

Hepatocellular Carcinoma: Prevention, Diagnosis, and Treatment

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Highlights of the Study

- Hepatocellular carcinoma is a global health challenge.
- Common risk factors include hepatitis B or C infections, excessive alcohol consumption, and metabolic dysfunction.
- Disease stage influences prognosis, therefore, implementing cost-effective surveillance and screening programs for high-risk groups saves lives.
- Treating advanced hepatocellular carcinoma remains a challenge; continued efforts in prevention, early detection, and treatment can significantly improve prognosis of this disease.

Keywords

Hepatocellular carcinoma · Risk factors · Prevention · Early detection · Ultrasound

Abstract

Hepatocellular carcinoma (HCC), the most prevalent form of liver cancer globally, poses a substantial health burden. Influenced by risk factors such as hepatitis B or C virus infections, chronic consumption of alcohol, and metabolic dysfunction, its exact etiology likely involves a complex interplay between viral infection, hepatocyte mutations, and chronic liver diseases like cirrhosis and metabolic dysfunction-associated steatohepatitis, and demographic variables like sex, race, and age. Disease stage significantly impacts the prognosis of HCC. There is significant potential for life-saving and socioeconomic benefits through the implementation of surveillance programs and the introduction of low-cost

screening measures for high-risk groups; these screening measures include ultrasound imaging and blood tests. Treatment options for HCC encompass liver resection, transplantation, transarterial chemoembolization, radiation therapy, chemotherapy, targeted therapy, and immunotherapy. Despite therapeutic advances, treating advanced HCC remains challenging, emphasizing the need for continued efforts in prevention, early detection, and development of treatments to improve prognosis and long-term survival.

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Introduction

Hepatocellular carcinoma (HCC) ranks as the fourth most common cancer globally, registering an incidence of 840,000 cases in 2018 [1]. Increasing incidence of liver

cancer, likely attributable to rising metabolic disorders such as obesity and type 2 diabetes [2], projects over 1 million new cases by 2025 [1]. HCC alone accounts for approximately 90% of all cases of liver cancer [1]. The prognosis of HCC closely correlates with the stage of the disease, with a 5-year survival rate ranging from 36% for early stage cases to a mere 13% for late-stage metastatic cases [3]. Although the risk factors causing HCC are relatively well-defined, the genetic determinants, such as tumor-driving mutations, remain incompletely understood. Early detection of HCC by surveillance of high-risk populations, primarily by noninvasive methods such as ultrasonography or assessment of levels of serum α -fetoprotein, therefore, may not only save lives but also yield positive socioeconomic impacts on countries, particularly in countries with high incidence of HCC [4, 5]. In this review, we analyze recent literature regarding the risk factors, mechanisms, diagnosis, prevention, and treatment of HCC. We propose that continued endeavors in prevention, early detection, and therapeutic advancements will enhance outcomes and increase the long-term survival rates of HCC patients.

Risk Factors of HCC

Risk factors associated with HCC are multifaceted and encompass various elements. The most important risk factors of HCC are infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), exposure to aflatoxin B1 (AFB1), excessive alcohol intake, metabolic dysfunction-associated steatohepatitis (MASH), and demographic factors like sex, race, and age. Geographically, regions with the highest incidence of HCC include East and Southeast Asia, Africa, and developed nations such as the USA [6].

Epidemiologic studies have elucidated that different risk factors have a distinct impact on HCC within specific regions. In Asia and Africa, over 60% of HCC are associated with HBV infection [7]. A majority of HBV-associated HCC (>85%) occur in individuals with cirrhosis [8]. HBV contributes to HCC through at least two mutually nonexclusive mechanisms. First, HBV is a DNA virus that can integrate into the host genome, which may lead to insertional mutagenesis that inactivates or alters the expression of genes in proximity. For example, *TERT*, the gene encoding telomerase, is one of the most frequently upregulated oncogenes in HCC. Insertion of HBV genes into the promoter region is a well-characterized mechanism to activate *TERT* in HCC. Other recurrent oncogenic mutations mediated by HBV insertion include *KMT2B*, which encodes a histone

lysine-specific methyltransferase, *SENP5*, which encodes a SUMO1/sentrin-specific peptidase, and *CCNA2* and *CCNE1*; both of these encode cyclins driving cell cycle progression [9]. Increased expression of telomerase and cyclins lead to unchecked cell proliferation, replicative stresses, and genomic reorganization, all of which are defining features of cancer. Besides insertional mutagenesis, HBV infection causes chronic inflammation and activation of the immune system. These immune responses lead to the death of hepatocytes, fibrosis, and cirrhosis which ultimately contribute to HCC. Furthermore, concurrent infection with the Hepatitis D virus in individuals already positive for HBV may heighten the risk of developing HCC [10].

Hepatitis C virus (HCV) infection is another significant risk factor for HCC, particularly in developed regions like North America, Europe, and Japan [11]. The precise mechanism by which HCV induces liver cancer is not well understood. In contrast to HBV, HCV is an RNA virus that does not integrate into the host genome [12]. HCV infection and replication in hepatocytes cause liver inflammation, which leads to cell death, fibrosis, cirrhosis, and eventually HCC [12]. Nearly, all HCV-associated HCC occur in patients with advanced hepatic fibrosis or cirrhosis [13]. Several HCV viral proteins, including the core protein, nonstructural protein 3 (NS3), and nonstructural protein 5A (NS5A), have been identified to modulate host signaling and immune response pathways [14, 15], contributing to uncontrolled hepatocyte growth and hepatocarcinogenesis. For example, the HCV core protein regulates host cell proliferation, apoptosis, and lipid metabolism by modulating various pathways that involve transforming growth factor β , vascular endothelial growth factor (VEGF), Wnt/ β -catenin, cyclooxygenase-2, and peroxisome proliferator-activated receptor α [15]. The viral NS3 protein promotes the ubiquitination and degradation of the protein phosphatase PPM1A, thereby enhancing the migration and invasion of HCC cells [14]. The viral NS5A protein attenuates interferon (IFN) responses and therefore makes the virus more resistant to the host immune system [16].

Dietary exposure to AFB1, a fungal toxin produced by *Aspergillus* species, also poses a significant risk for HCC [17]. AFB1 is a potent genotoxic carcinogen that forms DNA adducts and induces DNA damage [17]. Notably, exposure to AFB1 is the leading cause of HCC in regions such as Africa and Southeast Asia [18]. Additionally, exposure to AFB1 intensifies the already elevated risk of HCC in individuals infected with HBV [18].

Excessive alcohol consumption represents another noteworthy risk factor for HCC. While the precise underlying mechanism is poorly understood, prolonged

exposure to alcohol can exert liver damage through diverse pathways, including inflammation, endoplasmic reticulum stress, mitochondrial damage, and oxidative stress, which predispose individuals to conditions such as steatosis, hepatitis, and cirrhosis [19]. At the molecular level, alcohol may induce acetaldehyde toxicity, form adducts on proteins and DNA, generate excessive reactive oxygen species, and lead to changes in lipid metabolism [20]. Alcohol-related cirrhosis has been suggested to account for approximately 20–30% of the total HCC incidences [21]. In individuals with HBV infection, heavy alcohol consumers exhibited a significantly higher HCC risk compared to non-drinkers [22], indicating a synergistic role between alcohol and HBV in the development of HCC.

Patients with metabolic dysfunction-associated steatohepatitis (MASH), characterized by liver inflammation resulting from excessive fat accumulation in hepatocytes, have an increased risk of developing HCC. MASH is often associated with other metabolic conditions such as obesity and type 2 diabetes, and its prevalence has surged over the past few decades [2]. Similarly, MASH-associated HCC has increased over the years and has reached approximately 20% of the total incidence in developed countries [23]. While MASH can progress to cirrhosis, it should be noted that approximately 25–30% of MASH-associated HCC cases develop without cirrhosis [23, 24].

Genetic Mutations and Molecular Pathways Underlying HCC

Although the precise etiology of HCC remains to be fully elucidated, it is evident that HCC formation involves a multifaceted process, likely characterized by a complex interplay between viral infection, oncogenic mutations in hepatocytes, and chronic liver diseases such as alcoholic cirrhosis and MASH.

TERT activation represents the most frequently observed genetic mutation that is present in over 80% of HCC cases [25, 26]. In addition to insertional activation by HBV infection, *TERT* activation may also result from mechanisms such as chromosomal translocation and gene amplification [27, 28]. Mutations affecting the Wnt pathway have been identified in 30–50% of total HCC cases [26]. These mutations, including gain-of-function mutations in *CTNNB1*, which encodes β -catenin, and loss-of-function mutations in *APC* and *AXIN*, which encodes proteins inhibit Wnt signaling, all lead to the aberrant activation of the Wnt pathway. Interestingly, mutations in the Wnt pathway are more commonly observed in HCC patients without HBV

infections [29]. Other frequent HCC driver mutations include tumor suppressors such as *TP53*, *RB1*, and *PTEN* and oncogenes such as *CCNA2*, *CCNE1*, and genes associated with the Ras-MAPK and the PI3K-AKT-MTOR pathways. These mutations in general enable aggressive growth of tumor cells and are often associated with poor prognosis [25, 26]. Moreover, polymorphisms in *TM6SF2*, *PNPLA3*, and *HSD17B13* genes have also been implicated in HCC development [30, 31]. Recurrent chromosomal amplifications, such as 11q13 and 6q21, are frequently observed in HCC [25, 32]. These genomic regions harbor several commonly activated oncogenes including *VEGFA*, *MYC*, *CCND1*, and *FGF19* [25, 32]. Furthermore, patients with hereditary hemochromatosis (HH), often caused by an autosomal recessive mutation in the high iron gene (*HFE*), are predisposed to develop cirrhosis and HCC because of elevated iron deposition in the liver [33].

In addition to genetic mutations, the development of HCC is closely associated with the activation of several biological pathways in hepatocytes. For example, MASH and obesity, well-established risk factors for HCC, particularly in developed countries, can induce systemic endocrine abnormalities and impact immune functions [34]. MASH has been demonstrated to produce excessive oxidative stress, alter immune functions, and induce metabolic and inflammatory abnormalities [35]. Hepatocytes with excessive accumulation of fatty acids exhibit ER stress and oxidative stress [35]. In a mouse model of MASH, the induction of ER stress in hepatocytes was found to trigger hepatocarcinogenesis primarily by activating the NF- κ B and TNF-mediated inflammatory pathways [36]. Dysregulation of fatty acid catabolism in hepatocytes has been associated with a malfunction of mitochondria and an increased production of reactive oxygen species, which ultimately results in DNA damage [37]. The dysregulation of fatty acid catabolism in MASH can further contribute to HCC by promoting the expression of tumor-promoting cytokine IL-17A and excessive production of oncometabolites such as sphingolipid glucosylceramide [38, 39].

Chronic inflammation of the liver, often due to viral infection-induced hepatitis, excessive alcohol consumption, and MASH is also a significant risk factor for HCC. It has been estimated that approximately 90% of all cases of HCC are associated with chronic inflammation [40]. The liver harbors a significant population of immune cells and plays an essential role in immune response against bacterial and viral pathogens, as well as in the production of immune factors [41]. The interaction between HCC and the immune microenvironment of the liver has significant implications for disease progression. Cases of HCC with substantial immune cell infiltration generally

exhibit more favorable prognoses [40, 42]. Patients with autoimmune liver diseases, such as autoimmune hepatitis, are also known to have an increased risk of developing cirrhosis and HCC [43]. Therefore, in addition to genetic mutations, dysregulation of multiple biological pathways, including fatty acid catabolism, ER stress, oxidative stress, and inflammation, contributes to an increased risk of HCC development. The interplay between immune cells and tumor cells within the liver is currently the subject of extensive investigation [40].

The Stage and Molecular Classification of HCC

The prognosis of HCC correlates closely with the stage of the disease, with a 5-year survival rate ranging from 36% for early stage cases to only 13% for late-stage metastatic cases [3]. Various classification systems have been employed for HCC staging, such as the Barcelona Clinic Liver Cancer (BCLC) [44], Okuda [45], Cancer of the Liver Italian Program (CLIP), Italian Liver Cancer (ITALICA) [46], GReupe d'Etude et de Traitement du Carcinoma Hépatocellulaire (GRETCH) [47], Tumor Node Metastasis Staging (TNM) [48], Japan Integrated Stating (JIS) [49], Chinese University Prognostic Index (CUPI) [50], Eastern Staging [51], Hong Kong Liver Cancer (HKLC) [52], Model to Estimate Survival in Ambulatory HCC patients (MESIAH) [53], and China Liver Cancer (CNLC) systems [54, 55]. Despite the use of different criteria and variables to stage HCC, these systems commonly consider factors such as tumor size and number, vascular invasion, nodal spread, metastasis, liver function, and underlying liver disease. For instance, the widely used BCLC system classifies HCC into five stages, ranging from very early stage 0 (characterized by a single small tumor ≤ 2 cm without symptoms) to advanced stage C (in which cancer has spread within the liver and other body parts) and end-stage D (in which liver function is severely impaired and significant symptoms are present) [44]. Due to the heterogeneity of HCC, there is no globally accepted HCC staging system. Nonetheless, all existing systems have played a crucial role in patient stratification, treatment decisions, and prognosis [56].

HCC can also be classified based on underlying driver mutations and histopathological features into proliferation and nonproliferation tumors [57, 58]. Proliferation class tumors, accounting for approximately 50% of HCC cases, often carry mutations in the tumor suppressor gene *TP53* and amplification of genomic regions containing *FGF19* or *CCND1* [32]. Patients with proliferation class HCC are commonly associated with HBV infection and have poorer prognoses [32]. Depending on the activation of additional

oncogenic signaling pathways, proliferation class HCC can be subdivided into two subclasses: proliferation-progenitor subclass (approximately 30% of cases) and proliferation-Wnt-TGF β subclass (approximately 20% of cases) [58]. In the proliferation-progenitor subclass, tumor cells typically express progenitor markers such as α -fetoprotein (AFP) and EPCAM, while pathways promoting tumor proliferation such as PI3K-ATK-mTOR, RAS-MAPK, and IGF signaling are highly active [57]. In the proliferation-Wnt-TGF β subclass, the noncanonical Wnt pathway and TGF β signaling are activated in tumor cells [57].

Nonproliferation class tumors, accounting for the other 50% of HCC cases, are often associated with HCV infection and excessive alcohol consumption [32, 57]. Patients with nonproliferation HCC generally have better prognoses. Similarly, based on additional oncogenic pathways, nonproliferation HCC can be divided into two subclasses: canonical Wnt/ β -catenin pathway activated subclass and IFN α pathway activated subclass [32, 59].

Prevention and Surveillance

Prevention and surveillance strategies play crucial roles in addressing HCC, given the well-defined risk factors associated with its development. HCC commonly arises from underlying liver diseases, such as viral hepatitis, cirrhosis, MASH, and obesity, making prevention of these precursor liver diseases an effective approach to HCC prevention. One successful preventive measure is the administration of the HBV vaccine in regions with high HBV infections, which has significantly reduced the incidence of HCC [60]. Antiviral therapies targeting viral hepatitis, such as nucleotide and nucleoside analog drugs for HBV and IFNs for HCV, have proven highly effective in reducing HCC incidence [61–63]. Moreover, weight loss and medications like statins and metformin have been implicated in reducing HCC incidence in high-risk populations [64–66].

Early detection of HCC is crucial as the disease is often diagnosed only when symptoms become apparent, typically at an advanced stage. It is well-established that the 5-year survival rate of HCC is closely correlated with the stage of the disease [3]. Tumors of early stage HCC are small and more likely to be cured. Therefore, implementing surveillance programs to detect HCC at its earliest stage among high-risk populations would have a significant impact on saving lives and improving socioeconomic outcomes [4, 5]. Individuals with lower household income and education, who are usually less accessible to healthcare, are often regrettably associated with advanced disease and poorer prognosis in HCC patients [67].

The cost-effectiveness of a liver cancer surveillance program can be influenced by several key factors. First, targeting high-risk populations is essential for effective surveillance. For instance, by focusing on individuals with chronic liver disease or hepatitis B or C infection, who are at an increased risk of developing liver cancer, screening efforts can be directed toward those most likely to benefit from early detection and treatment. Second, employing cost-effective screening methods is crucial [68–70]. Utilizing relatively less expensive screening tools, such as ultrasound and blood tests, can help identify individuals who require further evaluation. Reserved use of more expensive imaging techniques like computed tomography (CT) scans or magnetic resonance imaging (MRI) for follow-up diagnosis in patients can optimize resource allocation and cost-effectiveness. Third, streamlining diagnostic and treatment pathways, including quickly referring patients who are diagnosed to appropriate treatment providers, are important. Furthermore, raising public awareness and educating the population about liver cancer and its risk factors is crucial, particularly in developing countries where knowledge may be limited. Increasing participation in surveillance programs can enhance the cost-effectiveness and overall impact of detecting liver cancer at an early stage [68–70].

Diagnosis

Diagnosis of liver cancer typically involves a comprehensive approach consisting of physical examination, imaging modalities, and laboratory investigations. The primary imaging tests for liver cancer diagnosis are ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). A liver biopsy may be performed to confirm the diagnosis. Furthermore, several laboratory tests, such as liver function tests and the alpha-fetoprotein (AFP) test, are routinely conducted for liver cancer diagnosis or monitoring disease progression [71–74].

Ultrasound often serves as the initial imaging modality in liver cancer diagnosis due to its noninvasive nature, relatively low cost, and absence of ionizing radiation exposure [71–74]. Ultrasound has reported sensitivity and specificity ranges of 51–87% and 80–100%, respectively, in diagnosing HCC [75–77]. However, the limitation of ultrasound is its inability to detect small tumors (<1 cm in diameter) or differentiate between cancerous and noncancerous lesions. Diagnosis of small tumors usually requires other imaging techniques such as CT scans and MRI. CT scans, which use X-rays to produce detailed images of the liver and surrounding tissues, are also commonly used in liver cancer

diagnosis [71–74]. CT scans can provide information about the size, location, and characteristics of liver tumors. This imaging technique involves acquiring multiple X-ray images of the liver from various angles, which are subsequently processed by a computer to generate detailed cross-sectional images. The sensitivity and specificity of CT scans in HCC diagnosis range from 63 to 76% and 87 to 98%, respectively [76, 78, 79]. MRI represents another commonly utilized imaging technique for liver cancer diagnosis [71–74], providing detailed information about the size, location, and characteristics of liver tumors, as well as information about blood flow. The documented sensitivity and specificity of MRI in HCC diagnosis ranged from 77 to 90% and 84 to 97%, respectively [76, 78, 79]. Recently, abbreviated MRI (AMRI), which involves fewer sequences than a complete MRI, has emerged as a promising tool for HCC screening and surveillance [80, 81]. AMRI demonstrated enhanced sensitivity and specificity than ultrasound for the detection of early stage HCC while also being more cost-effective in terms of imaging time and expenses compared to complete MRI protocols. These features make AMRI an alternative to other imaging approaches [80, 81].

A liver biopsy is often used in the diagnosis and management of liver cancer [71–74]. Both ultrasound and CT scans can be used to guide liver biopsies. Compared to imaging, a liver biopsy provides a direct examination of the liver tissue, which can help confirm the presence of cancer and provide important information about the characteristics of cancers, as well as guide treatment decisions.

Treatment

Treatment approaches for HCC encompass various modalities, including liver resection, liver transplant, transarterial chemoembolization (TACE), radiation therapy, chemotherapy, targeted therapy, and immunotherapy. Surgical intervention is typically employed when the tumor is small and localized, involving the removal of the cancerous portion of the liver. The amount of liver removed depends on the location and size of the tumor, and the patient's liver function. The 5-year survival of surgically treated HCC patients can reach 70–80% [74, 82]. Liver transplantation is an option for patients with early stage HCC who have cirrhosis and are unsuitable for liver resection [83]. Liver transplantation may achieve a 50–60% 10-year survival rate with a 10–20% recurrence rate [84].

TACE is a commonly used, image-guided, minimally invasive treatment for HCC [85]. This approach involves the delivery of a high dose of chemotherapy directly to

blood vessels supplying the tumor and the placement of an embolic agent inside these blood vessels, which effectively traps chemotherapy and obstructs blood flow to the tumor. By specifically targeting the blood vessels supplying the tumor, TACE minimizes exposure to chemotherapy to the rest of the body. TACE is most beneficial to patients with tumors predominantly within the liver, while its efficacy is limited in cases of widespread metastases [72]. Hepatic arterial infusion chemotherapy (HAIC) has been employed to treat advanced HCC patients with tumors refractory to TACE [86]. HAIC administers chemotherapy directly into the main blood vessel, the hepatic artery, supplying the liver. Compared to systemic chemotherapy, HAIC allows for a higher concentration of chemotherapy within the liver [86].

Radiofrequency or microwave-mediated tumor ablation is used to treat small tumors that are difficult to remove surgically. These methods use high-frequency radio waves or microwaves to heat and destroy cancer cells, with comparable survival rates to surgical intervention in early stage HCC patients with single small tumors (<4 cm in diameter) or 2 to 3 small tumors (<3 cm in diameter) [73, 82]. Several studies have documented similar efficacies between radiofrequency and microwave-mediated HCC ablation [87, 88].

Radiation therapy is a commonly employed treatment modality for HCC [89]. Radiation damages genomic DNA and induces apoptosis, which primarily affects rapidly dividing cells such as tumor cells. Several radiation therapy techniques have been reported for HCC treatment [89]. Conventional external beam radiation delivers high-energy radiation to the liver daily over several weeks. Stereotactic body radiation precisely targets the tumor using highly focused radiation beams and high doses in a limited number of sessions. Brachytherapy, which can be used for small liver tumors that cannot be surgically removed, has been used to eliminate tumor cells by placing radioactive seeds or pellets into the liver tissue adjacent to the tumor. Furthermore, radio-embolization, which involves injecting radioactive beads directly into the artery that supplies blood to the tumor, has also been used to restrict blood supply to the tumor and cause tumor cell death [90].

Systemic chemotherapy, which administers drugs intravenously or orally, is an important treatment modality for advanced HCC. One notable breakthrough is the development of Sorafenib (Nexavar®), an FDA-approved oral multi-tyrosine kinase inhibitor (TKI) that has been used since 2007 [91]. Before the availability of sorafenib, chemotherapy drugs were primarily chemicals that induced DNA damage or

disrupted DNA synthesis, often exhibiting high toxicity and modest effectiveness. Sorafenib represents the first targeted therapy drug that specifically inhibits multiple tyrosine kinases, such as the RAF kinase and VEGF receptors (VEGFR), which promote HCC tumor cell proliferation and tumor angiogenesis, respectively [91]. In patients with advanced HCC, sorafenib has demonstrated a significant slowing of tumor progression and improvement in overall survival [92].

Lenvatinib is another potent TKI that specifically inhibits the activities of VEGFR, FGF receptors, PDGF receptors, RET, and KIT. Lenvatinib has demonstrated non-inferiority to sorafenib and has been approved by the EMA and FDA as a first-line therapy [93].

In recent years, immunotherapy, particularly the use of immune checkpoint inhibitors (ICIs), has emerged as a promising therapeutic approach for advanced HCC, especially when combined with other treatment modalities [94]. The immune checkpoint is a regulatory mechanism in the immune system that prevents excessive immune reactions and maintains self-tolerance. However, cancer cells can exploit these checkpoints to evade immune destruction. By inhibiting immune checkpoints, such as the programmed cell death protein 1 and CTLA4 proteins on T cells, it is possible to enhance the immune system's ability to recognize and eliminate tumor cells [95]. Several ICI, including atezolizumab, durvalumab, and camrelizumab, which target the programmed cell death protein 1 pathway, as well as tremelimumab, a monoclonal antibody that acts against CTLA4, have been demonstrated effective in treating advanced HCC patients. For instance, in the recent HIMALAYA clinical study, tremelimumab in combination with durvalumab has been demonstrated to be superior to sorafenib in patients with unresectable HCC [96].

Several recent clinical studies have demonstrated that combined therapies targeting both the immune checkpoint and tyrosine kinase pathways are superior to sorafenib treatment alone in advanced HCC patients. In the Imbrave150 clinical study, the combination of the ICI atezolizumab with the VEGFR inhibitor bevacizumab showed improved overall survival compared to sorafenib in patients with unresectable HCC [97]. In the COSMIC-312 clinical study, the combined use of atezolizumab and cabozantinib, a TKI inhibitor of MET, VEGFR, and RET, significantly improved the overall survival of advanced HCC patients compared to sorafenib alone [98]. Additionally, the CARES-310 study demonstrated that the combination of the ICI camrelizumab with rivoceranib, a TKI of VEGFR2, provided a significant survival benefit compared to sorafenib in patients with unresectable HCC

[99]. Furthermore, a recent phase Ib/II clinical trial showed that the combination of camrelizumab with FOLFOX4, a chemotherapy regimen, demonstrated safety and promising antitumor activity in advanced HCC patients [100]. These findings highlight the potential of combined therapies in the treatment of advanced HCC.

Conclusion

Despite the challenges posed by advanced HCC, significant progress has been made in understanding its risk factors, mechanisms, diagnosis, and treatment over the past 2 decades. The well-characterized risk factors for HCC present an opportunity to implement comprehensive prevention and screening programs targeting high-risk populations, potentially saving lives by identifying HCC at early, treatable stages. In addition to prevention and early detection efforts, the development of novel targeted therapies and combined therapies involving ICI and TKI holds great promise for improving the prognosis of advanced HCC. Targeted therapies that specifically address critical molecules or pathways involved in HCC tumor growth and progression offer the potential for more effective and personalized treatment options. Furthermore, the combination of targeted therapies with immunotherapies, such as ICIs, can en-

hance the immune system's ability to recognize and eliminate cancer cells. Continued research and clinical trials in the field of HCC are essential for advancing our understanding of the disease and identifying innovative treatment approaches. Through ongoing efforts in prevention, early detection, and therapeutic development, there is hope for significant improvements in the outlook for advanced HCC, ultimately leading to better patient outcomes and an increased likelihood of long-term survival.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Fei Feng and Yue Zhao conceived the study, gathered references, and wrote the manuscript. Both authors approved the final manuscript.

References

- Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021;7(1):6. <https://doi.org/10.1038/s41572-020-00240-3>
- Mantovani A, Targher G. Type 2 diabetes mellitus and risk of hepatocellular carcinoma: spotlight on nonalcoholic fatty liver disease. *Ann Transl Med*. 2017;5(13):270. <https://doi.org/10.21037/atm.2017.04.41>
- Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17–48. <https://doi.org/10.3322/caac.21763>
- Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-effectiveness of hepatocellular carcinoma surveillance: an assessment of benefits and harms. *Am J Gastroenterol*. 2020;115(10):1642–9. <https://doi.org/10.14309/ajg.00000000000000715>
- Nguyen ALT, Nguyen HTT, Yee KC, Palmer AJ, Blizzard CL, de Graaff B. A systematic review and narrative synthesis of health economic evaluations of hepatocellular carcinoma screening strategies. *Value Health*. 2021;24(5):733–43. <https://doi.org/10.1016/j.jval.2020.11.014>
- Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: new trends. *J Hepatol*. 2020;72(2):250–61. <https://doi.org/10.1016/j.jhep.2019.08.025>
- Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7–33. <https://doi.org/10.3322/caac.21708>
- Yang JD, Kim WR, Coelho R, Mettler TA, Benson JT, Sanderson SO, et al. Cirrhosis is present in most patients with hepatitis B and hepatocellular carcinoma. *Clin Gastroenterol Hepatol*. 2011;9(1):64–70. <https://doi.org/10.1016/j.cgh.2010.08.019>
- Sung WK, Zheng H, Li S, Chen R, Liu X, Li Y, et al. Genome-wide survey of recurrent HBV integration in hepatocellular carcinoma. *Nat Genet*. 2012;44(7):765–9. <https://doi.org/10.1038/ng.2295>
- Puigvehi M, Moctezuma-Velazquez C, Villanueva A, Llovet JM. The oncogenic role of hepatitis delta virus in hepatocellular carcinoma. *JHEP Rep*. 2019;1(2):120–30. <https://doi.org/10.1016/j.jhepr.2019.05.001>
- Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. *JAMA Oncol*. 2017;3(12):1683–91. <https://doi.org/10.1001/jamaoncol.2017.3055>
- Hwang JP, LoConte NK, Rice JP, Foxhall LE, Sturgis EM, Merrill JK, et al. Oncologic implications of chronic hepatitis C virus infection. *J Oncol Pract*. 2019;15(12):629–37. <https://doi.org/10.1200/JOP.19.00370>
- Lok AS, Seeff LB, Morgan TR, di Bisceglie AM, Sterling RK, Curto TM, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. *Gastroenterology*. 2009;136(1):138–48. <https://doi.org/10.1053/j.gastro.2008.09.014>

- 14 Zhou Y, Zhao Y, Gao Y, Hu W, Qu Y, Lou N, et al. Hepatitis C virus NS3 protein enhances hepatocellular carcinoma cell invasion by promoting PPM1A ubiquitination and degradation. *J Exp Clin Cancer Res.* 2017;36(1):42. <https://doi.org/10.1186/s13046-017-0510-8>
- 15 Mahmoudvand S, Shokri S, Taherkhani R, Farshadpour F. Hepatitis C virus core protein modulates several signaling pathways involved in hepatocellular carcinoma. *World J Gastroenterol.* 2019;25(1):42–58. <https://doi.org/10.3748/wjg.v25.i1.42>
- 16 Enomoto N, Sakuma I, Asahina Y, Kurosaki M, Murakami T, Yamamoto C, et al. Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. *N Engl J Med.* 1996;334(2):77–81. <https://doi.org/10.1056/NEJM199601113340203>
- 17 Hamid AS, Tesfamariam IG, Zhang Y, Zhang ZG. Aflatoxin B1-induced hepatocellular carcinoma in developing countries: geographical distribution, mechanism of action and prevention. *Oncol Lett.* 2013;5(4):1087–92. <https://doi.org/10.3892/ol.2013.1169>
- 18 Kew MC. Synergistic interaction between aflatoxin B1 and hepatitis B virus in hepatocarcinogenesis. *Liver Int.* 2003;23(6):405–9. <https://doi.org/10.1111/j.1478-3231.2003.00869.x>
- 19 Subramaniam V, Chakravarthi S, Jegasothy R, Seng WY, Fuloria NK, Fuloria S, et al. Alcohol-associated liver disease: a review on its pathophysiology, diagnosis and drug therapy. *Toxicol Rep.* 2021;8:376–85. <https://doi.org/10.1016/j.toxrep.2021.02.010>
- 20 Taniai M. Alcohol and hepatocarcinogenesis. *Clin Mol Hepatol.* 2020;26(4):736–41. <https://doi.org/10.3350/cmh.2020.0203>
- 21 Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Risk for hepatocellular carcinoma in patients with alcoholic cirrhosis: a Danish nationwide cohort study. *Ann Intern Med.* 2012;156(12):841–W295. <https://doi.org/10.7326/0003-4819-156-12-201206190-00004>
- 22 Lin CW, Lin CC, Mo LR, Chang CY, Perng DS, Hsu CC, et al. Heavy alcohol consumption increases the incidence of hepatocellular carcinoma in hepatitis B virus-related cirrhosis. *J Hepatol.* 2013;58(4):730–5. <https://doi.org/10.1016/j.jhep.2012.11.045>
- 23 Welzel TM, Graubard BI, Quraishi S, Zeuzem S, Davila JA, El-Serag HB, et al. Population-attributable fractions of risk factors for hepatocellular carcinoma in the United States. *Am J Gastroenterol.* 2013;108(8):1314–21. <https://doi.org/10.1038/ajg.2013.160>
- 24 Mittal S, El-Serag HB, Sada YH, Kanwal F, Duan Z, Temple S, et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol.* 2016;14(1):124–31.e1. <https://doi.org/10.1016/j.cgh.2015.07.019>
- 25 Guichard C, Amaddeo G, Imbeaud S, Ladeiro Y, Pelletier L, Maad IB, et al. Integrated analysis of somatic mutations and focal copy-number changes identifies key genes and pathways in hepatocellular carcinoma. *Nat Genet.* 2012;44:694–8. <https://doi.org/10.1038/ng.2256>
- 26 Schulze K, Imbeaud S, Letouze E, Alexandrov LB, Calderaro J, Rebouissou S, et al. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. *Nat Genet.* 2015;47(5):505–11. <https://doi.org/10.1038/ng.3252>
- 27 Farazi PA, Glickman J, Jiang S, Yu A, Rudolph KL, DePinho RA. Differential impact of telomere dysfunction on initiation and progression of hepatocellular carcinoma. *Cancer Res.* 2003;63(16):5021–7.
- 28 Lechel A, Holstege H, Begus Y, Schienke A, Kamino K, Lehmann U, et al. Telomerase deletion limits progression of p53-mutant hepatocellular carcinoma with short telomeres in chronic liver disease. *Gastroenterology.* 2007;132(4):1465–75. <https://doi.org/10.1053/j.gastro.2007.01.045>
- 29 de La Coste A, Romagnolo B, Billuart P, Renard CA, Buendia MA, Soubrane O, et al. Somatic mutations of the beta-catenin gene are frequent in mouse and human hepatocellular carcinomas. *Proc Natl Acad Sci U S A.* 1998;95(15):8847–51. <https://doi.org/10.1073/pnas.95.15.8847>
- 30 Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet.* 2008;40(12):1461–5. <https://doi.org/10.1038/ng.257>
- 31 Buch S, Stickel F, Trepo E, Way M, Herrmann A, Nischalke HD, et al. A genome-wide association study confirms PNPLA3 and identifies TM6SF2 and MBOAT7 as risk loci for alcohol-related cirrhosis. *Nat Genet.* 2015;47(12):1443–8. <https://doi.org/10.1038/ng.3417>
- 32 Chiang DY, Villanueva A, Hoshida Y, Peix J, Newell P, Minguez B, et al. Focal gains of VEGFA and molecular classification of hepatocellular carcinoma. *Cancer Res.* 2008;68(16):6779–88. <https://doi.org/10.1158/0008-5472.CAN-08-0742>
- 33 Crawford DHG. Hereditary hemochromatosis types 1, 2, and 3. *Clin Liver Dis.* 2014;3(5):96–7. <https://doi.org/10.1002/cld.339>
- 34 Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of non-alcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology.* 2018;67(1):123–33. <https://doi.org/10.1002/hep.29466>
- 35 Anstee QM, Reeves HL, Kotsiliti E, Govaere O, Heikenwalder M. From NASH to HCC: current concepts and future challenges. *Nat Rev Gastroenterol Hepatol.* 2019;16(7):411–28. <https://doi.org/10.1038/s41575-019-0145-7>
- 36 Nakagawa H, Umemura A, Taniguchi K, Font-Burgada J, Dhar D, Ogata H, et al. ER stress cooperates with hypernutrition to trigger TNF-dependent spontaneous HCC development. *Cancer Cell.* 2014;26(3):331–43. <https://doi.org/10.1016/j.ccr.2014.07.001>
- 37 Nishida N, Yada N, Hagiwara S, Sakurai T, Kitano M, Kudo M. Unique features associated with hepatic oxidative DNA damage and DNA methylation in non-alcoholic fatty liver disease. *J Gastroenterol Hepatol.* 2016;31(9):1646–53. <https://doi.org/10.1111/jgh.13318>
- 38 Gomes AL, Teijeiro A, Buren S, Tummala KS, Yilmaz M, Waisman A, et al. Metabolic inflammation-associated IL-17A causes non-alcoholic steatohepatitis and hepatocellular carcinoma. *Cancer Cell.* 2016;30(1):161–75. <https://doi.org/10.1016/j.ccell.2016.05.020>
- 39 Guri Y, Colombi M, Dazert E, Hindupur SK, Roszik J, Moes S, et al. mTORC2 promotes tumorigenesis via lipid synthesis. *Cancer Cell.* 2017;32(6):807–23.e12. <https://doi.org/10.1016/j.ccell.2017.11.011>
- 40 Ringelhan M, Pfister D, O'Connor T, Pikarsky E, Heikenwalder M. The immunology of hepatocellular carcinoma. *Nat Immunol.* 2018;19(3):222–32. <https://doi.org/10.1038/s41590-018-0044-z>
- 41 Kubes P, Jenne C. Immune responses in the liver. *Annu Rev Immunol.* 2018;36:247–77. <https://doi.org/10.1146/annurev-immunol-051116-052415>
- 42 Sia D, Jiao Y, Martinez-Quetglas I, Kuchuk O, Villacorta-Martin C, Castro de Moura M, et al. Identification of an immune-specific class of hepatocellular carcinoma, based on molecular features. *Gastroenterology.* 2017;153(3):812–26. <https://doi.org/10.1053/j.gastro.2017.06.007>
- 43 Lleo A, de Boer YS, Liberal R, Colombo M. The risk of liver cancer in autoimmune liver diseases. *Ther Adv Med Oncol.* 2019;11:1758835919861914. <https://doi.org/10.1177/1758835919861914>
- 44 Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis.* 1999;19(3):329–38. <https://doi.org/10.1055/s-2007-1007122>
- 45 Okuda K, Obata H, Nakajima Y, Ohtsuki T, Okazaki N, Ohnishi K. Prognosis of primary hepatocellular carcinoma. *Hepatology.* 1984;4(1 Suppl 1):3S–6S. <https://doi.org/10.1002/hep.1840040703>
- 46 The Cancer of the Liver Italian Program Clip Investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. *Hepatology.* 1998;28(3):751–5. <https://doi.org/10.1002/hep.510280322>

- 47 Chevrete S, Trinchet JC, Mathieu D, Rached AA, Beaugrand M, Chastang C. A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. *J Hepatol.* 1999;31(1):133–41. [https://doi.org/10.1016/s0168-8278\(99\)80173-1](https://doi.org/10.1016/s0168-8278(99)80173-1)
- 48 Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N, et al. Simplified staging for hepatocellular carcinoma. *J Clin Oncol.* 2002;20(6):1527–36. <https://doi.org/10.1200/JCO.2002.20.6.1527>
- 49 Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). *J Gastroenterol.* 2003;38(3):207–15. <https://doi.org/10.1007/s005350300038>
- 50 Leung TW, Tang AM, Zee B, Lau WY, Lai PB, Leung KL, et al. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. *Cancer.* 2002;94(6):1760–9. <https://doi.org/10.1002/cncr.10384>
- 51 Yang T, Zhang J, Lu JH, Yang LQ, Yang GS, Wu MC, et al. A new staging system for resectable hepatocellular carcinoma: comparison with six existing staging systems in a large Chinese cohort. *J Cancer Res Clin Oncol.* 2011;137(5):739–50. <https://doi.org/10.1007/s00432-010-0935-3>
- 52 Yau T, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. *Gastroenterology.* 2014;146(7):1691–700. <https://doi.org/10.1053/j.gastro.2014.02.032>
- 53 Yang JD, Kim WR, Park KW, Chaiteerakij R, Kim B, Sanderson SO, et al. Model to estimate survival in ambulatory patients with hepatocellular carcinoma. *Hepatology.* 2012;56(2):614–21. <https://doi.org/10.1002/hep.25680>
- 54 Zhou J, Sun HC, Wang Z, Cong WM, Wang JH, Zeng MS, et al. Guidelines for diagnosis and treatment of primary liver cancer in China (2017 edition). *Liver Cancer.* 2018;7(3):235–60. <https://doi.org/10.1159/000488035>
- 55 Xie DY, Ren ZG, Zhou J, Fan J, Gao Q. 2019 Chinese clinical guidelines for the management of hepatocellular carcinoma: updates and insights. *Hepatobiliary Surg Nutr.* 2020;9(4):452–63. <https://doi.org/10.21037/hbsn-20-480>
- 56 Pons F, Varela M, Llovet JM. Staging systems in hepatocellular carcinoma. *HPB.* 2005;7(1):35–41. <https://doi.org/10.1080/13651820410024058>
- 57 The Cancer Genome Atlas Research Network. Comprehensive and integrative genomic characterization of hepatocellular carcinoma. *Cell.* 2017;169(7):1327–41.e23. <https://doi.org/10.1016/j.cell.2017.05.046>
- 58 Rebouissou S, Nault JC. Advances in molecular classification and precision oncology in hepatocellular carcinoma. *J Hepatol.* 2020;72(2):215–29. <https://doi.org/10.1016/j.jhep.2019.08.017>
- 59 Lachenmayer A, Alsinet C, Savic R, Cabellos L, Toffanin S, Hoshida Y, et al. Wnt-pathway activation in two molecular classes of hepatocellular carcinoma and experimental modulation by sorafenib. *Clin Cancer Res.* 2012;18:4997–5007. <https://doi.org/10.1158/1078-0432.CCR-11-2322>
- 60 Chang MH, You SL, Chen CJ, Liu CJ, Lee CM, Lin SM, et al. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. *J Natl Cancer Inst.* 2009;101(19):1348–55. <https://doi.org/10.1093/jnci/djp288>
- 61 Dohmen K, Kawano A, Takahashi K, Shigematsu H, Tanaka H, Haruno M, et al. The incidence and risk factors for the development of hepatocellular carcinoma after peginterferon plus ribavirin therapy for chronic hepatitis C. *Hepatogastroenterology.* 2013;60(128):2034–8.
- 62 Ogawa E, Furusyo N, Kajiura E, Takahashi K, Nomura H, Maruyama T, et al. Efficacy of pegylated interferon alpha-2b and ribavirin treatment on the risk of hepatocellular carcinoma in patients with chronic hepatitis C: a prospective, multicenter study. *J Hepatol.* 2013;58(3):495–501. <https://doi.org/10.1016/j.jhep.2012.10.017>
- 63 Wong GL, Chan HL, Mak CW, Lee SK, Ip ZM, Lam AT, et al. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. *Hepatology.* 2013;58(5):1537–47. <https://doi.org/10.1002/hep.26301>
- 64 Zhang H, Gao C, Fang L, Zhao HC, Yao SK. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients: a meta-analysis. *Scand J Gastroenterol.* 2013;48(1):78–87. <https://doi.org/10.3109/00365521.2012.719926>
- 65 Vargas JI, Arrese M, Shah VH, Arab JP. Use of statins in patients with chronic liver disease and cirrhosis: current views and prospects. *Curr Gastroenterol Rep.* 2017;19(9):43. <https://doi.org/10.1007/s11894-017-0584-7>
- 66 Aminian A, Wilson R, Al-Kurd A, Tu C, Milinovich A, Kroh M, et al. Association of bariatric surgery with cancer risk and mortality in adults with obesity. *JAMA.* 2022;327(24):2423–33. <https://doi.org/10.1001/jama.2022.9009>
- 67 Zheng Y, Zhang X, Lu J, Liu S, Qian Y. Association between socioeconomic status and survival in patients with hepatocellular carcinoma. *Cancer Med.* 2021;10(20):7347–59. <https://doi.org/10.1002/cam4.4223>
- 68 Kansagara D, Papak J, Pasha AS, O'Neil M, Freeman M, Relevo R, et al. Screening for hepatocellular carcinoma in chronic liver disease: a systematic review. *Ann Intern Med.* 2014;161(4):261–9. <https://doi.org/10.7326/M14-0558>
- 69 Harris PS, Hansen RM, Gray ME, Massoud OI, McGuire BM, Shoreibah MG. Hepatocellular carcinoma surveillance: an evidence-based approach. *World J Gastroenterol.* 2019;25(13):1550–9. <https://doi.org/10.3748/wjg.v25.i13.1550>
- 70 Pascual S, Miralles C, Bernabe JM, Irurzun J, Planells M. Surveillance and diagnosis of hepatocellular carcinoma: a systematic review. *World J Clin Cases.* 2019;7(16):2269–86. <https://doi.org/10.12998/wjcc.v7.i16.2269>
- 71 Korean Society of Abdominal Radiology. Diagnosis of hepatocellular carcinoma with gadoteric acid-enhanced MRI: 2016 consensus recommendations of the Korean society of abdominal radiology. *Korean J Radiol.* 2017;18(3):427–43. <https://doi.org/10.3348/kjr.2017.18.3.427>
- 72 Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int.* 2017;11(4):317–70. <https://doi.org/10.1007/s12072-017-9799-9>
- 73 Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology.* 2018;67(1):358–80. <https://doi.org/10.1002/hep.29086>
- 74 Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology.* 2018;68(2):723–50. <https://doi.org/10.1002/hep.29913>
- 75 Pocha C, Dieperink E, McMaken KA, Knott A, Thuras P, Ho SB. Surveillance for hepatocellular cancer with ultrasonography vs. computed tomography: a randomised study. *Aliment Pharmacol Ther.* 2013;38(3):303–12. <https://doi.org/10.1111/apt.12370>
- 76 Hanna RF, Miloushev VZ, Tang A, Finkelstone LA, Brejt SZ, Sandhu RS, et al. Comparative 13-year meta-analysis of the sensitivity and positive predictive value of ultrasound, CT, and MRI for detecting hepatocellular carcinoma. *Abdom Radiol.* 2016;41(1):71–90. <https://doi.org/10.1007/s00261-015-0592-8>
- 77 Yoon JH, Park JW, Lee JM. Noninvasive diagnosis of hepatocellular carcinoma: elaboration on Korean liver cancer study group: national cancer center korea practice guidelines compared with other guidelines and remaining issues. *Korean J Radiol.* 2016;17(1):7–24. <https://doi.org/10.3348/kjr.2016.17.1.7>

- 78 Lee YJ, Lee JM, Lee JS, Lee HY, Park BH, Kim YH, et al. Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging-a systematic review and meta-analysis. *Radiology*. 2015;275(1):97–109. <https://doi.org/10.1148/radiol.14140690>
- 79 Liu X, Jiang H, Chen J, Zhou Y, Huang Z, Song B. Gadoteric acid disodium-enhanced magnetic resonance imaging outperformed multidetector computed tomography in diagnosing small hepatocellular carcinoma: a meta-analysis. *Liver Transpl*. 2017;23(12):1505–18. <https://doi.org/10.1002/lt.24867>
- 80 An JY, Pena MA, Cunha GM, Booker MT, Taouli B, Yokoo T, et al. Abbreviated MRI for hepatocellular carcinoma screening and surveillance. *Radiographics*. 2020;40(7):1916–31. <https://doi.org/10.1148/rg.2020200104>
- 81 Carbonell G, Taouli B. Abbreviated MR protocols for chronic liver disease and liver cancer. *Magn Reson Imaging Clin N Am*. 2021;29(3):321–7. <https://doi.org/10.1016/j.mric.2021.05.003>
- 82 European Association for Study of Liver-European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *Eur J Cancer*. 2012;48(5):599–641. <https://doi.org/10.1016/j.ejca.2011.12.021>
- 83 Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334(11):693–9. <https://doi.org/10.1056/NEJM199603143341104>
- 84 Tabrizian P, Holzner ML, Mehta N, Halazun K, Agopian VG, Yao F, et al. Ten-year outcomes of liver transplant and downstaging for hepatocellular carcinoma. *JAMA Surg*. 2022;157(9):779–88. <https://doi.org/10.1001/jamasurg.2022.2800>
- 85 Chern MC, Chuang VP, Liang CT, Lin ZH, Kuo TM. Transcatheter arterial chemoembolization for advanced hepatocellular carcinoma with portal vein invasion: safety, efficacy, and prognostic factors. *J Vasc Interv Radiol*. 2014;25(1):32–40. <https://doi.org/10.1016/j.jvir.2013.10.013>
- 86 Obi S, Sato S, Kawai T. Current status of hepatic arterial infusion chemotherapy. *Liver Cancer*. 2015;4(3):188–99. <https://doi.org/10.1159/000367746>
- 87 Cheng RG, Bhattacharya R, Yeh MM, Padia SA. Irreversible electroporation can effectively ablate hepatocellular carcinoma to complete pathologic necrosis. *J Vasc Interv Radiol*. 2015;26(8):1184–8. <https://doi.org/10.1016/j.jvir.2015.05.014>
- 88 Hu J, Chen S, Wang X, Lin N, Yang J, Wu S. Image-guided percutaneous microwave ablation versus cryoablation for hepatocellular carcinoma in high-risk locations: intermediate-term results. *Cancer Manag Res*. 2019;11:9801–11. <https://doi.org/10.2147/CMAR.S227961>
- 89 Parikh ND, Cuneo K, Mendiratta-Lala M. Radiation Therapies for the treatment of hepatocellular carcinoma. *Clin Liver Dis*. 2021;17(5):341–6. <https://doi.org/10.1002/cld.1060>
- 90 Kim HC. Radioembolization for the treatment of hepatocellular carcinoma. *Clin Mol Hepatol*. 2017;23(2):109–14. <https://doi.org/10.3350/cmh.2017.0004>
- 91 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378–90. <https://doi.org/10.1056/NEJMoa0708857>
- 92 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10(1):25–34. [https://doi.org/10.1016/S1470-2045\(08\)70285-7](https://doi.org/10.1016/S1470-2045(08)70285-7)
- 93 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391(10126):1163–73. [https://doi.org/10.1016/S0140-6736\(18\)30207-1](https://doi.org/10.1016/S0140-6736(18)30207-1)
- 94 Sangro B, Sarobe P, Hervás-Stubbs S, Melero I. Advances in immunotherapy for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol*. 2021;18(8):525–43. <https://doi.org/10.1038/s41575-021-00438-0>
- 95 Tan S, Li D, Zhu X. Cancer immunotherapy: pros, cons and beyond. *Biomed Pharmacother*. 2020;124:109821. <https://doi.org/10.1016/j.biopha.2020.109821>
- 96 Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evid*. 2022;1(8):EVIDoa2100070. <https://doi.org/10.1056/EVIDoa2100070>
- 97 Finn RS, Qin S, Ikeda M, Galle PR, Dureux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–905. <https://doi.org/10.1056/NEJMoa1915745>
- 98 Kelley RK, Rimassa L, Cheng AL, Kaseb A, Qin S, Zhu AX, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2022;23(8):995–1008. [https://doi.org/10.1016/S1470-2045\(22\)00326-6](https://doi.org/10.1016/S1470-2045(22)00326-6)
- 99 Qin S, Chan SL, Gu S, Bai Y, Ren Z, Lin X, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. *Lancet*. 2023;402(10408):1133–46. [https://doi.org/10.1016/S0140-6736\(23\)00961-3](https://doi.org/10.1016/S0140-6736(23)00961-3)
- 100 Li H, Qin S, Liu Y, Chen Z, Ren Z, Xiong J, et al. Camrelizumab combined with FOLFOX4 regimen as first-line therapy for advanced hepatocellular carcinomas: a sub-cohort of a multicenter phase Ib/II study. *Drug Des Devel Ther*. 2021;15:1873–82. <https://doi.org/10.2147/DDDT.S304857>