

Review

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Review

The Oncology of Liver Cancer: Integrating Molecular Insights with Therapeutic Innovation

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Abstract

Liver cancer, predominantly hepatocellular carcinoma (HCC), represents a major global health challenge due to its rising incidence and high mortality rates. This review provides a comprehensive overview of liver cancer pathogenesis, emphasizing the complex interplay of viral infections, metabolic disorders, and genetic alterations driving tumor development. We detail the classification of primary liver cancers and highlight the distinctive molecular and clinical features of HCC and intrahepatic cholangiocarcinoma. Advances in research have led to improved understanding of tumor biology and immune microenvironment, fostering the emergence of targeted therapies and immunotherapies. From the historic reliance on surgical resection and sorafenib to the recent approval of immunotherapy combinations such as atezolizumab plus bevacizumab, therapeutic strategies have evolved substantially, offering improved patient outcomes. Despite these advances, challenges remain in early diagnosis, treatment resistance, and biomarker development. Future directions focus on personalized medicine, novel combination therapies, and global accessibility to enhance survival and quality of life for liver cancer patients. This review synthesizes current knowledge and future perspectives, aiming to inform ongoing efforts to combat this formidable malignancy.

Keywords: therapeutics; hepatocellular carcinoma; pathogenesis; etiology; precise medicine

1. Introduction

Liver cancer is among the most common and deadly malignancies worldwide, ranking as the fourth leading cause of cancer-related mortality [1]. Its incidence continues to rise globally, driven primarily by the increasing prevalence of chronic liver diseases, including viral hepatitis infections and metabolic syndromes [2]. Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancer cases, representing a significant clinical and public health challenge due to its aggressive nature and poor prognosis [3]. The complexity of liver cancer arises from the interplay of various etiological factors and molecular alterations, often compounded by late diagnosis and limited therapeutic options. Despite improvements in diagnostic imaging and the introduction of systemic therapies, such as multikinase inhibitors and immunotherapies, survival rates remain dismal for many patients [4, 5]. This underscores the critical need for comprehensive understanding of liver cancer biology, early detection methods, and more effective treatment strategies.

2. Cancer and Its General Mechanisms

Cancer is fundamentally a disease of dysregulated cell growth, involving genetic and epigenetic changes that disrupt cell cycle control, apoptosis, angiogenesis, and metastatic capability. In liver cancer, key mutations in genes such as TP53, CTNNB1, and others in the Wnt/ β -catenin pathway frequently occur [6, 7]. Chronic damage to the liver from viral, metabolic, or toxin-based insults leads to sustained inflammation, fibrosis, and oxidative stress, which together facilitate accumulation of DNA damage and promote a tumor-permissive microenvironment [8, 9]. The immune microenvironment in HCC also plays a significant role in enabling immune evasion, with tumor-associated macrophages, regulatory T cells, and checkpoint pathway activation being important mediators [10].

3. Types of Liver Cancer

The majority (\approx 75-85 %) of primary liver cancers are hepatocellular carcinoma (HCC), arising from hepatocytes in the setting of chronic liver injury [11, 12]. HCC is strongly associated with risk factors such as chronic hepatitis B and C infections, alcohol abuse, and increasingly NAFLD/NASH [13, 14]. Intrahepatic cholangiocarcinoma (iCCA), accounting for about 10-15 % of primary liver cancers, emerges from bile duct epithelium and often exhibits distinct molecular alterations (e.g. in IDH1/2, FGFR) and worse prognosis due to late presentation [15]. Rare forms include hepatoblastoma in children, and vascular tumors such as angiosarcoma; these are less common but have unique etiologies and biology [16].

Primary liver cancers encompass several histological types with distinct cellular origins and molecular characteristics, as summarized in Table 1.

Table 1. Types of Primary Liver Cancer: Clinical and Molecular Features.

Type	Cell of Origin	Prevalence (%)	Key Molecular Alterations	Prognosis
Hepatocellular Carcinoma (HCC)	Hepatocytes	75–85	TP53, CTNNB1 mutations	Variable, generally poor
Intrahepatic Cholangiocarcinoma (iCCA)	Bile duct epithelium	10–15	IDH1/2 mutations, FGFR fusions	Poor
Hepatoblastoma	Fetal liver progenitors	Rare (pediatric)	Various embryonic gene alterations	Variable, better with treatment
Angiosarcoma	Endothelial cells	Very rare	Complex karyotype	Very poor

4. Liver Cancer Etiology: Risk Factors and Pathogenesis

Chronic viral hepatitis (HBV, HCV) remains a dominant etiologic contributor to HCC, mediating ongoing liver inflammation, fibrosis, and promoting genetic instability over years [17, 18]. Alcohol use causes direct hepatocellular injury, promotes oxidative stress, and induces fibrotic pathways leading to cirrhosis, another strong risk for HCC [19]. NAFLD and its inflammatory form NASH have become major contributors in many regions, driven by obesity, insulin resistance, and metabolic syndrome [20]. Environmental toxins like aflatoxins also induce mutational signatures (e.g. in TP53) that increase HCC risk [21]. Genetic and epigenetic alterations contribute significantly: besides point mutations, copy number alterations, chromatin remodeling, and methylation changes are evident in many HCC tumors [22, 23].

To better understand the etiology of liver cancer, it is important to consider the major risk factors contributing to its development (Table 2).

Table 2. Major Risk Factors Associated with Liver Cancer.

Risk Factor	Mechanism/Contribution	References
Chronic Hepatitis B Virus (HBV)	Chronic inflammation, integration of viral DNA into host genome	[13,17]
Chronic Hepatitis C Virus (HCV)	Persistent liver injury, fibrosis	[13,17,18]
Alcohol Consumption	Hepatocyte toxicity, oxidative stress, fibrosis	[19]
Non-Alcoholic Fatty Liver Disease (NAFLD) / NASH	Metabolic syndrome, insulin resistance, inflammation	[20]
Aflatoxin Exposure	DNA mutagenesis (e.g., TP53 mutations)	[21]
Genetic/Epigenetic Alterations	Oncogenic mutations, chromatin remodeling	[22,23]

5. Past and Present Research Status in Liver Cancer

Historically, treatments were dominated by liver resection and transplantation for early disease, and systemic therapies were largely ineffective. For advanced HCC, chemotherapy had little survival benefit [24]. The approval of sorafenib in 2007 marked a milestone: sorafenib showed modest survival benefit (median OS ~10.7 months) in advanced HCC patients over placebo [25]. Later, the REFLECT trial demonstrated that lenvatinib was non-inferior to sorafenib for first-line treatment, with similar overall survival (~13.6 vs. ~12.3 months) and some improvements in progression-free survival (PFS) and response rates [26]. More recently, combinations of therapies have shown superior results: the IMbrave150 trial demonstrated atezolizumab + bevacizumab improved OS (19.2 vs 13.4 months) and PFS compared to sorafenib [27]. The HIMALAYA trial showed that tremelimumab + durvalumab also had better outcomes over sorafenib in first-line advanced settings, with median OS around 16.4 months [28].

Over the past two decades, multiple therapeutic agents have been developed and approved for advanced hepatocellular carcinoma, with their key features outlined in Table 3.

Table 3. Major Therapeutic Agents Approved for Advanced HCC.

Drug Name	Drug Class	Mechanism of Action	Approval Year	Key Clinical Trial(s)	Median OS Benefit
Sorafenib	Multikinase inhibitor	VEGFR, PDGFR, Raf kinase inhibition	2007	SHARP [25]	~3 months
Lenvatinib	Multikinase inhibitor	VEGFR, FGFR, PDGFR inhibition	2018	REFLECT [26]	Non-inferior to sorafenib
Atezolizumab + Bevacizumab	Immunotherapy + Anti-VEGF	PD-L1 blockade + VEGF inhibition	2020	IMbrave150 [27]	~6 months improvement
Tremelimumab + Durvalumab	Dual Immune Checkpoint Inhibitors	CTLA-4 and PD-L1 blockade	2022	HIMALAYA [28]	Improved OS
Regorafenib	Multikinase inhibitor	VEGFR, TIE2, PDGFR inhibition	2017	RESORCE [29]	~3 months

6. Therapeutic Advances in Liver Cancer Treatment

The systemic therapy landscape for HCC has expanded significantly. First-line options now include not just TKIs (sorafenib, lenvatinib) but immunotherapy combinations. Atezolizumab + bevacizumab and tremelimumab + durvalumab are now approved first-line treatments, showing better survival and tolerability compared to sorafenib in appropriate patients [27, 28]. For second-line settings, agents such as regorafenib, cabozantinib, ramucirumab (especially in patients with elevated AFP) have demonstrated survival benefits in patients who progressed on sorafenib [29, 30]. Immune checkpoint inhibitors (nivolumab, pembrolizumab) have shown durable responses in early trials and are being explored further, though some phase III trials did not meet predefined endpoints for

statistical significance [31, 32]. Combination therapies (ICI + anti-angiogenic, ICI + TKI, or locoregional + immunotherapy) are increasingly under study to overcome resistance and improve response rates [33, 34].

7. Future Directions and Needs

Despite progress, challenges persist. Early detection remains difficult; many patients present with advanced disease. Better biomarkers (molecular, imaging, or liquid biopsy) are needed to identify HCC earlier. Personalized treatment based on genetic, epigenetic, and immunological profiling could help choose therapies that are more likely to succeed in individual patients [35, 36]. Also, there is a need to understand and mitigate resistance to immunotherapy and targeted agents; exploring novel combinations, adaptive treatment regimens, and perhaps cell-based therapies like CAR-T or vaccines might be fruitful [37, 38]. Finally, improving safety profiles and access to therapies in lower-resource settings will be important for global impact [39, 40].

Despite therapeutic advances, several challenges remain in liver cancer management, highlighting the need for focused research priorities (Table 4).

Table 4. Challenges and Future Research Needs in Liver Cancer.

Challenge	Description	Potential Solutions	References
Early Detection	Lack of sensitive biomarkers; late diagnosis	Liquid biopsies, advanced imaging	[35,36]
Therapy Resistance	Resistance to TKIs and immunotherapies	Combination therapies, novel agents	[33,37]
Biomarker Development	Few predictive biomarkers for treatment response	Genomic and immune profiling	[35,36]
Access to Care	Disparities in healthcare availability worldwide	Affordable drugs, global policies	[39,40]
Personalized Medicine	Heterogeneous tumor biology and patient response	Molecular subtyping, precision oncology	[35]

8. Conclusions

Liver cancer, and hepatocellular carcinoma (HCC) in particular, remains a formidable global health challenge despite significant therapeutic advances over the past decade. The introduction of immune checkpoint inhibitors and combination regimens has redefined treatment paradigms and offered meaningful clinical benefit for some patients. However, overall outcomes remain suboptimal, with limited durability of response and a substantial proportion of patients failing to benefit from current therapies. These limitations highlight the pressing need for continued research focused on early detection, reliable predictive and prognostic biomarkers, and more effective, personalized treatment strategies.

The integration of molecular profiling, deeper understanding of the tumor immune microenvironment, and the development of novel therapeutic combinations hold promise for overcoming resistance and improving patient outcomes. Equally important is the global accessibility of these innovations, particularly in regions with high liver cancer incidence and limited healthcare resources. Moving forward, a multidisciplinary and precision medicine-driven approach will be essential to translate scientific progress into sustained survival benefits and improved quality of life for patients with liver cancer.

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