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Review Article

Hepatocellular Carcinoma: A Comprehensive Review of Pathophysiology, Risk Factors, Diagnosis and Treatment Strategies

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Abstract

Hepatocellular carcinoma (HCC) is a major cause of death in cirrhosis and the fourth most common cause of cancer-related mortality globally. Chronic liver diseases, such as cirrhosis and viral hepatitis, significantly increase the risk of HCC. Early detection and treatment are vital to improving patient outcomes. HCC development involves complex interactions between liver cells, genetic changes, and environmental factors. Diagnostic approaches include imaging tests, biomarkers, and liquid biopsy. Current treatments comprise surgery, liver transplantation, radiation therapy, and systemic therapies. Preventing HCC through lifestyle changes, such as reducing alcohol intake and maintaining a healthy weight, is crucial. Understanding HCC's molecular mechanisms is essential for developing effective treatments and improving patient outcomes.

Keywords: Hepatocellular carcinoma, Cancer diagnosis, Cirrhosis, chronic liver disease

INTRODUCTION:

Hepatocytes, the primary parenchymal cells of the liver, are the source of HCC. Over 80% of primary liver cancer cases worldwide are caused by HCC.[1, 2] When a tumor spreads to the liver from another area of the body, it is known as secondary liver cancer. One Mortalities in HCC are close to incidence rates globally, and the prognosis is dismal. Hepatocellular carcinoma (HCC) is a major cause of death in cirrhosis and the fourth most common cause of cancer-related mortality globally.[3] It is the second most common cause of cancer-related fatalities in men and the fourth most common type of cancer overall. Compared to women, men are more likely to acquire liver cancer. The ratio of males to women with HCC prevalence worldwide is 2.8:1.[1] Patients with cirrhosis are always at risk for hepatocellular cancer.[4] The characteristics of the tumor, the degree of underlying liver dysfunction, age, other medical comorbidities, and the availability of medical resources and local knowledge all influence the choice of treatment.[2] Significant advancements have been made in prevention, detection, diagnosis, and treatment, in addition to the acknowledgement of its therapeutic value.[4] Due to its phenomenal heterogeneity and the various etiologies that have contributed to its growth, HCC continues to be a tumor that requires fresh information in the realms of pathogenetics, remediation, and diagnostic, preventative, and personified drugs.[5] The benefits of surveillance on HCC to enhance patient survival and clinical findings have been proven by meta-analyses.[6] Since HCC is a widely vascularized tumor, changes in the tumor's vessel construction have a significant impact on the tumor's growth, spread, and recurrence.[7] A thorough, multidisciplinary strategy that takes into account both surgical and medicinal therapy as well as cancer surveillance is necessary for the clinical evaluation and management of HCC. HCC survival rates have grown because of the application of this strategy.[8] Apart from the many mutations that contribute to a heterogeneous cell population in HCC, tumor cells have distinct cell surface markers, exhibit variable gene expression, and exhibit dysregulated cellular pathways.[9] Early detection would ideally enable the identification of tumors that are curable and treated.[10]

PATHOPHYSIOLOGY:

The generation of HCC typically happens when there is ongoing liver damage that leads to cirrhosis. Chronic viral hepatitis (HCV and HBV), alcohol misuse, and metabolic dysfunction-associated steatotic liver disease (MASLD) or steatohepatitis (MASH) are the causes of the damage. When combined, these unusual characteristics highlight the vital need for early detection and intervention techniques in addition to shedding light on the complex interactions between chronic liver diseases and the development of HCC. Fibrosis advancement is regulated by a variety of hepatic cell types. There is growing evidence that liver sinusoidal endothelial cells (LSECs) use a range of scavenger receptors to control the molecular makeup of blood in circulation, which in turn controls the homeostasis and activities of other organs.[11] There are a number of hypothesized explanations for the pathophysiology and etiology of NASH development to HCC. While metabolic imbalance, lipotoxicity from hepatocyte lipid overload, oxidative stress, and immunological factors are the main drivers of neoplastic transformation of NAFLD, a number of other factors, including genetic markers, gut dysbiosis, and alcohol or tobacco abuse, may interact as risk modifiers.[12] One important stage in the viral carcinogenesis of hepatocellular carcinoma is cirrhosis. The main pathophysiology for oncogenesis in HBV is the integration of the hepatitis B viral genome into the host genome. 60% of HCC cases are caused by viral genome insertion in the human genome's telomerase reverse transcriptase (TERT) promoter regions, which results in mutation.[13]

MAJOR HEPATOCELLULAR CARCINOMA SUBTYPES: [14]

1. Fibrolamellar Hepatocellular Carcinoma
2. Scirrhous Hepatocellular Carcinoma
3. Macrotrabecular Hepatocellular Carcinoma
4. Lymphocyte-Rich Hepatocellular Carcinoma
5. Neutrophil-Rich Hepatocellular Carcinoma
6. Clear Cell Hepatocellular Carcinoma
7. Chromophobe Hepatocellular Carcinoma
8. Cirrhotomimetic Hepatocellular Carcinoma
9. Fibronodular Hepatocellular Carcinoma
10. Combined Hepatocellular-Cholangiocarcinoma

EPIDEMIOLOGY:

Although East Asia and Africa have the highest chronicity rates of HCC, much of Europe and the USA are seeing an increase in HCC occurrence and death.[15] Hepatocellular carcinoma (HCC) is the most frequent type of liver cancer, which affected approximately 23,700 people in Western Europe in 2018 (17,300 men and 6,400 women).[16] As the fourth most prevalent cause of cancer-related death globally, HCC is a severe illness that has a significant social-economic.[6] Cost and is a major cause of cancer-related death in many regions of the world.[2,15] By avoiding the risk factors, hepatocellular carcinoma-related mortality can be avoided.[4] With a brief upward trend, HCC, which is developing in the context of cirrhosis and chronic liver disease (CLD), was estimated to have caused 830,000 deaths and 906,000 new cases in 2020, making it the third most common cause of cancer-related deaths and the sixth most commonly diagnosed cancer.[3] Although the trend has slowed since 2015, the North American Association of Central Cancer Registries projects that 41,210 new cases of HCC will be detected in the US in 2023, a threefold increase over the previous forty years.[5] By 2025, liver cancer is predicted to impact over 1 million people yearly, making it a significant global health concern.[15] Only 0.5 to 1 instances of HCC occur before the age of 20, making it largely an adult-onset illness.[17]

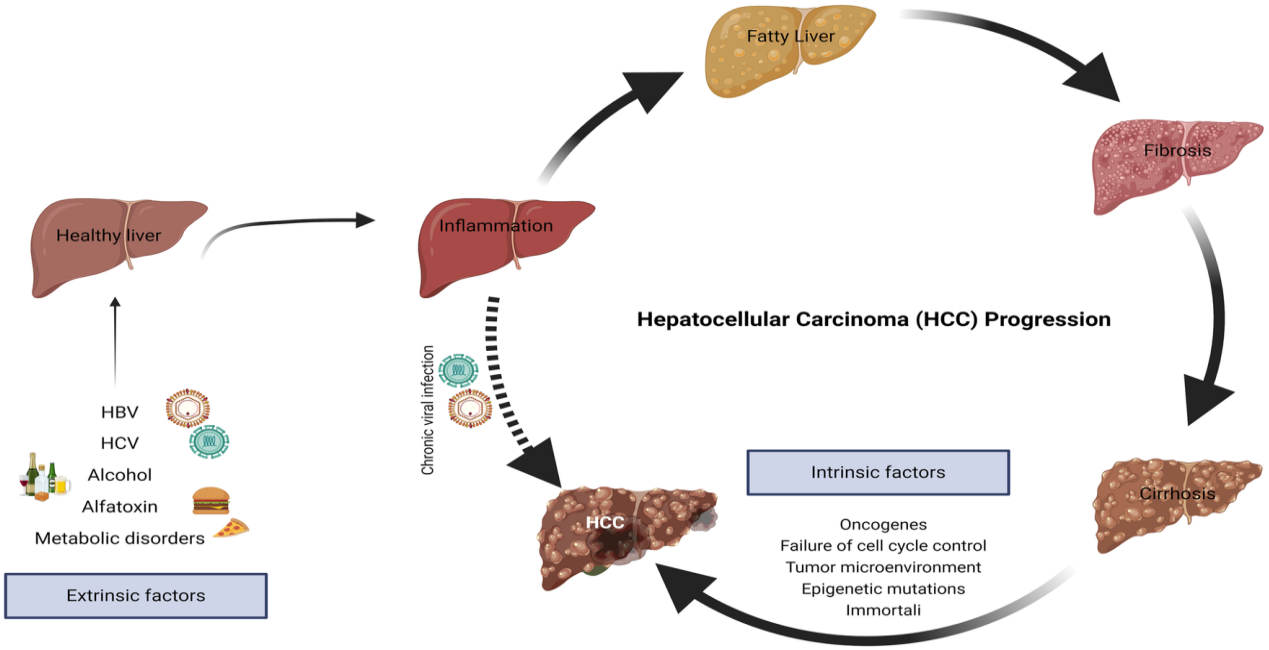

Figure 1: Schematic representation of multi-stage HCC development from common etiological factors.[9]

RISK FACTOR:

The majority of HCC tumors start from cirrhosis, which is most commonly caused by nonalcoholic fatty liver disease (NAFLD), a liver disease linked to alcohol.[18] Common risk factors include viral infections like hepatitis B/C virus (HCV) infections, chronic liver diseases (CLDs) like cirrhosis or fatty liver, alcohol misuse, and metabolic diseases like diabetes. Hemochromatosis, autoimmune hepatitis, and exposure to specific environmental contaminants are additional less frequent risk factors.[6,7] Numerous environmental toxins, such as arsenic, cadmium, mycotoxins, and aristolochic acid (AA), have been linked to both liver cancer and renal impairment, according to epidemiological and animal studies.[11] Alcohol use, constant HCV infection, and cryptogenic cirrhosis were the next most common causes of HCC, accounting for 49.8% of all cases. Remarkably, persistent HBV infection was present in all non-cirrhotic HCC cases (nine cases, 7.2 of all HCC cases). Subsequent research identified this persistent HBV infection as the primary risk factor for HCC development.[19] Renal impairment has been associated with an increased risk of cancer. A dysregulated immune system, defective DNA repair medium, compromised antioxidant defense, the build-up of carcinogenic composites due to decreased renal clearance, and the uremia milieu are some of the hypotheses put out to explain these associations.[11] Environmental exposures (e.g., aflatoxin, alcohol, tobacco, obesity, diabetes), viral factors (e.g., high HBV replication levels, HBV genotype, duration of infection, coinfection with HCV or HIV), and demographic characteristics (e.g., male sex, advanced age, Asian or African heritage, family history of HCC) are additional factors that increase risk among HBV carriers.[20]

SYMPTOMS:

Early-stage symptoms include fatigue, weight loss and abdominal pain; later-stage symptoms include fever, ascites and jaundice.[6] Due to the lack of early diagnostic indicators, the absence of specific symptoms in the early stages, and the low percentage (10–20%) of radical resectable HCC at diagnosis, most HCC patients are often found in an advanced stage with a dismal prognosis.[7]

PREVENTION:

The widespread presence of HCV infection can be reduced by blood donor screening programs, high-risk behavior education, and general blood handling safety measures. Recent decades have seen advancements in the prevention and treatment of CHB and CHC, especially in high-risk countries; however, more effective and sustainable reduction of these diseases is still needed.[21] Antiviral therapies for hepatitis B and hepatitis C can prevent but not completely eradicate HCC.[22] Since the introduction of universal HBV vaccination programs, the incidence and prevalence of HBV infection have decreased in many countries, making vaccination a crucial part of HBV preventive strategies worldwide.[21]

MAINTANING HEALTHY LIFESTYLE:

1. **Alcohol Consumption Reduction:**

Chronic alcohol use is a known risk factor for HCC because it results in liver cirrhosis and promotes carcinogenesis through mechanisms such oxidative stress, inflammation, and impaired immune surveillance. It has been demonstrated that lowering alcohol consumption lowers the prevalence of HCC, particularly in populations with high ALD rates.[23]

2. Weight Management and Physical activities:

A combination strategy for successful, long-term weight loss is advised to avoid hepatocellular carcinoma (HCC) linked to obesity. A person-centered adaptive approach to weight loss and maintenance can be developed by combining lifestyle, surgical, and/or pharmaceutical therapies.[24]

3. **Dietary Interventions:**

Hypercaloric diets high in cholesterol, trans and saturated fats, and beverages sweetened with fructose are the cause of MASLD. Additionally, these diets promote the accumulation of hepatic lipids and increase visceral adiposity. Dietary interventions play a significant role in the primary prevention of HCC by altering risk factors such obesity, metabolic syndrome, and MASLD and directly influencing liver carcinogenesis through bioactive chemicals. Eating a diet rich in fruits, vegetables, red meat, white meat, fish, dairy, and soy, as well as nuts[25] and whole grains, as advised by the Mediterranean diet, lowers the incidence of hepatic carcinogenesis because of their anti-inflammatory and antioxidant properties, which reduce inflammation and oxidative stress, two major factors in hepatic carcinogenesis.[23]

4. **Smoking cessation:**

Tobacco use is a known independent risk factor for HCC, as meta analyses have demonstrated that smokers have a significantly higher chance of developing the disease than non-smokers.[23]

DIAGNOSIS:

Even though HCC has unique radiographic features such venous washout, arterial hyperenhancement, and capsule enhancement, non-invasive imaging methods like computer tomography (CT) and magnetic resonance imaging (MRI) can often detect it.[6] Abdominal ultrasonography is the primary line of inquiry for surveillance in Thailand since it is affordable, non-invasive, and yields valuable data. While dynamic CT or MRI (with liver specific contrast) will be performed to assess any troubling nodules by ultrasonography in order to diagnosis HCC, liver biopsy is advised for unresolved imaging study determinations.[21] Hepatocellular carcinoma is difficult to treat since it is frequently linked to underlying liver morbidity.[26]

- **Laboratory tests:**

Abnormal results from liver function tests can occur, especially in children with cirrhosis of the liver. Nevertheless, there are no particular complete blood count diagnostic results connected to HCC. Alpha-1 antitrypsin level and phenotype, urine and plasma amino acid levels, urinary succinyl acetone for tyrosinemia, and hepatitis B and C serology are among the known risk factors that must be ruled out. If suspected, PFIC 2, Alagille syndrome, and tyrosinemia should all be genetically verified.[17]

- **Alphafetoprotein:**

Approximately 50% to 70% of patients with HCC have high levels of alphafetoprotein (AFP), a valuable diagnostic and prognostic marker of the disease.[15,16] It should be mentioned, nevertheless, that cirrhosis can also result in a sustained increase in AFP due to hepatic regeneration. While some recommend an even lower cutoff between 200 and 300 ng/mL, the majority of researchers concur that AFP levels above 400 to 500 ng/mL in a patient with cirrhosis strongly imply the diagnosis of HCC. Patients with metastases and more bulky illness typically had higher levels.[17]

- **AI for predicting incident hepatocellular carcinoma:**

Several previous case-control and cohort studies have developed predictive models for the development of HCC utilizing clinical, demographic, and/or laboratory risk markers selected using standard statistical approaches.[18] Early research on the use of artificial intelligence for polyp and adenoma identification and differentiation has shown promising results.[27]

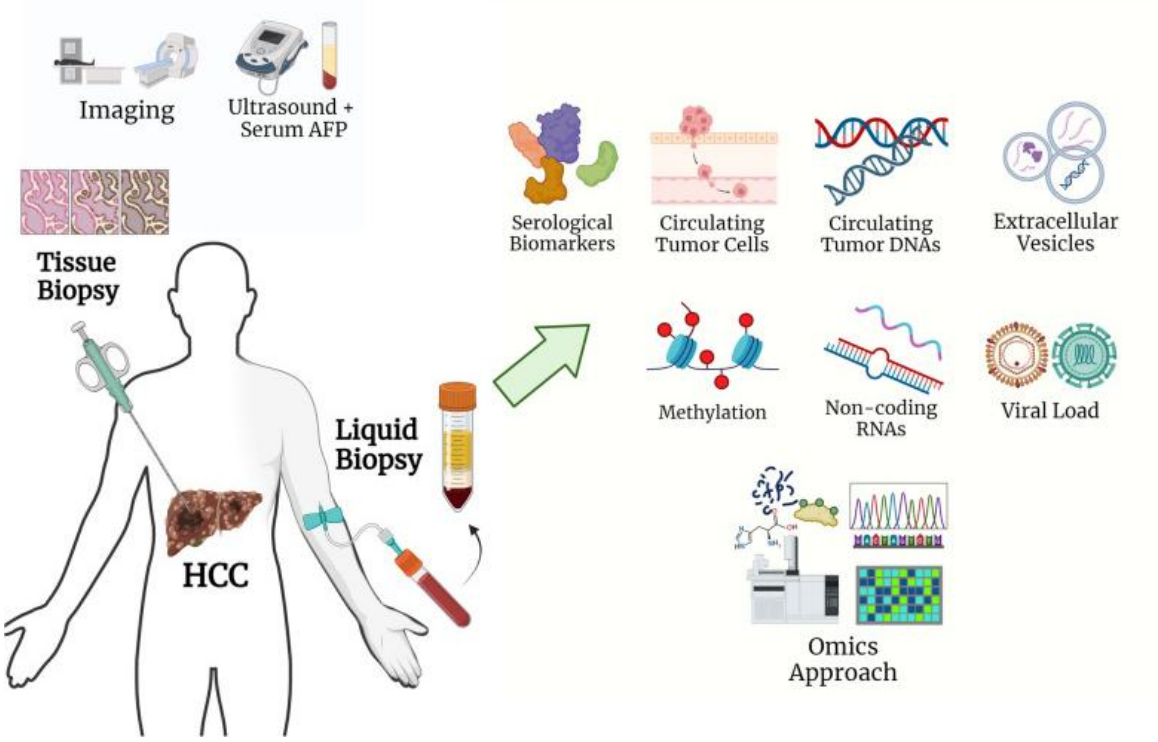

Figure 2: Biomarkers of HCC diagnosis.[6]

Description: Ultrasound and serum AFP readings are the mainstays of the current surveillance approach for hepatocellular carcinoma (HCC), with imaging modalities occasionally included. Tissue biopsy is frequently used to confirm the tumor's histological structure when diagnosis or treatment choices are unclear. A less intrusive option for learning more about tumor heterogeneity is liquid biopsy. Potential biomarkers have been identified by recent studies from a variety of sources, such as cells, vesicles, genetic materials, and serological components. Because they can reflect the complexity of HCC tumors, circulating tumor DNAs and omics stand out among these potential biomarkers. These technologies hold enormous potential for comprehending the complexities of HCC and creating more individualized and effective treatment plans.[6]

GLOBAL STRATAGIES FOR THE MANAGEMENT OF HCC

Treatment:

Chemotherapy and surgical resection are the standard treatments for all malignant liver tumors; total surgical resection is associated with the highest cure rates.[17] Although a biopsy is requested for confirmation of diagnosis in the event of atypical characteristics on imaging, patients with The Barcelona Clinic Liver Cancer (BCLC A) are offered ablation, resection, and transplantation as curative-intent therapy.[28]

Transarterial chemoembolization (TACE) is a standard treatment for intermediate-stage hepatocellular carcinoma (HCC).[29] Hepatocellular carcinoma (HCC) at its intermediate stage is commonly treated with transarterial chemoembolization (TACE).[27]

Radiotherapy:

Effective tumor control in advanced diseases has also been attained using radiotherapy, a therapeutic method of internal radiation therapy using radioisotopes. Conversely, because of the surrounding normal liver parenchyma's low tolerance, external beam radiation's use treating HCC has historically been restricted. However, the ability to deliver severe dosages to the tumor while preserving healthy tissues has been made possible by technological advancements in the planning and delivery of radiation treatments. Proton therapy and stereotactic body radiation, two sophisticated and highly conformal radiotherapy techniques that have been assessed for safety and effectiveness in treating HCC, show promising outcomes.[26] Contrast-enhanced ultrasound is an effective surveillance method for people who are at high risk for HCC. Other imaging should be performed if conventional ultrasonography is not accessible. [30]

Transplantation:

Hepatic resection and liver transplantation are two essential curative measures for HCC. While surgical resection is an option for a single lesion that is easily accessible by surgical procedure and is expected to have an appropriate liver volume, liver transplantation is the treatment for cirrhotic patients with HCC. The interdisciplinary team at each facility would talk about this therapy option. Because of the variation in HCC, liver condition, surgical skill, and health care center level, Thailand's national treatment outcome for hepatic resection has not been sufficiently organized, gathered, and published.[19] Downstaging HCC to meet Milan criteria is a proven method of providing liver transplantation to individuals with T3 disease. Patients who meet the downstaging criteria, which were established by the United Network for Organ Sharing (UNOS) because of numerous studies demonstrating the beneficial post-transplant outcomes of HCC downstaging, may be granted a standard HCC model for end-stage liver disease (MELD) exception.[31] HCC was suggested as an indication for OLT early in the revolutionary era of organ transplantation because it prevents HCC recurrence and the implications of liver disease progression, such as hepatic encephalopathy, ascites, and gastrointestinal bleeding. The latter specifically lends credence to the notion that OLT offers a superior long-term oncological prognosis compared to either LR or ablation.[32]

Biopsy:

Liquid biopsy is becoming a more popular alternative to tumor tissue biopsy. It makes it possible to investigate circulating tumor cells (CTCs), tumor biomarkers in the blood and other body fluids, and tumor nucleic acids including circulating tumor RNA (ctRNA) and circulating tumor DNA (ctDNA). The variety of primary and/or metastatic cancers is reflected in these materials. In particular, the presence of a heterogeneous population of CTCs in the blood indicates tumor heterogeneity in both genotype and phenotype. By examining the geographic distribution of CTCs, liquid biopsy might provide valuable information regarding tumor heterogeneity and perhaps predict metastases.[9] Even though optical biopsy is still a promising field, the accuracy of AI diagnosis in this procedure depends on how effectively surface microstructures can represent the histologic features of a lesion. In this context, tissue biopsy remains the gold standard.[25]

Systemic Treatment:

The tyrosine kinase inhibitor (TKI) sorafenib was the first-line standard of therapy for patients with advanced, incurable HCC from 2007 to 2018.[33] Sorafenib has been suggested for systemic treatment in patients of advanced HCC (BCLC stage C), well-preserved liver function, and ineligibility for locoregional treatment. Sorefenib has been demonstrated to increase survival for several months in advanced stages of HCC.[19] When compared to lenvatinib therapy, atezolizumab with bevacizumab therapy had a longer PFS and a lower incidence of serious adverse effects (AEs) while maintaining hepatic functional reserve. Except for patients who should not receive immunotherapies or who have hepatic impairment, combination therapy is therefore commonly selected as the first line of treatment.[34]

The most important recent development in HCC treatment was the FDA's approval of atezolizumab plus bevacizumab for patients with incurable HCC, based on the results of the IMBRAVE150 research.[29] By blocking cyclooxygenase-2 (COX-2), which reduces chronic liver inflammation, a key contributor to hepatocarcinogenesis, and the synthesis of pro-inflammatory prostaglandins, aspirin primarily demonstrates its chemopreventive effects.[23] The well-known antidiabetic medication metformin has shown promise in reducing the risk of HCC through a variety of methods. By triggering AMP-activated protein kinase (AMPK), which inhibits the mammalian target of rapamycin (mTOR) pathway, it inhibits the development and proliferation of tumor cells.[23]

Antiviral therapy:

The effect of antiviral drugs on the development of HCC in patients with HCV-cirrhosis has been the subject of numerous investigations. When treating chronic hepatitis C, achieving sustained virological response (SVR) is a primary goal. Numerous studies have shown that patients who got SVR had a decreased risk of HCC than non-responders, however there is inconsistent data when comparing non-responders to untreated controls.[22]

Liver regeneration microenvironment:

Regenerative microenvironment is essential for liver cancer prevention and treatment. Enhancing the hepatic microenvironment to encourage the regeneration of injured liver cells may be achievable via affecting immunological function, inflammation, and the vasculature. By rebalancing the dynamic imbalance between normal liver regeneration and repair and aberrant liver regeneration, this will aid in the prevention and treatment of liver cancer.[35]

CONCLUSION:

Hepatocellular carcinoma (HCC) continues to be a major cause of cancer-related morbidity and death globally, and its prevalence is rising due mainly to the increase in chronic liver illnesses such non-alcoholic fatty liver disease and hepatitis B and C infections. Improving prognosis and survival rates requires early diagnosis and enhanced diagnostic methods, including imaging and biomarker testing. Even while improvements in surgical procedures like liver transplantation and resection have produced encouraging outcomes, treating advanced HCC remains difficult for medical professionals. Although there are still obstacles in maximizing their usage and overcoming resistance mechanisms, the emergence of targeted treatments and immunotherapies gives patients with advanced disease new hope. Future studies are anticipated to uncover new therapeutic targets, enhance prognostic instruments, and develop better treatment approaches as our knowledge of the molecular and genetic landscape of HCC grows. These developments will ultimately improve the prognosis of HCC patients.

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