Chapter

Hepatocellular Carcinoma: A Pharmacological Aspect

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Abstract

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, deteriorating approximately 1000,000 lives. Annually rising HCC to the third most common cause of cancer mortality. Liver cancer varies geographically depending on multimodality treatments available for this heterogeneous malignancy. Conglomeration of treatments has been exercised to manage this type of cancer across distinct geographic regions. Unprecedented rise of scientific knowledge mining from the published literature is a boon to develop novel treatment modalities. We aim to focus such pharmacological aspects in HCC treatment that could effectively display the improved therapies. Extrapolating the details of liver cancer (classification, diagnosis, adequate treatments, therapeutic engineering involved in the therapy, causes, epidemiology, and survival ratio) and the result obtained through this research could be a magnificent approach in the advancement of drug delivery systems that could assist in clinical trials and further betterment of survival rate and improved therapy from this deadly cancer.

Keywords: category, symptoms, prognosis, pathophysiology, remedies, therapeutic engineering

1. Introduction

As per the current study performed by the international agency for research on cancer (World Health Organization), the number of liver cancer cases reported all over the globe was 841,080, i.e., 4.7% of the total cancer cases in year 2018. As per the reports of the American Cancer Society, there is an estimation of 42,030 new cases of liver cancer diagnosed in the United States alone for the year 2019. Three-fourths of those cases are of hepatocellular carcinoma (HCC) that is unquestionably the most serious and dreaded complication of chronic liver disease. The development of HCC is generally the terminal event of a long-standing, typically asymptomatic chronic liver disease, which originated decades earlier. Regardless of the etiology, the process begins with a frequently unrecognized acute or subacute liver insult that slowly advances to the development of cirrhosis, a potentially preneoplastic condition. Less commonly, HCC arises directly without antecedent cirrhosis. The average life expectancy after diagnosis of clinically apparent HCC is less than 12 months [1].

People with chronic liver diseases, such as cirrhosis caused by hepatitis B or hepatitis C infection, are most often prone to hepatocellular carcinoma. Hepatocellular carcinoma is traditionally related to liver cirrhosis and also with the ongoing process of liver necrosis or regeneration, where liver cirrhosis may be due to hepatitis B and C.

In regions of Africa, Asia, and China, intake of food contaminated with aflatoxins may be later associated with HCC, while in Europe only 30% of pediatric HCC cases are linked to liver cirrhosis, while others are de novo cases [2] .
As per the report of the American Cancer Society, 31,780 liver cancer deaths occurred in the United States alone for the year 2019. Incidence rates (%) in total population the disease is approximately 2.5 per 100,000 population [3]. It is one of the most common malignancies in adults and is more common in men than women (2–4:1) and blacks than whites. All over the world, millions of deaths per year (about 10% of all deaths in the adult age range) can be attributed to hepatocellular carcinoma. Depending on geographic location, the occurrence of hepatocellular carcinoma varies. While incidence in the Western world is less than 2 per 100,000 males, it is currently 40–60 per 100,000 in Africa and parts of the Far East. People of East Asian origin suffers the most from Hepatocellular carcinoma in United States. In the future, the prevalence of hepatocellular carcinoma may increase in the United States.

People with long-term liver diseases are most vulnerable to the risk of hepatocellular carcinoma. As people who already have signs and symptoms of chronic liver disease are majorly suffering from HCC. Prolonged yellow skin, easy bruising from blood clotting abnormalities, abdominal swelling, appetite loss, weight loss, pain in the abdominal cavity, nausea, feeling tired, or vomiting may be directly associated with HCC [4]. The mortality rate of the patients (both sexes) suffering from liver around the world in 2018 is 781,631. Among which 72.4% of the total mortality cases were recorded in Asia. As per the current statistics, a comprehensive approach is urgently required that involves primary and secondary prevention and increased access to treatment, and more funding for liver-related research is needed to address the high death rates associated with chronic liver disease and liver cancer to decrease the average mortality rate by giving adequate treatments.

1.1 Risk factors

Cirrhosis of the liver mostly causes HCC, whereas other factors also majorly influence the risk of HCC among which 60–70% of cirrhosis is estimated to cause by heavy alcohol consumption (**Figure 1**).

Recognized risk factors include:

- Toxins: alcohol abuse, aflatoxin, iron overload state (hemochromatosis)
- Metabolic: nonalcoholic steatohepatitis, type 2 diabetes (probably aided by obesity)

There is a variable significance of these risk factors globally [5]. In regions where hepatitis B infection is endemic, such as southeast China, this is the predominant cause. In populations largely protected by hepatitis B vaccination, such as the United States, HCC is most often linked to causes of cirrhosis such as chronic hepatitis C, alcohol abuse, and obesity. The chance of developing HCC in children and adolescents increases if they suffer from congenital liver disorders.

1.2 Symptoms

Patients with hepatocellular carcinoma are frequently asymptomatic especially if the disease is diagnosed at an early stage. The major symptoms include abnormal weight loss, mild to high fever, diarrhea, fatigue, and anorexia [6].

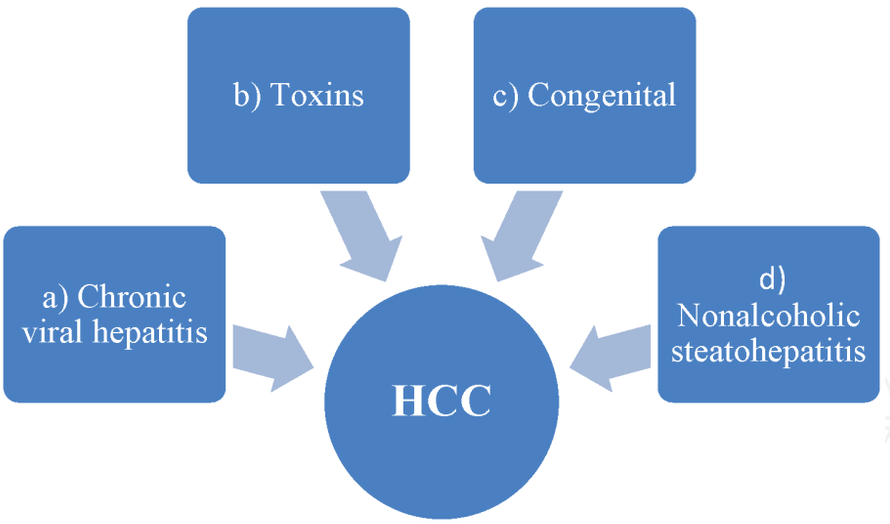

Figure 1.
Risk factors leading to the cause of HCC: (a) estimated cause of 80% cases globally, (b) alcohol abuse, aflatoxin; iron overload state (hemochromatosis); (c) alpha 1-antitrypsin deficiency; Wilson's disease.

Symptomatic patients—Patients with advanced lesions may present with mild to moderate upper abdominal pain, weight loss, early satiety, or a palpable mass in the upper abdomen [7]. Paraneoplastic syndrome may occasionally develop in a patient with HCC [8].

Hypoglycemia—Hypoglycemia, which usually occurs in advanced HCC, is thought to result from the tumor's high metabolic needs.Erythrocytosis—Tumor secretion of erythropoietin (EPO) majorly leads to erythrocytosis in HCC [9].

Hypercalcemia— Hypercalcemia can be present in association with osteolytic metastases, but it may also be seen in the absence of bony metastasis due to secretion of parathyroid hormone-related protein [10].

Diarrhea—Patients with HCC may infrequently present with intractable diarrhea and associated electrolyte disturbances (e.g., hyponatremia, hypokalemia, metabolic alkalosis). The underlying mechanism is not fully understood, but it may be related to secretion of peptides that cause intestinal secretion. These include vasoactive intestinal polypeptide, gastrin, and peptides with prostaglandin-like immunoreactivity [11]. Cutaneous features—Although skin changes are rare in patients with HCC, several cutaneous manifestations have been described; however, none is specific for the diagnosis [12].

It involves the following:

- Dermatomyositis may present with a variety of cutaneous findings (e.g., scaly, violaceous papules overlying bony prominences of the hands) and is associated with solid organ malignancies.

- Pemphigus foliaceus is a superficial blistering disease similar to pemphigus vulgaris, except it rarely involves the mucous membranes. Blisters often appear as shallow erosions associated with erythema, scale, and crust formation, and the appearance may resemble severe seborrheic dermatitis.

- Sudden appearance of multiple seborrheic keratosis is the sign of Leser-Trélat, with acanthosis nigricans and skin tags.

- Multiple, round, or oval, sharply demarcated scaling patches have been reported in South African black patients with HCC characterized as Pityriasis rotunda [13].

Other clinical presentations that may be seen in symptomatic patients with HCC are as follows.

A. Intraperitoneal bleeding due to tumor rupture. Tumor rupture is often associated with sudden onset of severe abdominal pain with distension and an acute drop in the hemoglobin and hypotension and is most commonly diagnosed by imaging the abdominal parts. A liver mass and free intraperitoneal blood can be demonstrated by doing computed tomography of the abdominal part [14]. Emergency angiography and embolization is required in case of bleeding as it can become a life-threatening complication [15]. If feasible, delayed resection may be considered although the risk of peritoneal dissemination is high [16].

B. Obstructive jaundice majorly caused by invasion of the biliary tree or due to compression of the intrahepatic duct.

C. Fever developing in association with central tumor necrosis.

D. Pyogenic liver abscess (very rare) [17].

1.3 Diagnosis

Early diagnosis of HCC is through screening or surveillance and is in treatable stage. Typically ultrasonography is performed every 6 months in screening and surveillance for abdominal imaging. A cross-sectional imaging of a detected nodule through ultrasonography using triple-phase CT or contrast-enhanced MRI is performed frequently. Increased tumor vascularity is observed in the arterial phase by radiographic features of HCC. Tumor invasion of the portal vein or lymph node enhancement identification is an additional imaging feature. Liver Imaging Reporting and Data System (LIRADS) systematically characterize these imaging findings diagnostic criteria that also incorporates tumor growth [18]. The resemblance of to normal hepatocytes to neoplastic cells assesses the degree of differentiation of HCC [19].

The possibility of tumor seeding during the biopsy, and the patients with chronic kidney disease represent a particular challenge since MRI contrast agents are contraindicated in end-stage renal disease given the risk of renal toxicity [20].

The evaluation after HCC diagnosis is done through different techniques.

A multidisciplinary setting is required to select therapy after the diagnosis of HCC is made for further evaluations. History and physical examination and serologic and imaging tests are obtained to assess the patient's liver reserve, performance status, comorbidities, extent of tumor spread, and potential eligibility for liver transplantation. "Staging and prognostic factors in hepatocellular carcinoma" are the Multidisciplinary evaluations [21].

1. Surgical resection

2. Liver transplantation

3. Locoregional therapies

4. Ablative therapies (radiofrequency ablation, microwave ablation, cryoablation)

5. Percutaneous ethanol or acetic acid ablation

6. Irreversible electroporation

7. Transarterial embolization (bland embolization, chemoembolization, radioembolization)

8. External beam radiotherapy

9. Systemic chemotherapy and immunotherapy

10. Laboratory tests—Complete blood count, platelets, renal function tests, prothrombin time, albumin

11. Liver biochemical and function tests (i.e., bilirubin, aminotransferases, alkaline phosphatase)

12. Imaging—Extent of tumor spread may be evaluated with the following imaging exams:

    a. Contrast-enhanced abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI) tailored for liver lesion evaluation (see "Modalities for HCC diagnosis" above)

    b. Chest CT without or with intravenous contrast.

    c. Whole body technetium-99m bone scan, if clinically indicated

2. Pathophysiology of HCC

2.1 Anatomy of the liver

The liver is one of the most complex and largest organs in the abdominal cavity. Lobules are the major microscopic functional units of the liver. Removal of endogenous and exogenous materials from the blood, carbohydrate homeostasis, complex metabolic processes including bile production, lipid metabolism, urea formation, and immune functions are some of the major functions performed by the liver. The upper posterior surface of the liver is outside of mesogastrium, a structure through which liver arises. The liver is connected to the anterior body wall by the ligamentum teres and falciform ligament. It connects to the stomach by the lesser omentum and the coronary and triangular ligaments to the diaphragm. The liver is the largest internal organ. The position of the liver is just beneath your right lung and under your right ribs. It has two lobes (sections) involving the right lobe and the left lobe. Women are in more risk to develop hepatic cancer and FNH tumors than men [22] (**Figure 2**).

Another type of cells in the liver called as bile ducts are the cells that line small tubes in the liver. The bile ducts carry bile from the liver to the gallbladder or directly to the intestines. It has many important functions: it breaks down and stores many of the nutrients absorbed from the intestine that your body needs to function. It delivers bile into the intestines to help absorb nutrients (especially fats). It breaks down alcohol, drugs, and toxic wastes in the blood, which then pass from the body through urine and stool. Several types of malignant (cancerous) and

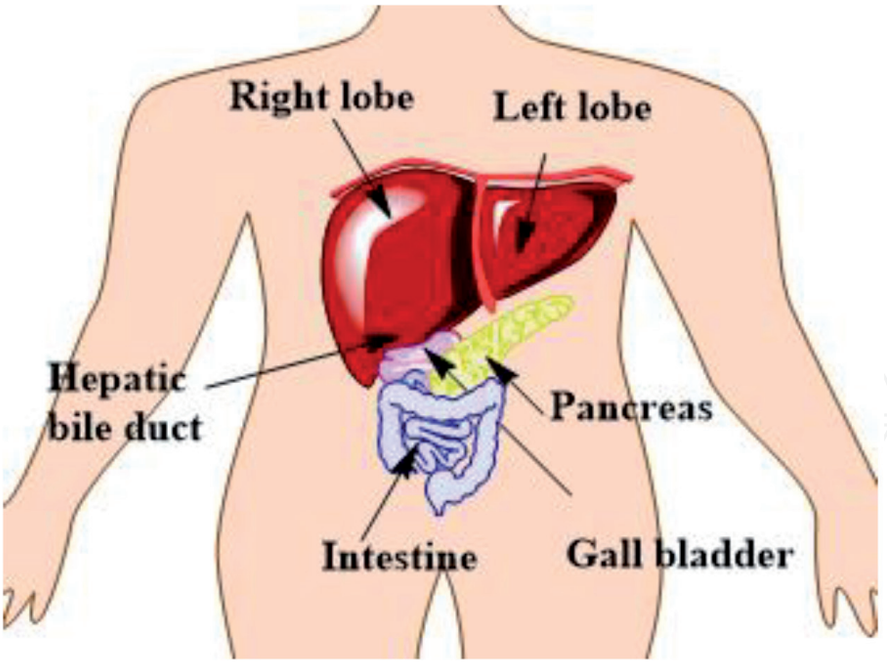

Figure 2.
Anatomy of the liver.

benign (noncancerous) tumors can be formed through different types of cells in the liver. These tumors generated via different cell origins have different root causes, different modes of treatments, and have a different outlook. Hepatitis infection was linked to HCC by Beasley in 1981 [23].

2.2 Category of liver cancer

2.2.1 Primary liver cancer

A cancer that starts in the liver is called primary liver cancer that can be more than one type.

2.2.1.1 Intrahepatic cholangiocarcinoma (bile duct cancer)

Intrahepatic cholangiocarcinomas covers 10–20% of cancers that start in the liver. This type of cancer mostly starts in the bile duct where carcinogenic conditions can be facilitated by the repetitions of inflammation [24].

2.2.1.2 Angiosarcoma and hemangiosarcoma

Cells lining the blood vessels of the liver are the rare causes of liver cancer. Exposure to vinyl chloride or to thorium dioxide (Thorotrast) may develop these cancers (see Liver cancer risk factors). Some other cases are thought to be caused by exposure to arsenic or radium or to an inherited condition known as hereditary hemochromatosis. It is difficult to investigate the exact cause for the development of cancer cells. These tumors grow quickly and are usually too widespread to be removed surgically by the time they are found. The pathogenesis of such HCC is made up of different genetic/epigenetic aberrations and alterations with many signaling pathways that lead to a known heterogeneity of the diseases' biologic and clinical behavior [25].

2.2.1.3 Hepatoblastoma

Children with the age of below 4 years develops this rare form of cancer, that usually seen in the younger age. Fetal liver cells are similar to the cells of hepatoblastoma. It is harder to treat such tumors if they spread outside the liver, where surgery and chemotherapy are the successful therapies in treating two out of three children suffering from such a tumor. The genetic pathways that are affecting hepablastoma have to be further studied and analyzed [26].

2.2.2 Secondary liver cancer (metastatic liver cancer)

Most of the time when cancer is found in the liver, it did not start there but has spread (metastasized) from somewhere else in the body, such as the pancreas, colon, stomach, breast, or lung. As this cancer spreads from its original site, it is called a secondary liver cancer.

2.2.2.1 Benign liver tumors

Sometimes larger growth of benign tumors causes problems, though they do not grow into nearby tissues or do not spread to other distant parts of the body. Surgery can be the best therapy for such a kind of cancer.

2.2.2.2 Hemangioma

Hemangiomas start in the blood vessels and are considered another most common type of liver cancer. They generally do not show any symptoms but need to operate in chronic cases Multidetector-row computed tomography (MDCT) [27].

2.2.2.3 Hepatic adenoma

This tumor starts from hepatocytes (the main type of liver cell) with symptoms like pain in the abdomen, lump in the stomach area, or blood loss. In such cases there is always a risk of tumor rapture or further growth into a vigorous liver cancer. Thus, surgery is the most effective treatment advised by the experts. Fibrolamellar, pseudoglandular (adenoid), pleomorphic (giant cell), and clear cell are microscopically, the four architectural and cytological types (patterns) of hepatocellular carcinoma [28].

2.3 Remedies and treatment (staging)

Patients with cirrhosis and varying degrees of hepatic dysfunction are majorly prone to HCC. A careful assessment of hepatic function in addition to tumor parameters is thus required for the adequate treatment of HCC. Patients are often managed by multidisciplinary teams at tertiary referral medical centers (**Figure 3**).

2.3.1 Drugs in market and drugs under clinical trial

Various chemotherapeutic potent drugs for the treatment of HCC have been efficiently developed, and many are in the pipeline under different phases of clinical trials. A brief enlisting of such drugs approved by the FDA and under clinical trials is depicted in **Tables 1** and **2** [29].

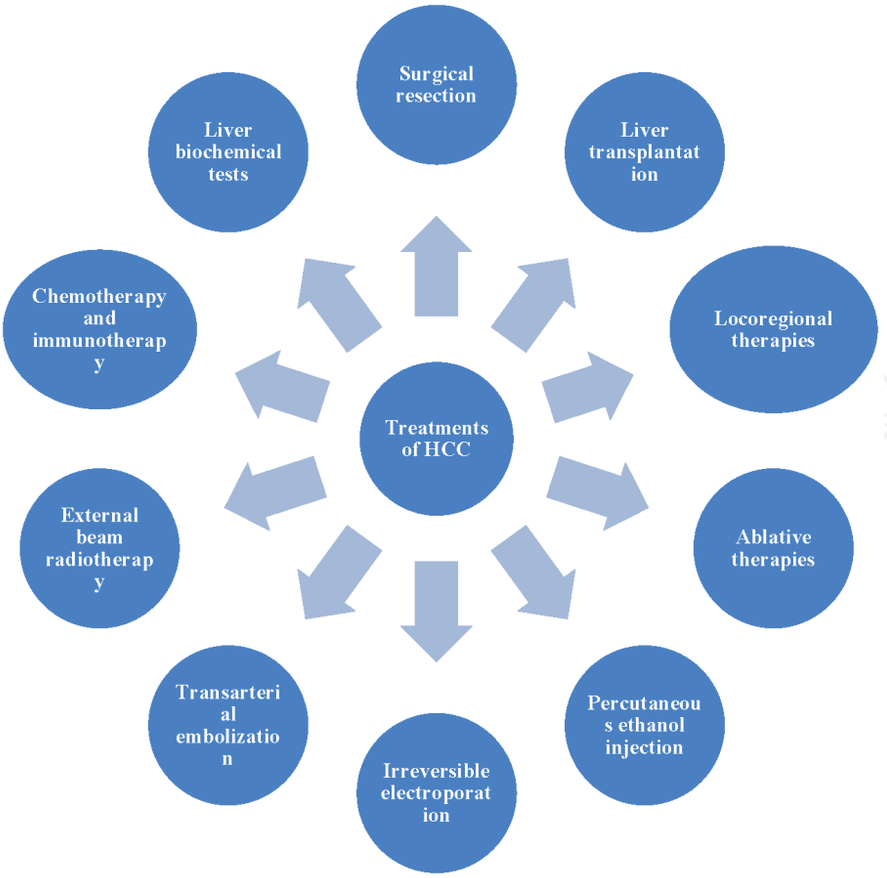

Figure 3.
Potential treatment options for HCC.

S. no.	Drugs	Company	Approved year
1	Sorafenib (Nexavar)	Bayer and Onyx	2007 in the United States
2	Regorafenib (Stivarga)	Bayer	2017 in the United States
3	Nivolumab (Opdivo)	Bristol-Myers Squibb	2017 in the United States
4	Lenvatinib (Lenvima)	Eisai Co.	2018 in the United States
5	Cabozantinib (Cabometyx)	Exelixis Inc.	2018 in Europe
6	Pembrolizumab (Keytruda)	Merck	2018 in the United States
7	Pembrolizumab	Merck	2018 in the United States
8	Rozlytrek (entrectinib)	Roche	2019 in the United States
9	Cabozantinib (Cabometyx)	Exelixis	2019 in the United States
10	Ramucirumab (Cyramza)	Eli Lilly	2019 in the United States
11	Atezolizumab	TECENTRIQ®	2019 in the United States

Table 1.
Recently approved drugs for the treatment of HCC [29].

2.4 Therapeutic engineering

The following therapeutic treatment engineering options are available to patients with hepatocellular carcinoma (**Figure 4**).

S. no.	Drugs	Developed by	Drugs in clinical trials
1	Milciclib (PHA-848125)	Tiziana Life Sciences	II Phase
2	Galunisertib (LY2157299)	Eli Lilly	II Phase
3	Ipafricept (OMP-54F28)	OncoMed	I Phase
4	Ipilimumab (Yervoy)	Bristol-Myers Squibb	II Phase
5	Brivanib	Bristol-Myers Squibb	III Phase

Table 2.
Drug candidates in the pipeline under different phases of clinical trials [30].

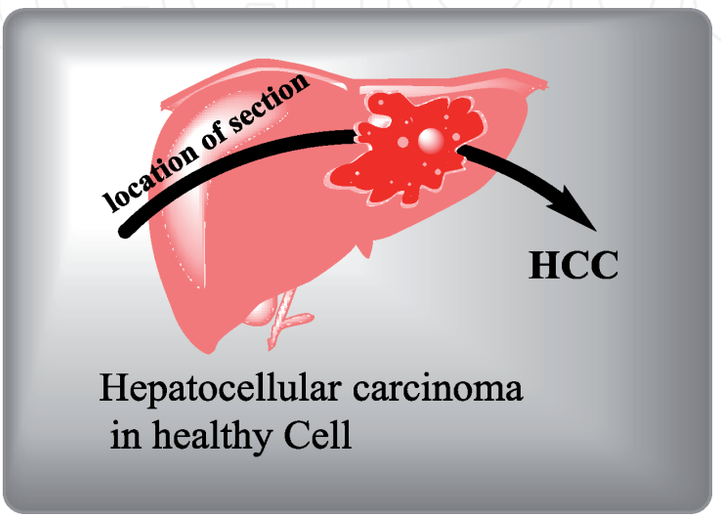

Figure 4.
Hepatocellular carcinoma in healthy cells.

2.4.1 Surgical therapy

Surgery is the treatment of choice for noncirrhotic patients suffering from HCC. However, only 20% of patients are potentially resectable at the time of presentation. In noncirrhotic patients, surgical mortality is less than 3% in experienced hands, but increases to 8% in patients with cirrhosis [3].

2.4.2 Liver resection

Surgery provides the best possibility for a cure. For that reason, every patient should be evaluated first and foremost for the possibility of resection. Organ removal can result in cure in early diagnosis states and overspreading of cancer in other organs.

Unfortunately, not all patients are eligible for liver resection. Resection is not indicated when (1) the tumor has spread to other parts of the liver or the body, (2) the size or location of the tumor resists the part of liver removal without compromising the total functionality of the organ, (3) the associated cirrhosis or disease limits the ability to safely operate upon or remove part of the liver, and (4) other medical conditions make surgery unsafe [3].

2.4.3 Cryosurgery

Cryosurgery is a technique utilizing subzero temperatures to destroy tumors. In most cases, the tumor is destroyed but not removed. The placement of one or more probes (cryoprobe) into the tumor site using ultrasound to guide the placement is adopted in such a technique [3] (**Figure 5**).

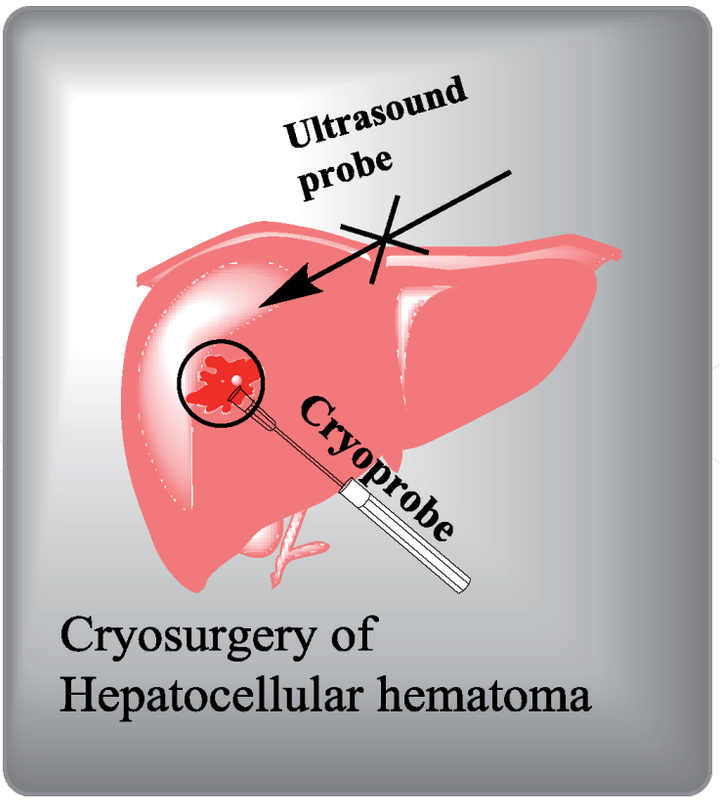

Figure 5.
Cryosurgery of hepatocellular carcinoma.

2.4.4 Radiofrequency ablation

Radiofrequency ablation (RFA) is a new technique that makes use of a "heating" probe to destroy tumors within the liver. A probe with thin tip is put into a tumor site. After deploying the tip array, an electrical current is applied, generating heat (80–100°C) that destroys the tumor (**Figure 6**).

This kind of technique can be done in an operating room or with a laparoscopic approach. RFA is used to treat the tumor, whereas the remaining parts of the tumor are removed by surgery.

2.4.5 Liver transplantation

In patients with small tumors and advanced cirrhosis (Child B or Child C) the treatment of choice is liver transplantation.

Patients who are not candidates for surgical resection or transplantation should be considered for other forms of treatment including cryosurgery, chemoembolization, ethanol or cisplatin infusion, or radiofrequency ablation (**Figure 7**).

2.4.6 Interventional radiological therapy

The most commonly performed procedures in the treatment of unresectable liver tumors (i.e., those that are inoperable) are hepatic artery chemoembolization and hepatic artery chemoradiation. Most hepatic tumors are supplied by the hepatic arterial system, as opposed to normal liver tissue, in which most of the blood supply comes from the portal venous system. Chemoembolization is considered superior over intravenous pump infusion therapy because it delivers drug with more target specification. System toxicity is reduced as 85% of the total drug administered in the body is trapped in the liver itself [3] (**Figure 8**).

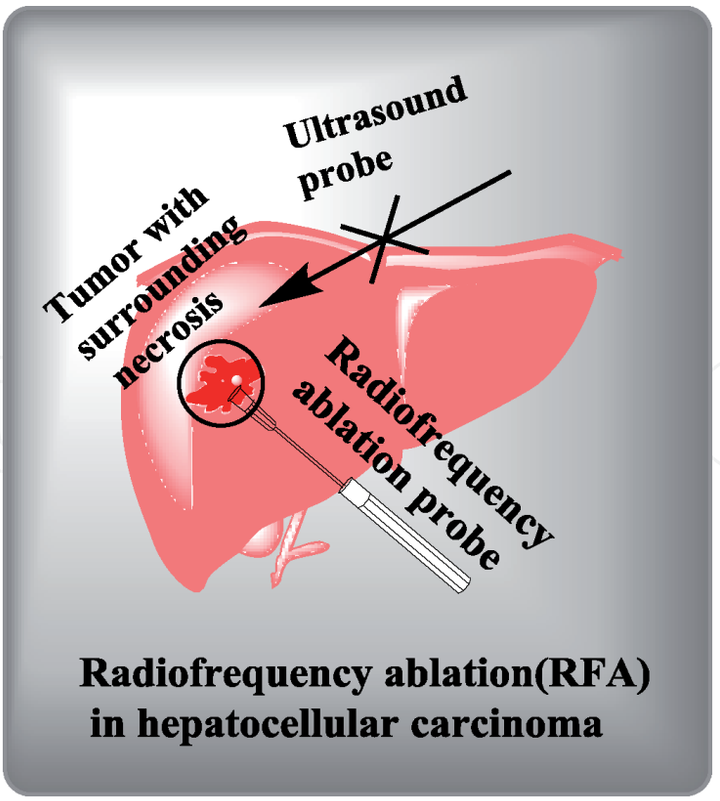

Figure 6.
Radiofrequency ablation in hepatocellular carcinoma.

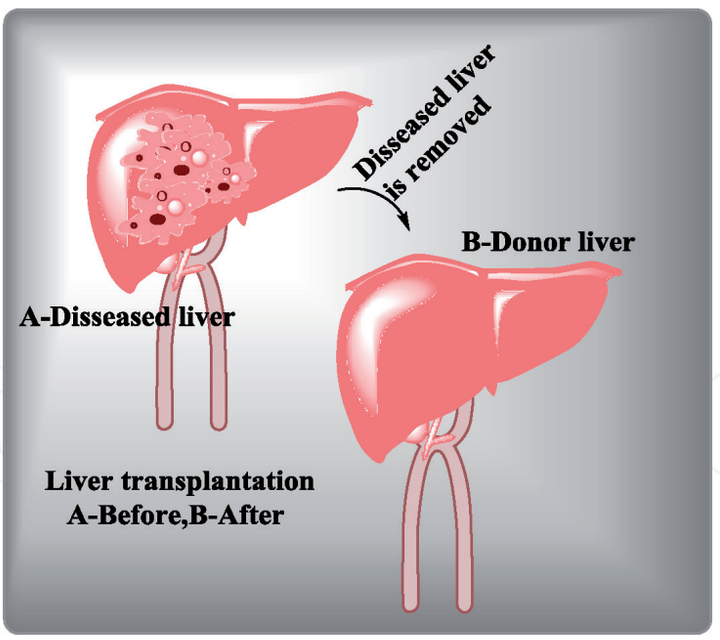

Figure 7.
Transplantation of the liver.

2.4.7 Ethanol injection by percutaneous method

Tumors less than 5 cm in diameter and patients with less than three lesions can be treated with percutaneous ethanol injection. It has been demonstrated that ethanol injection is more effective against hepatoma lesions than against metastatic lesions [3] (**Figure 9**).

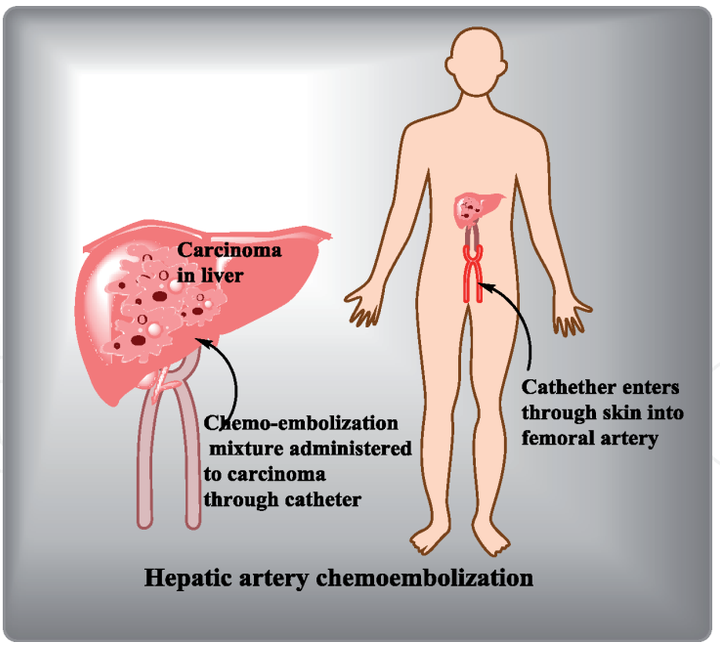

Figure 8.
Hepatic artery chemoembolization.

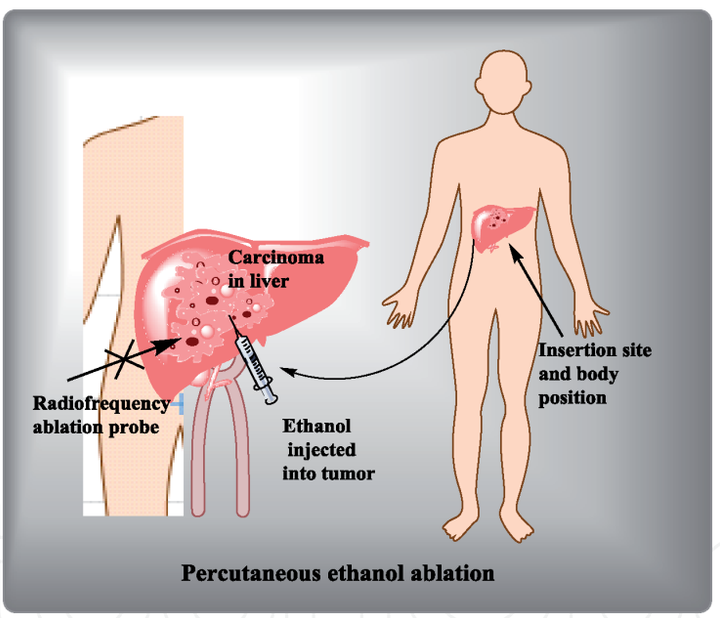

Figure 9.
Percutaneous ethanol injection in hepatic tumors.

Ultrasound vibrations are used to perform such a procedure. Ethanol is injected slowly into a lesion through a small needle that is inserted into the posterior aspect of the tumor. Patients may receive one or two sessions per week until the tumor is completely saturated. Post-procedural imaging, including CT and MRI, is typically conducted after 1 month and then every 4 months thereafter [3].

2.4.8 Percutaneous radiofrequency ablation

Frictional heat produced during percutaneous radiofrequency ablation causes destruction to the local tissues. This procedure is also performed under ultrasound guidance. A radiofrequency needle is inserted deep into the lesion, and multiple electrodes are deployed. The duration of the treatment varies from 6 to 15 minutes.

Only limited data are available regarding the use of this technique to treat unresectable liver tumors, but preliminary studies have shown a trend toward prolonged survival [3] (**Figure 10**).

2.4.8.1 Cisplatin gel infusion percutaneous

Unresectable liver tumors can be treated by cisplatin gel infusion technique that is a new and promising therapeutic option [3] (**Figure 11**).

Clinical trials of this technique are undergoing in the United States as it has been recently developed. It is almost similar to percutaneous ethanol injection method. This technique is also performed in ultrasound vibrations like the percutaneous method. Cisplatin gel is infused into the deepest part of the tumor through a small

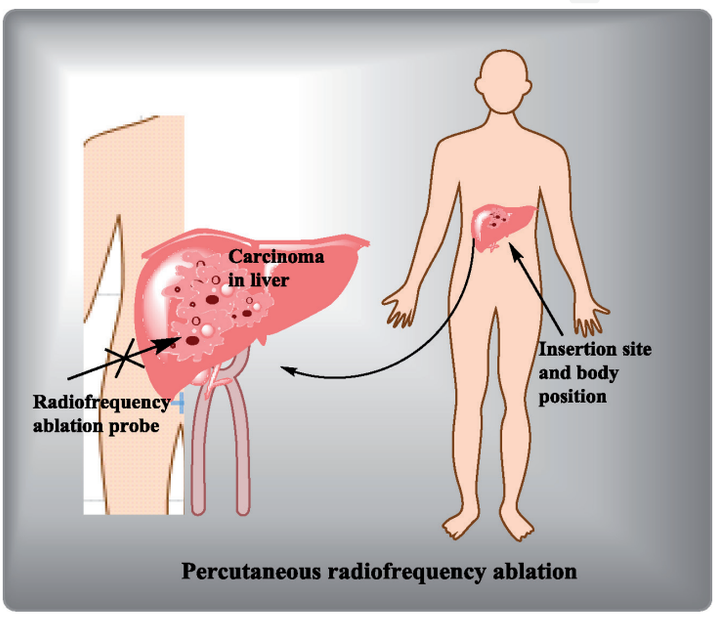

Figure 10.
Percutaneous radiofrequency ablation in hepatic tumors.

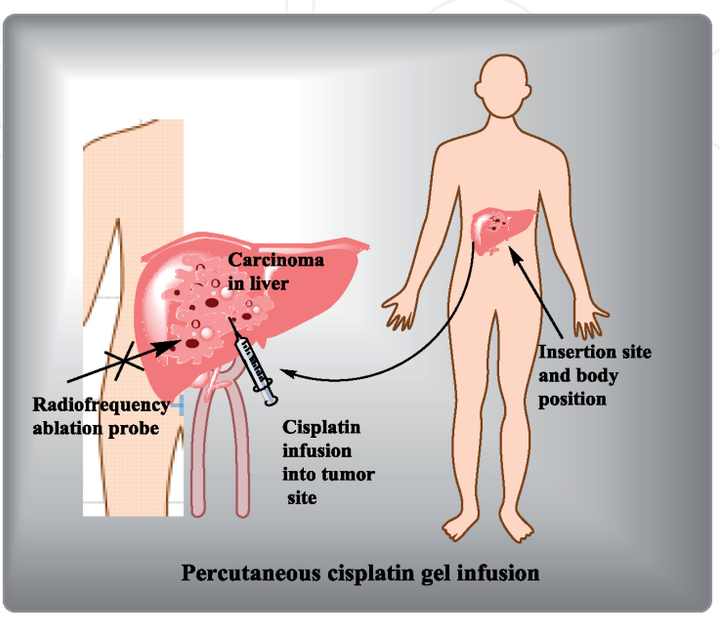

Figure 11.
Percutaneous cisplatin infusion in hepatic tumors.

needle. The chemotherapeutic drug is carried slowly by this gel into the tumor site. The gel slowly diffuses throughout the tumor and acts as a carrier of the chemotherapeutic drug [3].

3. Conclusion

These explanations and findings show that the etiology of HCC is extremely complex, with many confounding factors affecting disease course and patient prognosis. Excessive intake of alcohol, aflatoxin-contaminated food, obesity, and diabetes are the major risk factors for the development of HCC. A better understanding of HCC may offer us the best chance of achieving earlier diagnosis and intervention, which would ultimately improve the outlook for those at risk for developing HCC. These findings may support future studies in investigating the possibilities, developing adequate treatments with intra- and inter-variances of patients in mind, and aiming to improve the mortality for individuals with hepatocellular carcinoma.

4. Future directions

Despite many advances, the treatment of hepatocellular carcinoma is unsatisfactory. As per the current clinical data we can expect, gene therapy and immunotherapy may become more viable for the management and treatment of hepatocellular carcinoma in more safe and effective ways.

Acknowledgements

I thank all my coauthors who are listed, and the work was not funded by any institute or person.

Conflict of interest

We wish to declare that there are no known conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

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