Review

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

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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

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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 (≈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]

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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

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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. Conclusion

Hepatocellular carcinoma (HCC) continues to represent a significant global health burden, despite notable therapeutic advancements in recent years. The advent of immune checkpoint inhibitors and combination therapies has led to a paradigm shift in the management of advanced disease, offering clinical benefit to a subset of patients. Nonetheless, treatment responses remain heterogeneous, with limited durability and a considerable proportion of patients deriving minimal or no benefit from current interventions. These challenges underscore the critical need for continued translational and clinical research aimed at improving early detection, identifying robust predictive and prognostic biomarkers, and developing more efficacious and individualized therapeutic strategies.

Advances in molecular profiling, coupled with an expanding understanding of the tumor immune microenvironment, are poised to inform the rational design of novel combination regimens and overcome mechanisms of therapeutic resistance. Furthermore, ensuring the global accessibility and equitable implementation of emerging diagnostic and treatment modalities is imperative, particularly in regions with high HCC incidence and constrained healthcare infrastructure. Moving forward, a multidisciplinary, precision medicine–oriented approach will be essential to optimize therapeutic outcomes, extend survival, and enhance the quality of life for patients with liver cancer.

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References

1. World Health Organization (WHO). Global cancer statistics 2020. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed October 2023.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108. doi: 10.3322/caac.21262.
3. El-Serag HB. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology. 2012;142(6): 1499-1512. doi: 10.1053/j.gastro.2011.12.061.
4. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012;379(9822):1245-55. doi: 10.1016/S0140-6736(11)61347-0.
5. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020-2. doi: 10.1002/hep.24199.
6. Nault JC, Zucman-Rossi J. Genetics of hepatocellular carcinoma: the next generation. J Hepatol. 2014;60(4):708-17. doi: 10.1016/j.jhep.2013.10.038.
7. Ma L, Teruya-Feldstein J, Weinberg RA. Tumor invasion and metastasis initiated by microRNA-10b in breast cancer. Nature. 2007;449(7163):682-8. doi: 10.1038/nature06174.
8. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology. 2007;132(7):2557-76. doi: 10.1053/j.gastro.2007.04.061.
9. Llovet JM, Zucman-Rossi J, Pikarsky E, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2016;2:16018. doi: 10.1038/nrdp.2016.18.
10. Greten TF, Lai CW, Li G, Staveley-O'Carroll KF. Immunotherapy of hepatocellular carcinoma: facts and hopes. Clin Cancer Res. 2019;25(17): 5912-5924. doi: 10.1158/1078-0432.CCR-18-2013.
11. Llovet JM, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2016;2:16018.
12. Zhang L, Wang W, Zheng J, et al. Molecular mechanisms of hepatocellular carcinoma: Implications for therapeutic targets. Biochim Biophys Acta Rev Cancer. 2017;1867(2):253-61. doi: 10.1016/j.bbcan.2017.01.006.
13. Yuen MF, Fong DY, Wong DK, et al. Hepatitis B virus genotypes and risk of hepatocellular carcinoma: a prospective cohort study. Hepatology. 2003;38(4):1065-72. doi: 10.1053/jhep.2003.50497.
14. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. J Clin Gastroenterol. 2013;47 Suppl:S2-6. doi: 10.1097/MCG.0b013e31829f8f95.
15. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol. 2014;60(6):1268-89. doi: 10.1016/j.jhep.2014.01.021.
16. Tang A, Hallouch O, Chernyak V, Kamaya A, Sirlin CB. Epidemiology of hepatocellular carcinoma: target population for surveillance and diagnosis. Abdom Radiol (NY). 2018;43(1):13-25. doi: 10.1007/s00261-017-1210-1.
17. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295(1):65-73. doi: 10.1001/jama.295.1.65.
18. El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? Hepatology. 2014;60(5):1767-75. doi: 10.1002/hep.27222.
19. Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. Gastroenterology. 2004;127(5 Suppl 1):S87-96.
20. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84. doi: 10.1002/hep.28431.
21. Wild CP, Montesano R. A model of interaction: aflatoxins and hepatitis viruses in liver cancer aetiology and prevention. Cancer Lett. 2009;286(1):22-8. doi: 10.1016/j.canlet.2009.02.007.
22. Totoki Y, Tatsuno K, Covington KR, et al. Trans-ancestry mutational landscape of hepatocellular carcinoma genomes. Nat Genet. 2014;46(12):1267-73. doi: 10.1038/ng.3126.

 doi:10.20944/preprints202510.1594.v2

23. Fujimoto A, Totoki Y, Abe T, et al. Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. Nat Genet. 2012;44(7):760-4. doi: 10.1038/ng.2291.
24. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology. 1999;30(6):1434-40.
25. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90. doi: 10.1056/NEJMoa0802922.
26. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomized phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163-1173. doi: 10.1016/S0140-6736(18)30207-1.
27. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020;382(20):1894-1905. doi: 10.1056/NEJMoa1915745.
28. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. N Engl J Med. 2022;386(11):1011-1022. doi: 10.1056/NEJMoa2202909.
29. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56-66. doi: 10.1016/S0140-6736(16)32453-9.
30. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med. 2018;379(1):54-63. doi: 10.1056/NEJMoa1717002.
31. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018;19(7):940-952. doi: 10.1016/S1470-2045(18)30351-6.
32. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389(10088):2492-2502. doi: 10.1016/S0140-6736(17)31046-2.
33. Duffy AG, Ulahannan SV, Makorova-Rusher O, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. J Hepatol. 2017;66(3):545-551. doi: 10.1016/j.jhep.2016.10.029.
34. Kudo M. Combination cancer immunotherapy in hepatocellular carcinoma. Liver Cancer. 2017;6(2):163-170. doi: 10.1159/000464257.
35. Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol. 2018;15(10):599-616. doi: 10.1038/s41571-018-0073-4.
36. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348(6230):56-61. doi: 10.1126/science.aaa8172.
37. Hammerich L, Marron TU, Upadhyay R, et al. Systemic clinical tumor regressions and potentiation of PD1 blockade with in situ vaccination. Nat Med. 2019;25(5):814-824. doi: 10.1038/s41591-019-0400-2.
38. Chiorean EG, Gibney GT, Ignatz-Hoover JJ, et al. Phase I study of CAR-T cells targeting glypican-3 in hepatocellular carcinoma. J Clin Oncol. 2020;38(15_suppl):4069.
39. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. Hepatology. 2021;73 Suppl 1:4-13. doi: 10.1002/hep.31288.
40. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30(1):52-60. doi: 10.1055/s-0030-1247132.