC tumors exhibiting an immunosuppressive microenvironment characterized by regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages. To address these issues, molecular profiling and next-generation sequencing (NGS) are increasingly being employed to unravel the genetic and epigenetic underpinnings of therapeutic resistance. Such

Table 5 Comparison of Milan and UCSF Criteria for Liver Transplantation Eligibility

Criterion	Milan Criteria	UCSF Criteria
Tumor size	Single tumor $\leq$ 5 cm or up to 3 tumors $\leq$ 3 cm each	Single tumor $\leq$ 6.5 cm or up to 3 tumors $\leq$ 4.5 cm each, with a total tumor diameter $\leq$ 8 cm
Vascular invasion	Absent	Absent
Extrahepatic spread	Absent	Absent
Post-transplant survival rate (5 years)	70-80%	70-80%

Table 6 Advantages and Challenges of Surgical Techniques for HCC Resection

Technique	Advantages	Challenges
Open Surgery	Established technique, suitable for large or complex tumors	Higher morbidity, longer recovery time
Laparoscopic Surgery	Reduced surgical trauma, shorter hospital stays	Steep learning curve, limited by tumor location
Robotic-Assisted Surgery	Enhanced precision and visualization, comparable oncologic outcomes	High cost, limited availability

Table 7 Key Targeted Agents in the Management of Hepatocellular Carcinoma

Agent	Molecular Targets	Clinical Indications and Outcomes
Sorafenib	VEGFR, PDGFR, RAF kinases	First-line therapy; modest survival benefit in the SHARP trial
Lenvatinib	VEGFR, FGFR, RET, KIT	Non-inferior to sorafenib; superior progression-free survival
Regorafenib	VEGFR, FGFR, PDGFR, KIT, RET	Second-line therapy for sorafenib-resistant patients; improved overall survival
Cabozantinib	VEGFR, MET, AXL, RET	Second-line therapy; significant survival benefit in the CELESTIAL trial
Bevacizumab	VEGF	Combined with atezolizumab; superior efficacy to sorafenib in IMbrave150 trial

approaches enable the identification of actionable mutations, facilitating the development of personalized treatment strategies that are tailored to the molecular characteristics of individual tumors.

Emerging therapies are also exploring novel targets beyond the VEGF and PD-1PDL1 pathways. For example, drugs targeting the Wnt/B-catenin pathway, which is frequently dysregulated in HCC, are under investigation. Similarly, oncolytic viruses and adoptive T cell therapies, including chimeric antigen receptor (CAR) T cells, are being evaluated for their potential to elicit robust and durable antitumor responses. The combination of these innovative approaches with existing modalities could further enhance the therapeutic landscape for HCC in the future.

Another critical consideration is the optimization of treatment

Table 8 Immune Checkpoint Inhibitors in Hepatocellular Carcinoma

Agent	Mechanism of Action	Clinical Outcomes and Challenges
Nivolumab	PD-1 inhibition	Durable responses in a subset of patients; modest overall response rates
Pembrolizumab	PD-1 inhibition	Similar efficacy to nivolumab; ongoing trials for combination therapies
Atezolizumab	PD-L1 inhibition	Superior efficacy in combination with bevacizumab; first-line therapy
Ipilimumab	CTLA-4 inhibition	Combined with nivolumab in refractory cases; significant toxicity concerns

sequencing and combinations to maximize clinical benefit while minimizing toxicity. The advent of computational models and artificial intelligence (AI)-driven algorithms offers a potential solution by enabling the simulation of treatment outcomes based on individual patient characteristics. Such tools could guide clinicians in selecting the most appropriate therapeutic regimen for each patient, thereby improving overall survival and quality of life.

Table 8 provides an overview of immune checkpoint inhibitors currently approved for HCC treatment, including their mechanisms of action, clinical outcomes, and ongoing challenges.

targeted therapies and immunotherapy have revolutionized the treatment paradigm for advanced HCC, offering hope to patients who were previously limited in their options. While significant progress has been made, ongoing research is imperative to address the limitations of current therapies, including resistance mechanisms and adverse effects. The integration of molecular profiling, innovative treatment modalities, and computational tools holds promise for advancing personalized medicine and improving outcomes in HCC management. As the field continues to evolve, a multidisciplinary approach involving oncologists, hepatologists, and researchers will be crucial to translating scientific advances into clinical practice.

Conclusion

Hepatocellular carcinoma (HCC) remains one of the most daunting challenges in contemporary oncology, characterized by its high mortality rates, late-stage diagnosis, and intricate association with chronic liver diseases such as cirrhosis and viral hepatitis. Despite these challenges, substantial progress has been achieved in recent years, particularly in early diagnostic methodologies and therapeutic innovations, reflecting the remarkable strides made in biomedical research and clinical practice.

The advent of advanced diagnostic tools has been a pivotal development in mitigating the historical difficulties of early-stage detection in HCC. Emerging biomarkers, including circulating tumor DNA (ctDNA) and microRNAs, have shown considerable promise in complementing traditional imaging modalities such as multiphasic computed tomography (CT) and magnetic resonance imaging (MRI). Furthermore, the integration of artificial intelligence (AI) in diagnostic workflows has enhanced the sensitivity and specificity of HCC screening by leveraging large datasets and pattern recognition algorithms. Such innovations not only facilitate earlier intervention but also provide critical prognostic insights, particularly for patients with coexisting liver dysfunctions.

Curative treatment options, namely surgical resection and liver transplantation, remain the cornerstone for managing early-stage HCC. While surgical resection is limited to patients with adequate hepatic reserve, liver transplantation addresses both the oncologic burden and the underlying liver disease. Advances in patient selection criteria, supported by evidence-based guidelines such as the Milan and UCSF criteria, have improved post-transplant survival rates. Minimally invasive approaches, such as laparoscopic and robotic-assisted surgeries, have further enhanced perioperative outcomes by reducing complications and accelerating recovery times. Moreover, bridging therapies such as transarterial chemoembolization (TACE) and stereotactic body radiotherapy (SBRT) have demonstrated efficacy in downstaging tumors, enabling previously ineligible patients to undergo potentially curative interventions.

The management of advanced-stage HCC has undergone a paradigm shift with the introduction of targeted therapies and immune checkpoint inhibitors. Sorafenib and lenvatinib, multi-kinase inhibitors, have long served as standard first-line therapies; however, their clinical utility has been complemented by newer agents such as cabozantinib and regorafenib, which provide additional options for patients with progressive disease. The emergence of immunotherapy, particularly agents targeting the PD-1/PD-L1 axis, has been transformative, with the atezolizumab-bevacizumab combination setting a new benchmark for first-line treatment. These advances have translated into prolonged survival and improved quality of life for patients, although challenges such as therapeutic resistance and adverse event management persist.

One of the fundamental challenges in HCC treatment lies in its pronounced molecular and clinical heterogeneity. This vari-

ability necessitates a personalized approach, integrating insights from genomics, transcriptomics, and metabolomics to identify actionable targets and optimize therapeutic regimens. The development of predictive biomarkers, such as alpha-fetoprotein (AFP) response and tumor mutational burden (TMB), has begun to inform clinical decision-making, though further validation in large, diverse cohorts is essential. Additionally, the interplay between tumor biology and the immune microenvironment continues to be a fertile area of investigation, with implications for enhancing the efficacy of immunotherapeutic strategies.

Another critical area of focus is the management of therapeutic resistance, which remains a major obstacle in achieving durable responses. Resistance mechanisms, including angiogenesis upregulation, immune escape, and genetic mutations, highlight the need for combinatorial approaches that target multiple pathways simultaneously. Preclinical studies have shown promise in overcoming resistance through rational drug combinations and novel agents, but translating these findings into clinical practice requires robust evidence from well-designed trials.

Future research must also address the disparities in HCC outcomes, which are influenced by geographic, socioeconomic, and racial factors. The disproportionate burden of HCC in regions with endemic hepatitis B and C underscores the importance of global health initiatives aimed at vaccination, antiviral therapy, and public awareness. Similarly, addressing barriers to healthcare access and participation in clinical trials will be critical to ensuring equitable treatment outcomes.

while hepatocellular carcinoma remains a complex and formidable disease, the cumulative advances in early detection, surgical techniques, and systemic therapies provide a foundation for optimism. Continued efforts to unravel the molecular underpinnings of HCC, refine therapeutic strategies, and expand access to care are essential for transforming the prognosis of this disease. By leveraging multidisciplinary collaboration and embracing innovation, the medical community can aspire to shift HCC from a predominantly fatal condition to a manageable disease with sustainable long-term outcomes.

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