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# Hepatocellular Carcinoma: A Review

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## Abstract

The most frequent primary liver cancer is hepatocellular carcinoma (HCC), which is also the main cause of cancer-related death globally. HCC is the ninth most common cancer-related cause of death in the US. Incidence and death are still increasing despite improvements in screening methods, prevention strategies, and new technologies for both diagnosis and treatment. Regardless of the etiology, cirrhosis continues to be the predominant risk factor for the development of HCC. Hepatitis B and C are separate risk factors for cirrhosis development. Given that alcohol misuse is five times more prevalent than hepatitis C in the United States, alcohol intake continues to be a significant extra risk factor. Without pathologic confirmation, the diagnosis is established. The term "screening" refers to the use of both serological indicators such as -fetoprotein and radiologic tests such as ultrasonography, computerized tomography, and magnetic resonance imaging at intervals of six months. However, only orthotopic liver transplantation (OLT) or surgical excision is curative among the many available treatment options. Patients who meet or are downstaged into the Milan or University of San Francisco criteria are eligible for OLT. Radiation therapy, systemic chemotherapy, cryoablation, percutaneous ethanol injection, transarterial chemoembolization, radiofrequency ablation, microwave ablation, molecularly targeted therapies, and percutaneous ethanol injection are further treatment options.

**Keywords:** three decades, surveillance, hepatocellular carcinoma, advancement, and treatment.

## Introduction

The most frequent primary liver cancer is hepatocellular carcinoma (HCC), which is also the main cause of cancer-related death globally. HCC is the ninth most common cancer-related cause of death in the US.[1] The most common liver cancer, known as hepatocellular carcinoma (HCC), is also the second largest cause of cancer-related death in the US. It is regarded as the third most common cause of cancer death worldwide and the fifth most frequently identified cancer in males and the seventh most frequently detected cancer in women in the United States.[2] According to the National Cancer Institute's database, the incidence of liver cancer increased by 3.1% year from 2008 to 2012 in several regions of the world, including Europe, North America, and Latin America. According to current estimates, Asia and Africa have the highest rates of liver cancer worldwide. About 80% of HCC cases are caused by the hepatitis B virus (HBV) and the hepatitis C virus (HCV), with HBV accounting for 50% to 80% of virus-associated HCC cases and HCV for 10% to 25%.[4,5] Men are diagnosed with HCC more frequently than women, which may be related to men's greater rates of HBV, HCV, and alcohol use, all of which contribute to enhanced carcinogenicity.1 Increased rates of obesity, aflatoxin exposure, and nonalcoholic fatty liver disease are some factors that have been linked to an increase in HCC.[2]

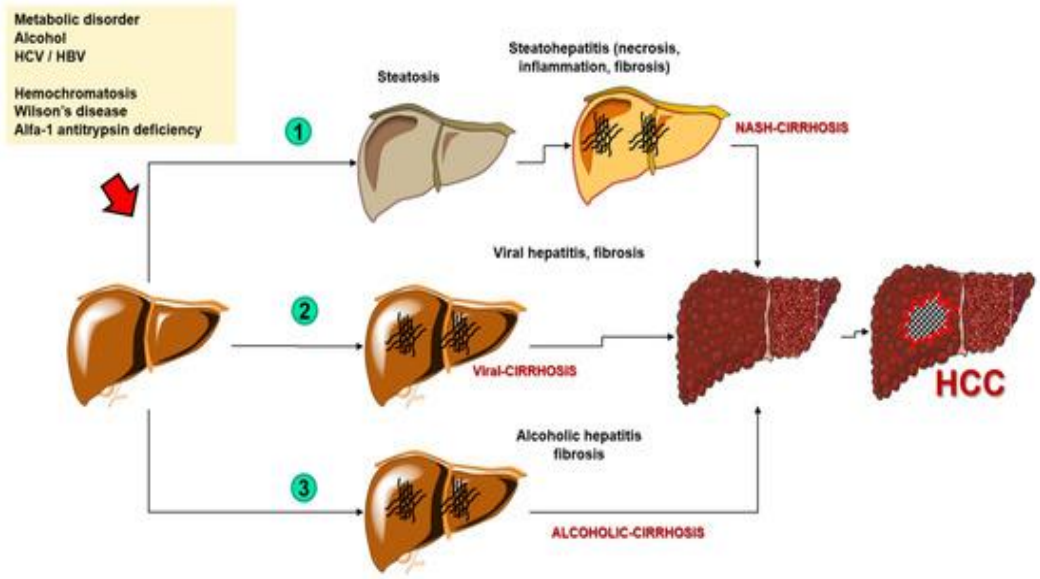



**Figure 1.** The process of carcinogenesis of the hepatocellular carcinoma. Abbreviations: HCC—hepatocellular carcinoma; NASH—nonalcoholic steatohepatitis; HCV—hepatitis C virus; HBV—hepatitis B virus.

## Etiology

The course of the disease and the characteristics of the patients are directly impacted by a number of factors related to the etiology of HCC.[5] The Asia-Pacific, Mongolia, China, and sub-Saharan Eastern and Western Africa regions have recorded the highest rates of HCC worldwide.[6] With France, Japan, and Italy excluded, industrialized nations have a lower prevalence of HCC. Since hepatitis B, C, and D viruses (HBV, HCV, and HDV) are strongly associated

with the development of HCC, the incidence of these infectious viral illnesses around the world parallels that of HCC. The progression of liver cirrhosis to HCC occurs in 80–90% of patients.[7] Cirrhosis is considered to be the primary risk factor for the development of HCC, and HCV and HBV are recognized as the primary causes of cirrhosis. In actuality, cirrhosis results from the necrosis of hepatocytes, which causes the formation of fibrosis-forming scar tissue.[8] HCC is frequently cited as the primary cause of HBV infection.[9] Patients who have chronic hepatitis B, or HBV infection that has persisted for virtually their whole lifetimes, are at a higher risk of developing HCC associated to HBV.[9]

**Risk Elements**

About 50% of all HCC cases are linked to HBV infection, while 25% are linked to HCV [10]. HBV is a double-stranded DNA virus that can integrate its DNA into hepatic cells. It can also function as a mutagenic agent, induce secondary chromosomal rearrangements, and result in rising genomic instability [11]. Because of this, people with HBV infection have a 100-fold increased chance of developing HCC compared to those without infection [12]. Cirrhosis brought on by hepatitis C virus infection is the main cause of HCC in Europe, Japan, Latin America, and the United States, with an annual incidence ranging from 2% to 8% [10, 11]. Patients with HCV generally have a 17-fold increased risk of developing HCC compared to those who are not infected [12–14]. Because HCV is an RNA-containing virus that cannot integrate into the host genome, it causes HCC by a variety of indirect processes, including changes to apoptotic pathways and tumor growth [15, 16]. HCC risk has been linked to both obesity and diabetes mellitus. In comparison to people who are not obese and do not have diabetes, these patients have a twofold increased risk of getting HCC. Another significant risk factor for HCC is alcohol use, which rises as levels of consumption do [17]. Alcohol use of 40 to 60 grams per day over a prolonged period of time is strongly linked to HCC. Aspergillus flavus and related fungi generate the mycotoxin known as aflatoxin, which contaminates foods that have been stored, including rice, corn, soybeans, and peanuts. It is one of the main risk factors for HCC in several parts of the world, particularly in Asia and Africa. Due to aflatoxin's ability to alter the p53 tumour suppressor gene and harm the DNA of liver cells, chronic exposure to the substance is strongly linked to HCC.

**Diagnosis**

HCC is frequently asymptomatic in patients, and when symptoms do appear, they are frequently shared with those of chronic liver disease, such as weakness, weight loss, fever, yellowing of the skin and eyes, pain in the right upper abdominal side, and swelling of the abdomen. Active surveillance and greater awareness of HCC in high-risk patients, particularly those with cirrhosis, have led to an increase in the diagnosis of asymptomatic patients during the past few decades. Every six months, these patients should be screened for HCC [20].and the most used tools are ultrasonography and serum alpha-fetoprotein (AFP) values [19]. Additionally, it has been demonstrated that the blood

level of AFP is less beneficial than previously thought and does not necessarily correlate with the progression of the tumour. [21]

**Treatment**

Unfortunately, the diagnosis of HCC is frequently made after the disease is advanced and the patient has developed symptoms and some liver damage. There is essentially no viable medication that would increase survival at this late stage. Furthermore, the morbidity related to therapy is too great. Unfortunately, many patients do not receive a thorough screening. In a study using the Marketscan claims database, it was found that over 700,000 individuals had at least one claim for NAFLD, NASH, or HCV, and that more than one-quarter of people with HCC had no prior knowledge of liver illness. In this study, routine HCC screening was done on 22.3% of hepatitis C patients and 21.1% of NASH patients. Even in academic centres where patients are closely monitored by knowledgeable hepatologists, up to one-third of the patients had erratic HCC surveillance.[22] Many people can and should be identified with early disease and retained liver function with appropriate screening and attention. Currently, there are a number of surgical and nonsurgical therapy methods available that can increase survival.

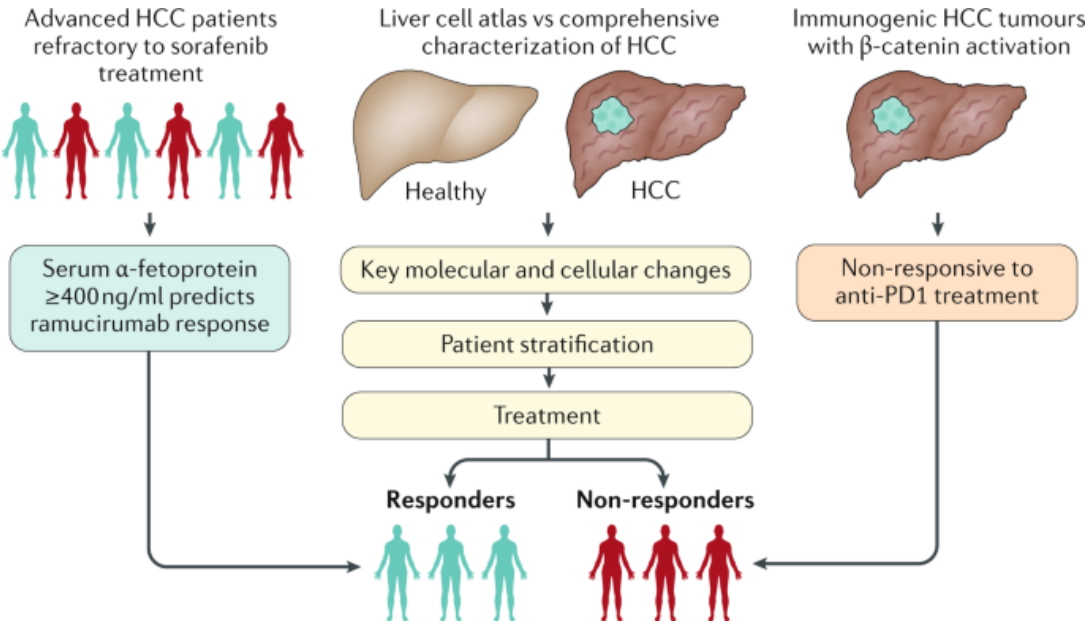
**Surgical methods**

**Resection**

The standard of care for noncirrhotic patients is surgical resection, which has a 5-year survival rate of 41%-74% and the best curative rate.[23] The tumor's ability to be removed depends on several factors, including its size, location, underlying liver function, and whether or not the liver's residual volume will permit removal without significantly raising postresection morbidity and mortality. As long as R0 resection is feasible, resection is regarded as the first-line therapy. Laparoscopic liver resection, which currently plays a crucial part in the treatment of HCC, is safer and more successful in cirrhotic patients than standard open surgery. Resection serves as the main therapy for advanced tumours and is a viable alternative or stopgap measure before liver transplantation. When choosing between laparoscopic and open resection, only technical viability should be taken into consideration. The size and location of the tumour, as well as liver function, have both been presented as criteria to help in the identification of suitable candidates for surgery.[24]

**Liver transplantation**

For patients with decompensated cirrhosis, orthotopic liver transplantation (OLT) is the most curative option, and HCC is the only solid malignancy that can be treated with transplantation. A seminal study by Mazzaferro et al.113, known as the Milan criteria, had 50 patients who received transplants for HCC and met certain criteria. These particular requirements included a 4-year survival rate of 75%, a single HCC tumour measuring less than 5 cm, or three tumours measuring less than 3 cm each. The Milan criteria have been established as an independent predictive indicator of outcome after OLT in a recent systematic evaluation of 90 trials that examined 17,780 patients over a 15-year period.




It has also been researched to expand the Milan criterion, particularly by removing the constraints on tumor size. In studies conducted both retrospectively and prospectively, the University of California San Francisco (UCSF) criteria, which include 1) a single lesion 6.5 cm or 2) three or fewer nodules with the largest lesion 4.5 cm and with a total diameter 8 cm, have shown survival and recurrence rates that are comparable to those of patients using the Milan criteria. The survival rates after 1 and 5 years were 90% and 75%, respectively. Regardless of tumour biology, the Milan and UCSF criteria both take the quantity and size of the tumor into account. Poorly differentiated tumours were not included in the University of Toronto's procedure for biopsying big tumours up to 10 cm in diameter. Prior to transplantation, these patients received severe ablative therapy, and both Milan criteria and extended criteria patients had identical survival rates.[25]

**Nonsurgical methods**

**Transarterial Chemoembolization**

TACE is the first-line treatment most frequently utilised for downstaging tumours that meet criteria and for locoregional HCC.TACE can be used as neoadjuvant therapy before HR and RFA to either reduce tumour volume or even target micrometastasis. The neoangiogenic characteristics of HCC and its method of action on the tumor's hepatic artery supply provide as justification for the use of TACE. The tumour receives its initial blood supply from the portal system as it grows. Even a well-differentiated HCC depends largely on hepatic arterial supply because as the tumour grows, the blood flow becomes arterialized. The pathologic foundation for the radiologic findings used to identify HCC is provided by this tumour characteristic. The hepatic artery branch embolisation causes selective tumour hypoxia, which eventually results in tumour necrosis. This is achieved by significantly reducing arterial blood flow with the aid of catheter-based, image-guided particle infusion. TACE therapy has historically been prohibited by the presence of portal vein tumour thrombosis. When a portal vein obstruction from a tumour thrombus compromises blood flow to the afflicted area of the liver, the stoppage of hepatic arterial blood flow can cause substantial hepatic necrosis.

**Transartetial radiation**

Transarterial radioembolization is an internal radiation treatment that uses a catheter to deliver tiny microspheres containing radioisotopes to the tumour. Similar to TACE, Yttrium-90 (Y-90) microspheres or iodine-131-labeled lipiodol are delivered. The use of this treatment on cirrhotic individuals with HCC has been proven to be both secure and successful. The fact that Y-90 is indicated in cases of portal vein neoplastic thrombosis whereas TACE has traditionally been viewed as a contraindication is one of the main advantages it has over TACE. The side effects are typically bearable. The most frequent adverse reactions are weariness, nausea, and abdominal pain. Postembolization syndrome, which includes fever, persistent nausea, general malaise, appetite loss, and stomach pain, is less common with TACE. To check for arterioportal shunting, a pretreatment evaluation is required, which frequently includes an arteriogram, superior mesenteric angiography, and celiac trunk angiogram. To reduce unintentional deposition of microspheres outside the targeted location, coil embolisation of these colateral arteries might be required.

There are several limitations of RFA:

1. for tumors >3 cm, complete necrosis is rarely observed;
2. there is difficulty in ablating tumors that are adjacent to major blood vessels;
3. it is difficult to reach certain segments of the liver (ie, Segment 1) percutaneously;
4. subcapsular lesions can rupture into peritoneum;
5. bladder injury can occur with ablation of segment IVb
6. in livers with multinodular cirrhosis, targeting lesions

under ultrasound guidance can be difficult[26]

**Microwave Ablation**

Microwave ablation (MWA) is a possibly curative ablative technique that can be used both percutaneously and intraoperatively. The only difference between MWA and RFA is that MWA uses electromagnetic waves with frequencies greater than 900 kHz to irradiate and ablate tumour foci.As a result, the MWA field's temperature rises quickly to levels beyond 100°C without being adversely affected by tissue resistance, resulting in a quicker and more even ablation. Compared to RFA, this carries a higher chance of more serious injury to nearby structures. Recent research using upgraded MWA modalities suggest potential, although earlier studies contrasting MWA with RFA showed no statistical difference in efficiency. Recent research using upgraded MWA modalities suggest potential, although earlier studies contrasting MWA with RFA showed no statistical difference in efficiency. It is necessary to assess the clinical advantage of MWA over RFA and its potential to show higher rates of tumour necrosis with fewer treatments overall.

## Conclusion

HCC is an aggressive malignancy that typically manifests in an advanced stage and occurs in conjunction with cirrhosis and chronic liver disease. Advanced tumour stages and concurrent liver impairment make curative therapy even more difficult. HCC and other cancers can be prevented if the right precautions are taken, such as HBV vaccination, widespread blood product screening, the use of safe injection techniques, the treatment and education of alcoholics and intravenous drug users, and the start of antiviral therapy. The overall survival rate has significantly increased as surgical and nonsurgical methods continue to advance. OLT is still the only curative surgical surgery, although many HCC patients cannot receive it due to a lack of accessible organs. Sorafenib has demonstrated to be a distinct neoantigenic targeted drug with positive outcomes. To evaluate survival and tumour regression, studies need to look into different biomarkers both on their own and in combination with other modalities.

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