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Review Article

CURRENT ADVANCES AND FUTURE PERSPECTIVES IN THE MULTIDISCIPLINARY MANAGEMENT OF HEPATOCELLULAR CARCINOMA

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) represents the most common primary malignant tumor of the liver and accounts for approximately 75–85% of all primary liver cancers worldwide [1]. It remains a major global health challenge and ranks among the leading causes of cancer-related mortality, with a continuously increasing disease burden in many regions due to the rising prevalence of metabolic liver disease, obesity, diabetes mellitus, and chronic viral hepatitis [2].

The clinical management of HCC is particularly complex because the disease develops within the setting of chronic liver injury, cirrhosis, and impaired hepatic function. Unlike many solid malignancies, treatment decisions must consider both tumor characteristics and the functional reserve of the underlying liver [3]. Although advances in surveillance, imaging, surgical techniques, locoregional therapies, and systemic treatments have significantly improved outcomes, high recurrence rates, treatment resistance, and biological heterogeneity remain major clinical challenges [4].

Historically, treatment strategies for HCC were primarily focused on surgical resection, liver transplantation, and local ablative therapies in selected patients. However, the therapeutic landscape has rapidly evolved with the emergence of molecularly targeted therapies, immune checkpoint inhibitors, combination immunotherapy, and precision oncology approaches [5]. Modern HCC management increasingly requires collaboration among hepatobiliary surgeons, hepatologists, oncologists, radiologists, interventional

specialists, pathologists, genetic experts, and nutrition specialists through multidisciplinary team (MDT) approaches [6].

Aim and Objectives:

Primary Objective: This review aims to provide a comprehensive analysis of current advances and future perspectives in the multidisciplinary management of hepatocellular carcinoma, emphasizing the integration of surgical treatment, immunotherapy, targeted therapy, and precision medicine.

Secondary Objectives: The specific objectives are:

1. To summarize recent developments in surgical management, including hepatic resection, minimally invasive liver surgery, and liver transplantation.
2. To evaluate current evidence regarding systemic therapies, including targeted agents and immune checkpoint inhibitors.
3. To discuss the emerging role of molecular biomarkers, genomic profiling, liquid biopsy, and artificial intelligence in individualized HCC management.
4. To analyze current controversies and unresolved clinical challenges regarding treatment sequencing, patient selection, and personalized therapeutic strategies.
5. To identify future research directions that may improve survival outcomes and quality of life among patients with HCC.

Methods:

Literature Search Strategy: A comprehensive literature search was performed according to evidence-based principles for narrative review methodology. Electronic databases including PubMed/MEDLINE, Scopus, Web of Science, Embase, and the Cochrane Library were searched for relevant publications between January 2000 and June 2026.

The search strategy incorporated Medical Subject Headings (MeSH) terms and free-text keywords related to HCC management.

The primary search strategy included:

("Hepatocellular carcinoma" OR "HCC" OR "primary liver cancer")

AND

("hepatectomy" OR "liver resection" OR "liver transplantation" OR "surgery")

AND

("immunotherapy" OR "immune checkpoint inhibitor" OR "targeted therapy" OR "systemic therapy")

AND

("precision medicine" OR "genomics" OR "biomarker" OR "liquid biopsy" OR "artificial intelligence")

AND

("survival" OR "prognosis" OR "clinical outcome" OR "recurrence")

Additional searches were conducted using references from major guidelines, consensus statements, and landmark clinical trials.

Study Selection Criteria:

Inclusion Criteria: Studies were included when they fulfilled the following criteria:

1. Human studies involving patients with hepatocellular carcinoma.
2. Articles published in peer-reviewed scientific journals.
3. Studies written in English language.
4. Publications evaluating:
    - Surgical management
    - Liver transplantation
    - Locoregional treatment
    - Systemic therapy
    - Immunotherapy
    - Molecular biomarkers
    - Precision medicine approaches
5. Study designs including:
    - Randomized controlled trials
    - Prospective cohort studies
    - Retrospective clinical studies
    - Systematic reviews
    - Meta-analyses
    - International guidelines
    - Expert consensus recommendations

Exclusion Criteria: The following publications were excluded:

1. Animal studies.
2. Laboratory studies without direct clinical application.
3. Case reports and small case series.
4. Conference abstracts without full publication.
5. Duplicate studies.
6. Articles lacking clinically relevant outcomes.

Data Extraction: Relevant information was extracted from selected publications, including:

Study Characteristics:

- First author
- Publication year
- Country of origin
- Study design
- Sample size
- Follow-up duration

Patient Characteristics:

- Age distribution
- Sex
- Liver disease etiology
- Child–Pugh classification
- Performance status
- Tumor stage

Treatment Characteristics:

- Surgical intervention
- Locoregional therapy
- Systemic therapy
- Immunotherapy regimen
- Combination strategies

Clinical Outcomes:

- Overall survival (OS)
- Disease-free survival (DFS)
- Progression-free survival (PFS)
- Tumor response rate
- Recurrence rate
- Treatment-related complications

Quality Assessment: Although this manuscript represents a narrative/state-of-the-art review, methodological quality considerations were incorporated using established evidence assessment principles. Relevant studies were evaluated according to:

Newcastle–Ottawa Scale (NOS): Used for assessing observational cohort and case-control studies, evaluating:

- Selection of study population
- Comparability between groups
- Outcome assessment

Cochrane Risk of Bias Tool: Applied to randomized controlled trials to evaluate:

- Random sequence generation
- Allocation concealment
- Blinding
- Missing outcome data
- Selective reporting

PRISMA Recommendations: The literature identification and selection process was structured according to

PRISMA principles where applicable [7].

Keywords: Hepatocellular carcinoma; Liver cancer; Hepatectomy; Liver transplantation; Immunotherapy; Immune checkpoint inhibitors; Precision medicine; Multidisciplinary management

INTRODUCTION

Epidemiology and Global Disease Burden of Hepatocellular Carcinoma:

Hepatocellular carcinoma is the predominant histological subtype of primary liver malignancy and represents approximately 75–85% of all liver cancer cases worldwide [1]. According to global cancer statistics, liver cancer remains among the most common causes of cancer mortality, accounting for more than 800,000 deaths annually worldwide [2].

The epidemiological distribution of HCC demonstrates substantial geographic variation due to differences in viral hepatitis prevalence, environmental exposures, metabolic disorders, healthcare accessibility, and preventive strategies [2,3].

Eastern Asia, particularly China, continues to experience a significant proportion of the global HCC burden because of the historical prevalence of chronic hepatitis B virus (HBV) infection [8]. In contrast, Western countries have observed increasing HCC incidence associated with metabolic dysfunction-associated steatotic liver disease (MASLD), obesity, diabetes mellitus, and alcohol-related liver disease [9].

Chronic HBV and hepatitis C virus (HCV) infections remain major etiological drivers of hepatocarcinogenesis. Persistent viral-induced inflammation promotes hepatocyte injury, fibrosis progression, cirrhosis development, and malignant transformation [10]. Furthermore, metabolic risk factors have become increasingly important contributors to HCC development, particularly in regions where viral hepatitis control programs have improved [11].

Major Risk Factors Associated With HCC Development:

The development of HCC is a multifactorial process involving environmental, infectious, metabolic, and genetic factors.

Major established risk factors include:

Chronic Hepatitis B Virus Infection: HBV remains one of the strongest risk factors for HCC development. Unlike HCV, HBV can directly contribute to carcinogenesis through viral DNA integration into host genomes and activation of oncogenic pathways [12].

Chronic Hepatitis C Virus Infection: HCV promotes hepatocarcinogenesis primarily through chronic inflammation, oxidative stress, and progressive fibrosis. Although antiviral therapies have reduced HCV-associated complications, patients with established cirrhosis remain at continued risk for HCC development [13].

Liver Cirrhosis: Approximately 80–90% of HCC cases occur in patients with underlying cirrhosis. Fibrosis-associated changes create a pro-carcinogenic environment characterized by chronic inflammation, immune

dysfunction, and abnormal cellular regeneration [14].

Metabolic Dysfunction-Associated Steatotic Liver Disease: The increasing prevalence of obesity, diabetes mellitus, and metabolic syndrome has resulted in MASLD becoming an important emerging cause of HCC globally [15].

Current Clinical Challenges in Hepatocellular Carcinoma Management:

Despite substantial improvements in surveillance, diagnosis, and treatment, hepatocellular carcinoma remains one of the most challenging malignancies in clinical oncology because of its complex interaction between tumor biology, liver function, and patient-related factors [16].

Challenges in Early Detection:

Early diagnosis is critical because patients diagnosed at an early stage may benefit from potentially curative therapies, including surgical resection, liver transplantation, and local ablative techniques [17]. However, early detection remains difficult because HCC frequently develops silently and many patients present only after symptoms occur or when the disease has already progressed beyond curative treatment options [18].

Current surveillance strategies, including ultrasound examination with or without serum alpha-fetoprotein (AFP), have improved early detection rates; however, limitations remain, particularly in patients with obesity, advanced fibrosis, nodular cirrhotic liver morphology, or AFP-negative tumors [19].

Although advanced imaging modalities such as multiphasic computed tomography (CT) and magnetic resonance imaging (MRI) have improved diagnostic accuracy, accessibility, cost, and interpretation variability remain important limitations, particularly in resource-limited healthcare systems [20].

Tumor Biological Heterogeneity:

HCC is characterized by extensive molecular and clinical heterogeneity, which significantly influences treatment response and prognosis [21].

Different etiological backgrounds, including HBV infection, HCV infection, alcohol-related liver disease, and metabolic dysfunction-associated liver disease, produce distinct molecular profiles and immune microenvironments [22].

Genomic studies have identified several recurrent molecular alterations associated with HCC development, including:

- **TERT promoter mutations**
- **TP53 alterations**
- **CTNNB1 mutations**
- **Chromatin remodeling gene abnormalities**
- **PI3K/AKT/mTOR pathway activation**

These molecular differences contribute to variations in tumor growth patterns, metastatic potential, immune escape mechanisms, and therapeutic sensitivity [23].

However, despite advances in molecular classification, routine clinical implementation of genomic-guided treatment remains limited because validated predictive biomarkers are still lacking for most therapeutic approaches [24].

High Risk of Tumor Recurrence: One of the major clinical challenges following curative-intent treatment is tumor recurrence.

Even after successful hepatic resection or liver transplantation, recurrence rates remain significant due to:

1. Microscopic residual disease
2. Intrahepatic metastatic spread
3. Persistent carcinogenic liver environment
4. Tumor molecular aggressiveness[25]

Following hepatectomy, recurrence occurs in a substantial proportion of patients within five years, limiting long-term survival outcomes [26]. Recurrence patterns may represent either:

- Early recurrence caused by intrahepatic dissemination of the primary tumor
- Late recurrence caused by new tumor development in chronically diseased liver tissue[27].

Accurate prediction of recurrence risk remains essential for postoperative surveillance strategies and consideration of adjuvant therapies.

Complexity of Treatment Selection:

Unlike many other malignancies, HCC treatment decisions must consider both oncological factors and liver functional reserve [28].

Important factors influencing therapeutic selection include:

Tumor-related factors:

- Tumor size
- Tumor number
- Vascular invasion
- Extrahepatic spread
- Molecular characteristics

Liver-related factors:

- Child–Pugh classification
- Model for End-Stage Liver Disease (MELD) score
- Portal hypertension
- Future liver remnant volume

Patient-related factors:

- Age
- Performance status
- Comorbidities

- Treatment preference[29]

The Barcelona Clinic Liver Cancer (BCLC) staging system integrates these variables and provides treatment recommendations; however, debate continues regarding whether rigid staging algorithms adequately reflect the biological complexity of HCC [30].

Evolution of Hepatocellular Carcinoma Management Strategies:

The therapeutic landscape of HCC has undergone remarkable transformation over the past several decades. Management has evolved from primarily surgical intervention toward a comprehensive multidisciplinary approach integrating surgery, interventional oncology, systemic therapy, and molecular medicine [31].

The Surgical Era: Resection and Liver Transplantation:

Historically, hepatic resection represented the primary potentially curative treatment for HCC. Advances in surgical anatomy, vascular control techniques, anesthesia, and perioperative management have significantly improved the safety of liver surgery [32].

Modern hepatectomy strategies emphasize:

- Anatomical precision
- Preservation of functional liver parenchyma
- Adequate oncological margins
- Prevention of postoperative liver failure[33]

For patients with cirrhosis and early-stage HCC, liver transplantation provides the unique advantage of removing both tumor tissue and the underlying diseased liver, resulting in excellent long-term outcomes in appropriately selected patients [34].

The establishment of the Milan criteria represented a landmark development in transplantation oncology, demonstrating that carefully selected HCC patients could achieve survival outcomes comparable to patients transplanted for non-malignant liver diseases [35].

The Minimally Invasive Surgery Era:

The development of laparoscopic and robotic liver surgery has significantly changed modern hepatobiliary practice.

Compared with conventional open surgery, minimally invasive hepatectomy has demonstrated advantages including:

- Reduced intraoperative blood loss
- Lower postoperative pain
- Shorter hospitalization
- Faster recovery
- Improved cosmetic outcomes

while maintaining comparable oncological effectiveness in selected patients [36].

Robotic platforms have further expanded the feasibility of complex liver procedures by providing three-dimensional visualization, improved instrument articulation, and enhanced surgical ergonomics [37].

However, limitations remain, including:

- High equipment costs
- Learning curve requirements
- Limited availability

The Systemic Therapy Era:

For many years, treatment options for advanced HCC were limited. The introduction of sorafenib represented the first major breakthrough in systemic therapy.

The SHARP trial demonstrated that sorafenib significantly improved overall survival compared with placebo in patients with advanced HCC, establishing targeted therapy as a standard treatment approach [38].

Subsequently, additional molecular targeted agents expanded systemic treatment options, including:

- Lenvatinib
- Regorafenib
- Cabozantinib
- Ramucirumab[39].

The Immunotherapy Revolution:

The discovery of immune checkpoint pathways has transformed cancer treatment, including HCC management.

HCC develops within an immunosuppressive microenvironment characterized by:

- Increased regulatory T cells
- Exhausted T lymphocytes
- Increased PD-1/PD-L1 signaling
- Immunosuppressive cytokine production[40]

Immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 pathways have demonstrated significant clinical activity.

The IMbrave150 trial established atezolizumab plus bevacizumab as a new first-line standard therapy for unresectable HCC after demonstrating superior survival outcomes compared with sorafenib [41].

The HIMALAYA trial further demonstrated the efficacy of tremelimumab combined with durvalumab, providing another important immunotherapeutic strategy [42].

The Precision Medicine Era:

Recent advances in molecular biology have shifted HCC management toward personalized treatment strategies.

Precision medicine incorporates:

- Genomic profiling

- Molecular classification
- Biomarker discovery
- Liquid biopsy
- Radiomics
- Artificial intelligence

to optimize patient selection and therapeutic decision-making [43].

Liquid biopsy approaches analyzing circulating tumor DNA (ctDNA), circulating tumor cells, and extracellular vesicles have emerged as promising non-invasive methods for monitoring tumor evolution and treatment response [44].

Artificial intelligence-based models have demonstrated potential applications in:

- Early HCC detection
- Imaging interpretation
- Recurrence prediction
- Treatment response assessment

[45].

Knowledge Gap and Rationale for This Review:

Although major therapeutic advances have improved HCC outcomes, several important questions remain unresolved.

Current challenges include:

1. Limited predictive biomarkers for immunotherapy response.
2. Lack of universally accepted criteria for integrating surgery with systemic therapy.
3. Uncertainty regarding optimal sequencing of treatments.
4. Difficulty translating molecular discoveries into routine clinical practice.
5. Need for validated artificial intelligence-based clinical decision systems.

[46]

The rapid expansion of therapeutic options requires updated evaluation of evidence across multiple disciplines. A comprehensive review integrating surgical oncology, systemic therapy, immunology, and precision medicine is therefore essential.

Aim of the Review:

This narrative review aims to provide a comprehensive and contemporary overview of multidisciplinary hepatocellular carcinoma management.

Specifically, this article discusses:

- Current surgical strategies
- Advances in minimally invasive liver surgery
- Liver transplantation

- Locoregional therapies
- Targeted therapies
- Immunotherapy
- Molecular biomarkers
- Artificial intelligence
- Future directions in precision oncology

The ultimate goal is to highlight how integrated multidisciplinary approaches can improve patient selection, therapeutic outcomes, and personalized management of HCC.

MATERIALS AND METHODS

Study Design:

This article was designed as a **narrative state-of-the-art review** focusing on contemporary advances and future perspectives in the multidisciplinary management of hepatocellular carcinoma (HCC). The review was conducted using principles of evidence-based medicine and structured literature synthesis methods commonly applied in high-quality clinical review articles.

The purpose of this review was not only to summarize established therapeutic strategies but also to critically evaluate emerging approaches, including immunotherapy, molecular-guided treatment, artificial intelligence (AI), and precision oncology.

The methodology followed key elements recommended by the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework**, although the article was constructed as a narrative review rather than a formal systematic review with quantitative meta-analysis [47].

Literature Search Strategy:

A comprehensive literature search was performed using internationally recognized biomedical databases:

- PubMed/MEDLINE
- Scopus
- Web of Science Core Collection
- Embase
- Cochrane Library

The search period included studies published from **January 2000 to June 2026**.

The search strategy was developed using controlled vocabulary (MeSH terms) and free-text keywords related to HCC epidemiology, diagnosis, surgery, systemic therapy, immunotherapy, and precision medicine.

The primary search strategy included combinations of:

Disease-related terms:

("Hepatocellular carcinoma" OR "HCC" OR "primary liver cancer" OR "liver malignancy")

AND

Surgical treatment terms:

("hepatectomy" OR "liver resection" OR "liver transplantation" OR "laparoscopic liver surgery" OR "robotic hepatectomy")

AND

Systemic treatment terms:

("immunotherapy" OR "immune checkpoint inhibitor" OR "PD-1 inhibitor" OR "PD-L1 inhibitor" OR "targeted therapy" OR "tyrosine kinase inhibitor")

AND

Precision medicine terms:

("precision medicine" OR "molecular classification" OR "genomics" OR "biomarker" OR "liquid biopsy" OR "artificial intelligence" OR "radiomics")

AND

Outcome-related terms:

("survival" OR "prognosis" OR "recurrence" OR "treatment response" OR "clinical outcome")

Study Selection Process:

All identified publications were screened based on title, abstract, and full-text review.

The selection process consisted of:

1. Identification of potentially relevant publications.
2. Removal of duplicate articles.
3. Screening according to predefined inclusion and exclusion criteria.
4. Full-text evaluation of eligible studies.
5. Final selection of clinically relevant evidence.

Inclusion Criteria:

Studies were considered eligible if they met the following criteria:

Population

- Adult patients diagnosed with hepatocellular carcinoma.

Publication Type

Included:

- Randomized controlled trials
- Prospective clinical studies
- Retrospective cohort studies
- Meta-analyses
- Systematic reviews
- Clinical guidelines

- International consensus statements
- Translational studies with direct clinical relevance

Intervention Areas

Studies evaluating:

- Hepatic resection
- Liver transplantation
- Ablative therapies
- Transarterial therapies
- Targeted therapy
- Immunotherapy
- Combination treatment strategies
- Biomarkers
- Precision medicine
- Artificial intelligence applications

Outcomes

Studies reporting:

- Overall survival (OS)
- Disease-free survival (DFS)
- Progression-free survival (PFS)
- Recurrence rates
- Treatment response
- Complications
- Safety outcomes

Exclusion Criteria:

Studies were excluded if they involved:

- Animal experiments without human validation
- Laboratory studies without clinical implications
- Case reports
- Small uncontrolled case series
- Conference abstracts without full publication
- Duplicate datasets
- Non-English publications
- Articles lacking clinically meaningful outcomes

Data Extraction:

Relevant information was extracted systematically from included studies.

The extracted variables included:

Study Characteristics

- First author
- Publication year
- Country
- Study design
- Sample size
- Follow-up duration

Patient Characteristics

- Age
- Sex
- Etiology of liver disease
- HBV/HCV status
- Cirrhosis status
- Child–Pugh classification
- Tumor stage
- Performance status

Treatment Characteristics

Extracted treatment variables included:

Surgical approaches

- Open hepatectomy
- Laparoscopic hepatectomy
- Robotic hepatectomy
- Liver transplantation

Locoregional therapies

- Radiofrequency ablation
- Microwave ablation
- Transarterial chemoembolization
- Radioembolization

Systemic therapies

- Sorafenib
- Lenvatinib
- Immune checkpoint inhibitors
- Combination immunotherapy

Outcome Assessment

Clinical outcomes included:

- Overall survival
- Disease-free survival
- Recurrence-free survival
- Objective response rate
- Adverse events
- Postoperative complications

Quality Assessment:

Because this article included evidence from different study designs, appropriate quality assessment frameworks were considered.

Newcastle–Ottawa Scale (NOS)

Observational studies were evaluated according to:

1. Selection of study population
2. Comparability between groups
3. Outcome assessment[48]

Cochrane Risk of Bias Tool

Randomized controlled trials were evaluated according to:

- Random sequence generation
- Allocation concealment
- Blinding
- Incomplete outcome data
- Selective reporting[49]

RESULTS

Current Understanding of HCC Biology and Pathogenesis:

Hepatocellular carcinoma develops through a complex interaction between chronic liver injury, genetic alterations, epigenetic changes, immune dysfunction, and tumor microenvironment remodeling [50]. Unlike many other cancers, HCC usually arises in a chronically diseased liver environment characterized by fibrosis, inflammation, and impaired regeneration. This unique biological background strongly influences tumor progression and treatment response [51].

Chronic Liver Injury and Hepatocarcinogenesis:

The development of HCC generally follows a multistep sequence:

Chronic inflammation → hepatocyte injury → fibrosis → cirrhosis → dysplastic nodules → malignant transformation[52]

Persistent inflammatory stimulation results in:

- Reactive oxygen species accumulation
- DNA damage
- Abnormal cellular proliferation
- Immune escape

which ultimately promote malignant transformation [53].

Molecular Pathways Involved in HCC Development:

Comprehensive genomic studies have identified multiple signaling pathways involved in HCC initiation and progression.

Wnt/β-Catenin Pathway:

Aberrant activation of Wnt signaling is among the most frequent molecular alterations in HCC. CTNNB1 mutations result in abnormal β-catenin accumulation and promote tumor growth, stem cell characteristics, and immune exclusion [54].

TP53 Pathway:

TP53 mutations are strongly associated with genomic instability, aggressive tumor behavior, and poor prognosis, particularly in HBV-related HCC [55].

PI3K/AKT/mTOR Pathway:

Activation of the PI3K/AKT/mTOR pathway contributes to:

- Tumor proliferation
- Angiogenesis
- Metabolic adaptation
- Drug resistance[56]

Telomerase Activation:

TERT promoter mutations represent one of the earliest and most frequent genetic events during hepatocarcinogenesis, contributing to cellular immortality and malignant progression [57].

Tumor Microenvironment and Immune Escape:

The HCC tumor microenvironment contains multiple immunosuppressive components, including:

- Regulatory T cells
- Tumor-associated macrophages
- Myeloid-derived suppressor cells
- Cancer-associated fibroblasts

These populations contribute to immune tolerance, angiogenesis, invasion, and resistance to therapy [58].

The immune suppressive nature of HCC provides the biological rationale for immune checkpoint blockade therapies targeting PD-1, PD-L1, and CTLA-4 pathways [59].

Diagnostic Advances in Hepatocellular Carcinoma:

Surveillance Strategies:

Early detection significantly improves treatment opportunities and long-term survival. International guidelines recommend surveillance of high-risk populations, particularly individuals with cirrhosis or chronic HBV infection, using ultrasound every six months with or without AFP testing [60].

However, ultrasound sensitivity decreases in patients with:

- Obesity
- Advanced fibrosis
- Nodular liver morphology

Therefore, alternative surveillance strategies are being investigated [61].

Imaging-Based Diagnosis:

Multiphasic contrast-enhanced CT and MRI remain central diagnostic modalities.

Characteristic imaging findings include:

- Arterial phase hyperenhancement
- Portal venous washout
- Delayed enhancement patterns

which reflect abnormal tumor vascular architecture [62].

MRI, particularly hepatobiliary contrast-enhanced MRI, provides improved sensitivity for small lesions and is increasingly used for early diagnosis and treatment planning [63].

Biomarkers, Liquid Biopsy, and Molecular Diagnosis:

Serum Biomarkers in HCC Detection and Prognostication

Serum biomarkers remain an important component of HCC surveillance, diagnosis, prognosis assessment, and treatment monitoring. Among currently available biomarkers, alpha-fetoprotein (AFP) remains the most widely used; however, its clinical utility is limited by insufficient sensitivity and specificity [64].

Approximately one-third of HCC patients may have normal AFP levels, particularly those with small tumors or certain molecular subtypes, limiting its effectiveness as a standalone diagnostic marker [65].

Other serum biomarkers have been investigated to improve diagnostic accuracy, including:

- Protein induced by vitamin K absence or antagonist-II (PIVKA-II/DCP)
- Glypican-3 (GPC3)
- Golgi protein 73 (GP73)
- Osteopontin
- MicroRNAs[66]

PIVKA-II has demonstrated value in detecting HCC and predicting aggressive tumor characteristics, including vascular invasion and recurrence risk [67]. In several Asian countries, particularly Japan and China, PIVKA-II is increasingly incorporated into clinical practice alongside AFP for improved diagnostic performance [68].

Liquid Biopsy and Circulating Tumor Biomarkers

Liquid biopsy represents an emerging non-invasive approach for molecular characterization of HCC through analysis of tumor-derived materials circulating in blood.

Potential components include:

- Circulating tumor DNA (ctDNA)
- Circulating tumor cells (CTCs)
- Extracellular vesicles
- Tumor-derived RNA molecules[69]

ctDNA analysis provides information regarding tumor-specific genomic alterations and may allow:

- Early detection
- Monitoring of treatment response
- Detection of minimal residual disease
- Identification of emerging resistance mechanisms[70]

However, several limitations currently prevent routine clinical implementation, including low circulating tumor DNA levels in early-stage disease, technical variability, and lack of standardized analytical platforms [71].

Artificial Intelligence in HCC Diagnosis

Artificial intelligence (AI) has emerged as a promising technology capable of improving diagnostic accuracy, risk prediction, and treatment planning.

AI applications include:

1. Automated lesion detection on CT and MRI
2. Radiomics-based tumor characterization
3. Prediction of microvascular invasion
4. Recurrence risk estimation
5. Treatment response assessment [72]

Deep learning algorithms have demonstrated performance comparable to experienced radiologists in selected imaging tasks. However, clinical translation requires external validation, standardized datasets, and regulatory approval before widespread adoption [73].

Current Treatment Strategies for Hepatocellular Carcinoma:

Treatment selection for HCC requires comprehensive assessment of:

- Tumor burden
- Liver function
- Performance status
- Vascular invasion
- Extrahepatic disease

- Patient preference

The Barcelona Clinic Liver Cancer (BCLC) staging system remains the most widely accepted framework for treatment allocation, integrating tumor stage, liver function, and patient condition [74].

Current therapeutic modalities include:

- Surgical resection
- Liver transplantation
- Local ablation
- Transarterial therapy
- Radiation therapy
- Systemic therapy [75]

Surgical Management of HCC:

Hepatic Resection

Hepatic resection remains one of the principal curative treatment options for patients with resectable HCC and preserved liver function [76].

The fundamental goals of liver resection include:

1. Complete tumor removal with negative margins
2. Preservation of adequate functional liver volume
3. Prevention of postoperative liver failure [77]

Advances in surgical techniques, anesthesia, intraoperative ultrasound, and perioperative management have significantly improved outcomes after hepatectomy [78].

Patient Selection for Hepatectomy

Historically, hepatectomy was mainly recommended for patients with solitary tumors without cirrhosis. However, improvements in surgical techniques and perioperative care have expanded indications [79].

Current selection criteria consider:

Tumor Factors

- Number of lesions
- Tumor size
- Vascular invasion
- Extrahepatic spread

Liver Factors

- Child–Pugh score
- MELD score
- Portal hypertension
- Future liver remnant volume

Patient Factors

- Age
- Functional status
- Comorbidities [80]

Anatomical Versus Non-Anatomical Hepatectomy

Anatomical hepatectomy involves removal of the hepatic segment supplied by the tumor-bearing portal territory. The theoretical advantage is elimination of microscopic tumor spread through portal venous branches [81].

Several studies have suggested improved disease-free survival after anatomical resection, especially in patients with tumors demonstrating portal venous invasion [82].

However, non-anatomical limited resection may preserve more functional liver tissue and is particularly valuable in patients with cirrhosis or reduced hepatic reserve [83].

Therefore, surgical strategy should be individualized according to:

- Tumor biology
- Liver function
- Anatomical location
- Surgeon expertise

Advances in Minimally Invasive Liver Surgery:

Laparoscopic Hepatectomy

Laparoscopic liver surgery has become increasingly accepted worldwide following improvements in surgical experience and technology.

Compared with open hepatectomy, laparoscopic approaches demonstrate:

- Reduced intraoperative blood loss
- Lower postoperative pain
- Shorter hospitalization
- Faster recovery
- Reduced abdominal wall trauma

while maintaining comparable oncological outcomes in selected patients [84].

The International Consensus Conference on Laparoscopic Liver Surgery established that laparoscopic resection is appropriate for selected minor liver resections and can be performed safely for major resections in experienced centers [85].

Advantages of Laparoscopic Hepatectomy

Potential advantages include:

Advantage	Clinical Impact
Reduced blood loss	Lower transfusion requirements
Smaller incision	Improved postoperative recovery

Advantage	Clinical Impact
Reduced inflammatory response	Faster rehabilitation
Shorter hospitalization	Reduced healthcare burden
Improved visualization	Enhanced surgical precision

[86]

Limitations of Laparoscopic Hepatectomy

Despite its advantages, laparoscopic hepatectomy has limitations:

- Steep learning curve
- Difficulty controlling major bleeding
- Limited tactile feedback
- Challenges in posterior-superior tumors
- Requirement for advanced surgical expertise [87]

Robotic Hepatectomy

Robotic platforms have further expanded minimally invasive liver surgery by providing:

- Three-dimensional high-definition visualization
- Wristed instruments
- Tremor filtration
- Improved suturing capability [88]

Robotic surgery may be particularly advantageous for complex liver resections requiring precise dissection around vascular structures.

However, disadvantages include:

- High equipment costs
- Longer setup time
- Limited availability
- Need for specialized training [89]

Liver Transplantation for HCC:

Liver transplantation provides a unique therapeutic advantage by simultaneously treating:

1. The malignant tumor
2. The underlying cirrhotic liver [90]

For carefully selected patients, transplantation provides excellent long-term survival and lower recurrence risk compared with other treatments.

Milan Criteria and Transplant Selection

The Milan criteria remain the internationally accepted benchmark for selecting HCC patients for liver transplantation:

- Single tumor ≤5 cm

OR

- Up to three tumors, each ≤3 cm

AND

- No macrovascular invasion
- No extrahepatic spread [91]

Patients meeting Milan criteria achieve excellent outcomes, with 5-year survival rates exceeding 70% in many transplant programs [92].

Expanded Transplant Criteria

Because Milan criteria exclude some patients who may still benefit from transplantation, several expanded criteria have been proposed.

Examples include:

- UCSF criteria
- Up-to-seven criteria
- Biological selection models [93]

Modern selection increasingly incorporates tumor biology, including:

- AFP level
- Tumor differentiation
- Response to locoregional therapy
- Imaging characteristics

rather than relying solely on anatomical tumor burden [94].

Locoregional Treatment Approaches:

Locoregional therapies play an essential role in patients who are unsuitable for surgery or transplantation.

Major approaches include:

Radiofrequency Ablation (RFA)

RFA is widely used for small early-stage HCC and achieves excellent local control in appropriately selected patients [95].

Microwave Ablation (MWA)

MWA provides several theoretical advantages:

- Larger ablation zones
- Faster treatment
- Less susceptibility to heat-sink effects

and has become increasingly utilized worldwide [96].

Transarterial Chemoembolization (TACE)

TACE remains the standard treatment for many patients with intermediate-stage HCC according to BCLC

recommendations [97].

The procedure combines:

- Selective arterial embolization
- Local chemotherapy delivery

resulting in tumor ischemia and necrosis.

Systemic Therapy: From Targeted Therapy to Immunotherapy:

Systemic therapy has undergone a fundamental transformation over the last two decades. Previously, patients with advanced hepatocellular carcinoma had limited therapeutic options and poor survival outcomes. The introduction of molecular targeted agents and immune-based therapies has significantly changed the treatment paradigm, transforming advanced HCC into a disease where personalized systemic strategies can achieve meaningful clinical benefit [98].

Molecular Targeted Therapy:

Sorafenib: The First Successful Systemic Therapy

Sorafenib, an oral multikinase inhibitor targeting RAF kinases, VEGFR, PDGFR, and other signaling pathways, was the first systemic therapy demonstrated to improve survival in advanced HCC [99].

The landmark **SHARP trial** evaluated sorafenib versus placebo in patients with advanced HCC and demonstrated a statistically significant improvement in overall survival. Median survival increased from 7.9 months with placebo to 10.7 months with sorafenib, establishing sorafenib as the global standard first-line therapy for more than a decade [100].

A parallel Asia-Pacific phase III trial confirmed the survival benefit of sorafenib among Asian patients, including populations with a high prevalence of HBV-associated HCC [101].

Despite its effectiveness, sorafenib has limitations:

- Modest survival improvement
- Drug resistance development
- Hand-foot skin reaction
- Hypertension
- Fatigue
- Gastrointestinal toxicity [102]

Lenvatinib:

Lenvatinib is an oral tyrosine kinase inhibitor targeting:

- VEGFR1–3
- FGFR1–4
- PDGFRα
- RET
- KIT [103]

The phase III **REFLECT trial** demonstrated that lenvatinib was non-inferior to sorafenib as first-line treatment for advanced HCC [104].

Compared with sorafenib, lenvatinib demonstrated:

- Higher objective response rate
- Longer progression-free survival
- Similar overall survival

However, adverse effects including hypertension, proteinuria, and fatigue require careful monitoring [105].

Second-Line Targeted Therapies:

For patients experiencing disease progression after first-line therapy, several second-line treatments have demonstrated clinical benefit.

Regorafenib

The RESORCE trial demonstrated improved survival outcomes with regorafenib in patients who tolerated and progressed on sorafenib therapy [106].

Cabozantinib

Cabozantinib, targeting VEGFR, MET, and AXL pathways, improved overall survival in previously treated HCC patients in the CELESTIAL trial [107].

Ramucirumab

Ramucirumab, a VEGFR-2 antibody, demonstrated survival benefit in patients with elevated AFP levels (≥400 ng/mL), identifying AFP as a potential predictive biomarker [108].

Immunotherapy in Hepatocellular Carcinoma:

Biological Rationale for Immune-Based Treatment

HCC develops within an immunologically complex environment characterized by chronic inflammation and immune dysfunction.

Major mechanisms of immune escape include:

- Increased PD-1 expression on exhausted T cells
- PD-L1 upregulation on tumor cells
- Expansion of regulatory T cells
- Increased immunosuppressive cytokines [109]

These findings provided the biological rationale for immune checkpoint blockade therapy.

Immune Checkpoint Inhibitors:

PD-1/PD-L1 Pathway Blockade

Antibodies targeting PD-1 or PD-L1 restore T-cell activity against tumor cells.

Important agents include:

- Nivolumab
- Pembrolizumab

- Atezolizumab
- Durvalumab [110]

Early-phase studies demonstrated meaningful anti-tumor activity in patients with advanced HCC previously treated with sorafenib [111].

Atezolizumab Plus Bevacizumab: A New Standard of Care:

The combination of atezolizumab (anti-PD-L1 antibody) and bevacizumab (anti-VEGF antibody) represents one of the most important breakthroughs in HCC treatment.

The phase III **IMbrave150 trial** compared:

- Atezolizumab + bevacizumab

versus

- Sorafenib

in patients with unresectable HCC.

The combination therapy significantly improved:

- Overall survival
- Progression-free survival
- Objective response rate

and established immunotherapy-based combination treatment as a preferred first-line option for many patients with advanced HCC [112].

The 2021 updated analysis confirmed sustained survival benefit and durable responses with this regimen [113].

Durvalumab Plus Tremelimumab (STRIDE Regimen):

The HIMALAYA trial evaluated a combination of:

- Tremelimumab (CTLA-4 inhibitor)
- Durvalumab (PD-L1 inhibitor)

known as the **STRIDE regimen**.

The trial demonstrated improved overall survival compared with sorafenib, providing another effective first-line immunotherapy strategy for advanced HCC [114].

Current Challenges in Immunotherapy:

Despite remarkable progress, several challenges remain.

Primary Resistance

Some patients demonstrate minimal response due to:

- Immune-excluded tumor phenotype
- Low tumor mutation burden
- β-catenin activation
- Immunosuppressive microenvironment [115]

Predictive Biomarkers

Unlike other cancers, PD-L1 expression alone has limited predictive value in HCC.

Potential biomarkers under investigation include:

- Tumor mutational burden
- Gene expression signatures
- Immune cell infiltration patterns
- Gut microbiome composition
- Circulating immune markers [116]

Treatment Sequencing

The optimal sequence between:

- Surgery
- Immunotherapy
- Locoregional therapy
- Targeted therapy

remains an area of active research.

Combination Strategies: Integrating Surgery With Systemic Therapy:

A major emerging concept in HCC management is the integration of systemic therapies with potentially curative local treatments.

Neoadjuvant Therapy

Neoadjuvant immunotherapy aims to:

- Reduce tumor burden
- Improve surgical feasibility
- Eliminate microscopic disease
- Activate anti-tumor immunity [117]

Early clinical studies suggest potential benefits; however, randomized evidence is still developing.

Adjuvant Therapy after Hepatectomy

Because recurrence remains common after surgical resection, postoperative systemic therapy has been investigated.

Recent studies have explored:

- Immune checkpoint inhibitors
- Anti-angiogenic therapy
- Combination approaches

to reduce recurrence risk.

The role of adjuvant immunotherapy continues to evolve, with ongoing trials expected to clarify patient selection and optimal treatment duration [118].

Precision Medicine in Hepatocellular Carcinoma:

Precision medicine aims to move HCC treatment from generalized algorithms toward individualized therapeutic decisions based on tumor biology and patient characteristics.

Key components include:

1. Genomic profiling
2. Molecular classification
3. Biomarker-driven therapy
4. Liquid biopsy
5. AI-based prediction models [119]

Genomic Classification of HCC:

Large-scale genomic studies have demonstrated that HCC consists of multiple molecular subclasses.

Major molecular characteristics include:

Proliferation Class

Associated with:

- High genomic instability
- TP53 alterations
- Aggressive behavior

Non-Proliferation Class

Associated with:

- CTNNB1 mutations
- More differentiated tumors
- Immune exclusion [120]

Although these classifications provide biological insight, clinical application remains limited because effective molecularly targeted therapies are still lacking for most genomic subtypes.

Liquid Biopsy and Real-Time Tumor Monitoring:

Liquid biopsy provides a minimally invasive approach for monitoring tumor evolution.

Potential applications include:

- Early recurrence detection
- Treatment response evaluation
- Identification of resistance mutations
- Minimal residual disease monitoring [121]

Circulating tumor DNA analysis may eventually allow dynamic treatment adjustment according to tumor evolution.

Artificial Intelligence and Digital Transformation in HCC Management:

Artificial intelligence has emerged as a transformative technology throughout the HCC care pathway.

Potential applications include:

Diagnosis

- Automated lesion detection
- Imaging classification
- Differential diagnosis

Surgical Planning

- Three-dimensional reconstruction
- Virtual surgical simulation
- Prediction of postoperative liver function

Prognostic Prediction

- Recurrence prediction
- Survival modeling
- Treatment response prediction [122]

Radiomics approaches extract quantitative imaging features that may reveal biological information not visible to conventional interpretation [123].

However, widespread implementation requires:

- Large validated datasets
- Standardization
- Regulatory frameworks
- Clinician acceptance [124]

Multidisciplinary Management of Hepatocellular Carcinoma:

Modern hepatocellular carcinoma management has shifted from isolated specialty-based decision-making toward a **multidisciplinary team (MDT) model**, recognizing that optimal outcomes require integration of surgical expertise, oncological treatment, radiological assessment, pathological evaluation, and supportive care [125].

The complexity of HCC arises from the simultaneous presence of two interacting diseases:

1. A malignant tumor requiring oncological control
2. Chronic liver disease requiring preservation of hepatic function

Therefore, treatment decisions must balance tumor eradication with maintenance of liver function and quality of life [126].

Components of the HCC Multidisciplinary Team:

A comprehensive HCC MDT generally includes:

Hepatobiliary Surgeons

Responsible for:

- Assessment of surgical resectability

- Hepatectomy planning
- Liver transplantation evaluation
- Management of postoperative complications

Surgical expertise remains essential because selected patients with localized disease may achieve long-term survival through curative-intent procedures [127].

Hepatologists

Hepatologists contribute to:

- Assessment of chronic liver disease
- Cirrhosis management
- Antiviral therapy optimization
- Portal hypertension evaluation
- Liver function preservation

The optimization of underlying liver disease is critical because hepatic dysfunction strongly influences treatment tolerance and survival outcomes [128].

Medical Oncologists

Medical oncologists guide:

- Systemic therapy selection
- Immunotherapy administration
- Targeted therapy management
- Treatment response assessment

The expanding role of immunotherapy has increased the importance of oncology involvement throughout the disease course [129].

Interventional Radiologists

Interventional radiologists provide expertise in:

- Radiofrequency ablation
- Microwave ablation
- Transarterial chemoembolization
- Radioembolization

These approaches are particularly important for patients who are unsuitable for surgery or transplantation [130].

Radiologists and Nuclear Medicine Specialists

Radiologists contribute through:

- Tumor staging
- Imaging-based diagnosis
- Treatment response evaluation

- Surveillance

Advanced imaging interpretation is essential for accurate staging and treatment planning [131].

Pathologists and Molecular Specialists

Pathological and molecular evaluation contributes to:

- Tumor differentiation assessment
- Biomarker analysis
- Genomic characterization
- Research-based precision treatment

The future of HCC care increasingly depends on integrating molecular information into clinical decisions [132].

Nutrition and Supportive Care Specialists

Nutritional assessment is increasingly recognized as an important component of HCC management because malnutrition and sarcopenia negatively affect:

- Surgical recovery
- Treatment tolerance
- Survival outcomes [133]

Benefits of Multidisciplinary Decision-Making:

Studies evaluating MDT-based care have demonstrated improvements in:

- Treatment selection
- Guideline adherence
- Patient outcomes
- Clinical trial enrollment [134]

MDT discussions allow individualized treatment planning by integrating:

- Tumor stage
- Liver function
- Patient characteristics
- Available therapies

rather than relying solely on standardized algorithms.

Prognostic Factors in Hepatocellular Carcinoma:

Accurate prognostic assessment is essential for treatment selection, surveillance planning, and patient counseling.

Prognostic factors can be categorized into:

1. Clinical factors
2. Laboratory factors
3. Radiological factors

4. Pathological factors
5. Molecular factors

Clinical Prognostic Factors:

Age and Performance Status

Advanced age and poor performance status are associated with reduced treatment tolerance and inferior survival outcomes [135].

The Eastern Cooperative Oncology Group (ECOG) performance status remains an important factor incorporated into many HCC treatment algorithms.

Liver Function

Underlying liver function is one of the strongest predictors of survival.

Important assessment systems include:

- Child–Pugh score
- MELD score
- ALBI grade

The albumin–bilirubin (ALBI) grade has gained increasing attention because it provides objective assessment of hepatic reserve without subjective clinical parameters [136].

Tumor Stage

Tumor burden remains a major prognostic determinant.

Important features include:

- Tumor size
- Tumor number
- Macrovascular invasion
- Extrahepatic spread

Patients with vascular invasion generally have significantly poorer outcomes because of increased metastatic potential [137].

Laboratory Biomarkers:

Alpha-Fetoprotein (AFP)

Elevated AFP levels are associated with:

- Increased tumor aggressiveness
- Vascular invasion
- Higher recurrence risk [138]

AFP is also increasingly used as a biological selection criterion in transplantation evaluation.

Inflammatory Biomarkers

Systemic inflammatory markers have demonstrated prognostic value.

Examples include:

- Neutrophil-to-lymphocyte ratio (NLR)
- Platelet-to-lymphocyte ratio (PLR)
- C-reactive protein

These markers reflect tumor-associated inflammation and immune status [139].

Pathological Prognostic Factors:

Important pathological characteristics include:

- Tumor differentiation
- Microvascular invasion
- Satellite nodules
- Tumor necrosis
- Margin status

Microvascular invasion represents one of the strongest predictors of recurrence following hepatectomy and transplantation [140].

Molecular Prognostic Factors:

Emerging molecular predictors include:

- TP53 mutations
- CTNNB1 alterations
- Gene expression signatures
- Immune-related profiles

However, routine clinical application remains limited due to insufficient prospective validation [141].

Future Technologies and Emerging Directions:

The future of HCC management will likely depend on integrating biological information, advanced technologies, and individualized treatment strategies.

Artificial Intelligence-Driven Precision Oncology:

AI-based platforms may improve:

- Early diagnosis
- Surgical planning
- Risk prediction
- Treatment selection

Future AI systems may integrate:

- Imaging data
- Genomic information
- Clinical records
- Pathological findings

to generate individualized therapeutic recommendations [142].

Multi-Omics Approaches:

Future precision medicine will increasingly rely on integration of multiple biological layers:

- Genomics
- Transcriptomics
- Proteomics
- Metabolomics
- Epigenomics [143]

These approaches may identify novel therapeutic targets and predictive biomarkers.

Combination Immunotherapy Strategies:

Future research is expected to focus on:

- Dual checkpoint inhibition
- Immunotherapy plus targeted therapy
- Immunotherapy combined with locoregional treatment
- Personalized vaccine approaches [144]

The challenge will be identifying which patients are most likely to benefit from specific combinations.

Tumor Microenvironment Modification:

Because immune resistance remains a major limitation, future therapies may target:

- Tumor-associated macrophages
- Regulatory T cells
- Fibroblast-mediated immunosuppression
- Angiogenic pathways [145]

Digital Health and Remote Monitoring:

Digital health technologies may improve:

- Post-treatment surveillance
- Patient adherence
- Symptom monitoring
- Early detection of recurrence

Integration of electronic health records with AI-based systems may enable continuous personalized management.

Tables:

Author	Year	Country	Study Design	Sample Size	Main Findings
Llovet et al.	2008	International	Randomized controlled trial	602	Sorafenib improved survival in advanced HCC [100]
Cheng et al.	2009	Asia-Pacific	Randomized controlled trial	226	Confirmed sorafenib benefit in Asian patients [101]
Kudo et al.	2018	International	Phase III RCT	954	Lenvatinib non-inferior to sorafenib [104]
Bruix et al.	2017	International	Phase III trial	573	Regorafenib improved survival after sorafenib [106]
Abou-Alfa et al.	2018	International	Phase III trial	707	Cabozantinib improved survival [107]
Finn et al.	2020	International	Phase III RCT	501	Atezolizumab plus bevacizumab improved outcomes [112]
Kelley et al.	2022	International	Phase III RCT	782	Durvalumab/tremelimumab improved survival [114]

Table 1: Baseline Characteristics of Representative Landmark Studies in HCC Management

Treatment	Indications	Advantages	Limitations	Outcomes
Hepatectomy	Resectable HCC with adequate liver function	Curative potential	Recurrence risk	Long-term survival in selected patients
Liver transplantation	Early HCC with cirrhosis	Treats tumor and liver disease	Organ shortage	Excellent survival in selected patients
Ablation	Small tumors	Minimally invasive	Tumor size limitation	High local control
TACE	Intermediate-stage HCC	Effective tumor control	Repeated procedures needed	Disease stabilization

Treatment	Indications	Advantages	Limitations	Outcomes
Targeted therapy	Advanced disease	Systemic control	Drug toxicity	Survival improvement
Immunotherapy	Advanced/unresectable HCC	Durable responses	Resistance mechanisms	Improved survival

Table 2: Current Treatment Modalities for HCC

Figure 1: Comprehensive Multidisciplinary Management Algorithm for Hepatocellular Carcinoma

Placement:

After Section 3.3 (Current Treatment Strategies)

Figure Description:

The algorithm should demonstrate:

Patient With Suspected HCC

↓

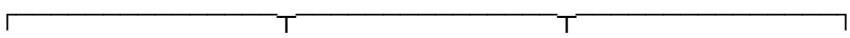
Diagnosis and Staging

(CT/MRI + Biomarkers + Liver Function)

↓

BCLC Stage Assessment

↓



Early Stage Intermediate Advanced Stage

↓ ↓ ↓

Hepatectomy TACE/MWA Systemic Therapy

Transplant Combination Immunotherapy

Ablation Therapy Targeted Therapy

↓

Multidisciplinary Team Evaluation

↓

Follow-up:

Imaging + Biomarkers + Recurrence Monitoring

Figure 2: HCC Pathogenesis-to-Treatment Pathway

Placement:

After Introduction Section

Figure Description:

A biological pathway showing:

Risk Factors

HBV
HCV
Alcohol
MASLD

Metabolic Syndrome

↓

Chronic Liver Injury

↓

Fibrosis/Cirrhosis

↓

Genetic Alterations

TP53
CTNNB1
TERT

Epigenetic Changes

↓

Hepatocellular Carcinoma

↓

Diagnosis

Imaging
Biomarkers
Liquid Biopsy

↓

Treatment

Surgery
Transplantation
Immunotherapy
Precision Medicine

Figure 3: Multidisciplinary Team Model for HCC Management

Placement:

Section 3.9 Multidisciplinary Management

Figure Description:

Central circle:

Hepatocellular Carcinoma Patient

Surrounding specialists:

- Hepatobiliary Surgeon
- Hepatologist
- Medical Oncologist
- Interventional Radiologist
- Radiologist
- Pathologist
- Genetic Specialist
- Nutrition Specialist
- Palliative Care Team

The figure should emphasize:

"Patient-centered individualized treatment planning."

Figure 4: Future Research Directions in Precision HCC Medicine

Placement:

Figure Description:

Precision HCC Medicine

↓

Genomics AI Liquid Biopsy Immunotherapy

↓

Biomarker Discovery

↓

Individualized Treatment Selection

↓

Improved Survival and Quality of Life

DISCUSSION

Principal Findings:

This comprehensive review highlights the rapid transformation of hepatocellular carcinoma management from traditional stage-based treatment toward an integrated multidisciplinary and precision medicine approach.

The major findings demonstrate that:

1. Surgical resection and transplantation remain essential curative strategies for selected patients.
2. Minimally invasive surgical approaches have expanded treatment possibilities while reducing perioperative morbidity.
3. Systemic therapy has undergone substantial advancement, particularly following the emergence of immune checkpoint inhibitors.
4. Precision medicine approaches incorporating biomarkers, genomics, artificial intelligence, and liquid biopsy represent the future direction of individualized HCC care.

Comparison with Previous Literature:

Historically, HCC treatment was limited by the dual challenge of malignancy and underlying liver dysfunction. Earlier treatment models primarily focused on tumor size and anatomical resectability.

The development of the BCLC staging system represented an important advancement by integrating:

- Tumor characteristics
- Liver function
- Patient performance status

into therapeutic decision-making [74].

However, increasing evidence suggests that rigid application of staging systems may not fully capture tumor biology and individual patient variability [146].

Recent studies have demonstrated that selected patients beyond traditional criteria may benefit from aggressive approaches, including expanded surgical indications, combination therapies, and transplantation strategies [147].

Clinical Implications:

Surgical Decision-Making

Modern hepatobiliary surgery requires careful patient selection rather than simple application of tumor size criteria.

Advanced surgical planning incorporating:

- Three-dimensional reconstruction
- Intraoperative ultrasound
- Fluorescence imaging
- Future liver remnant assessment

has improved safety and expanded resection possibilities [148].

Integration of Immunotherapy

The emergence of immunotherapy has changed treatment algorithms for advanced HCC.

Combination approaches such as:

- PD-L1 inhibition plus VEGF blockade
- Dual immune checkpoint blockade

have demonstrated meaningful survival improvements [112,114].

Future clinical practice will likely involve earlier integration of immunotherapy with surgery and locoregional treatment.

Importance of Multidisciplinary Care

MDT-based decision-making allows individualized treatment selection by combining expertise across multiple specialties.

This approach is particularly important for:

- Complex surgical cases
- Recurrent disease
- Borderline resectable tumors
- Patients requiring combined treatment strategies [125].

Current Controversies:

Surgical Expansion beyond Traditional Criteria:

One ongoing debate concerns whether patients with:

- Multiple tumors
- Portal vein invasion
- Large tumors

should undergo aggressive surgical treatment.

While selected patients may achieve meaningful survival, appropriate selection remains challenging [149].

Optimal Sequencing of Immunotherapy and Surgery:

Important unanswered questions include:

- Should immunotherapy be administered before surgery?
- Which patients benefit from neoadjuvant therapy?
- How should response be assessed?

Clinical trials addressing these questions are ongoing.

Biomarker-Guided Treatment Selection:

Although molecular classification has improved understanding of HCC biology, clinically validated predictive biomarkers remain limited.

Future studies must identify reliable biomarkers capable of predicting:

- Immunotherapy response
- Drug resistance
- Recurrence risk

Future Perspectives:

The future management of HCC will likely involve:

1. Personalized Treatment Algorithms

Combining:

- Clinical data
- Imaging
- Genomics
- Immune profiling

to determine optimal therapy.

2. AI-Enhanced Clinical Decision Systems

AI may assist physicians by integrating large-scale clinical information to predict:

- Treatment response
- Recurrence probability
- Survival outcomes

3. Combination Therapeutic Strategies

Future research will focus on combinations of:

- Surgery
- Immunotherapy
- Targeted therapy
- Locoregional treatment

to maximize tumor control.

4. Translational Research

Improved collaboration between laboratory scientists and clinicians will accelerate discovery of:

- New biomarkers
- Novel therapeutic targets
- Personalized treatment approaches

LIMITATIONS

This review has several limitations.

First, as a narrative review, potential selection bias cannot be completely excluded despite comprehensive literature searching.

Second, significant heterogeneity exists among published studies regarding:

- Patient populations
- Tumor stages
- Treatment protocols
- Outcome definitions

Third, many emerging technologies, including AI, liquid biopsy, and molecular-guided therapy, remain under clinical investigation and require prospective validation.

Fourth, differences in healthcare systems, resource availability, and institutional expertise may influence the applicability of certain treatment strategies worldwide.

CONCLUSION

Hepatocellular carcinoma management has entered a new era characterized by multidisciplinary collaboration, surgical innovation, immunotherapy, and precision oncology.

While hepatic resection and transplantation remain fundamental curative approaches, advances in

systemic therapy, particularly immune checkpoint inhibitors, have dramatically changed outcomes for patients with advanced disease.

Future progress will depend on integrating molecular biomarkers, artificial intelligence, liquid biopsy, and personalized therapeutic strategies into routine clinical practice.

A truly individualized approach combining tumor biology, liver function, patient characteristics, and emerging technologies represents the future direction of HCC management.

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