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A systematic review on hepatocellular carcinoma: diagnosis and therapies for patients

Avinash Shankar Bhosale*[1], Mahesh Babanrao Thorat[2], Bhushan Raghunath Pawar[3], Dr. Gurdeep Singh[4], Dr. M. K. Gupta[5]

*[1]Department of Pharmacy, Oriental University, Indore, Madhya Pradesh, India,

[2]Department of Pharmacy, Oriental University, Indore, Madhya Pradesh, India

[3]Department of Pharmacy, Oriental University, Indore, Madhya Pradesh, India

[4]Department of Pharmacy, Oriental University, Indore, Madhya Pradesh, India

[5]Department of Pharmacy, Oriental University, Indore, Madhya Pradesh, India

ABSTRACT

Hepatocellular carcinoma is the most common primary malignancy of the liver in adults. Hepatocellular carcinoma (HCC) represents one of the most challenging potentially curable tumors with high incidence, prevalence and mortality rates. HCC is the fifth most common cancer and the third cause of cancer-related mortality worldwide. Its incidence is clearly arising comprised by the prevalence of major risk factors mainly hepatitis B and hepatitis C. The population at risk is composed of chronic liver patients at the stage of extensive fibrosis or cirrhosis. The monitoring programs of this population have allowed early detection of disease management to promote a radical therapy. Understanding the carcinogenic process and the mastery of the staging systems remain essential keys in diagnosis and treatment of HCC. Recent advances in diagnosis and new treatments have made important impacts on the disease by increasing survival rates and improving quality of life for HCC patients.

Keywords: Hepatocellular carcinoma (HCC), hepatitis B and hepatitis C, radical therapy, new treatments.

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***Address for Correspondence:**

Avinash Shankar Bhosale, Department of Pharmacy, Oriental University, Indore, Madhya Pradesh, India

INTRODUCTION

The liver is a vital organ of vertebrates and some other animals [1]. In the human it is located in the upper right quadrant of the abdomen, below the diaphragm. The liver has a wide range of functions, including detoxification various metabolites, protein synthesis, and the production of biochemicals necessary for digestion. The liver's main job is to filter the blood from the digestive tract, before passing it to the rest of the body. The liver also detoxifies chemicals and metabolizes drugs. As it does so, the liver secretes bile that ends up back in the intestines. The liver also makes proteins important for blood clotting and other functions [2].

Liver cancer is a tumour that initially forms in the tissue of the liver. Different types of liver cancer exist according to the type of cancerous cells. Hepatocellular carcinoma (HCC) is the most frequent type of liver cancer. It accounts for 90% of all liver cancers. Hepatocellular Carcinoma (HCC) is the sixth most common cancer worldwide, accounting for 7% of all cancers and an estimated incidence of 749,000 new cases every year. It is considered to be the third cause of cancer related deaths (692,000 cases). The highest incidence rates of HCC (around 85% of cases) are present in East Asia, sub-Saharan Africa, and Melanesia [3].

Hepatocellular carcinoma begins in hepatocytes, the main cells of the liver. Hepatocellular carcinoma is a malignant tumor composed of cells resembling hepatocytes; however, the resemblance varies with the degree of differentiation. Hepatocellular carcinoma is commonly associated with cirrhosis (Figure no-2).

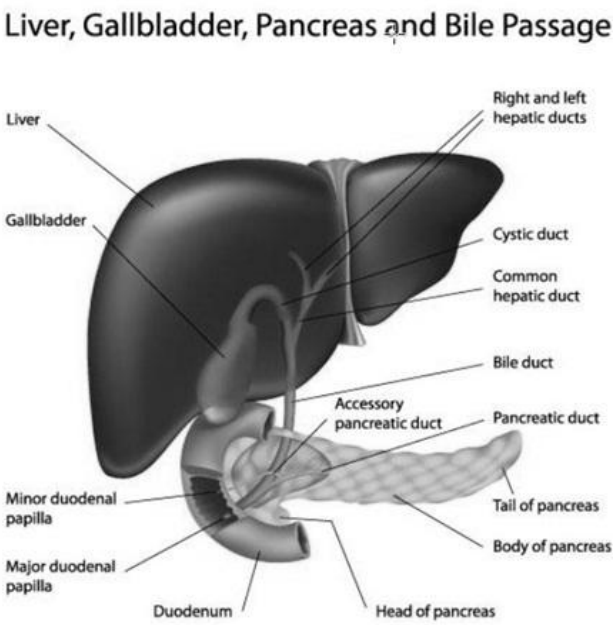

Figure-1: Anatomy of the liver and surrounding organs

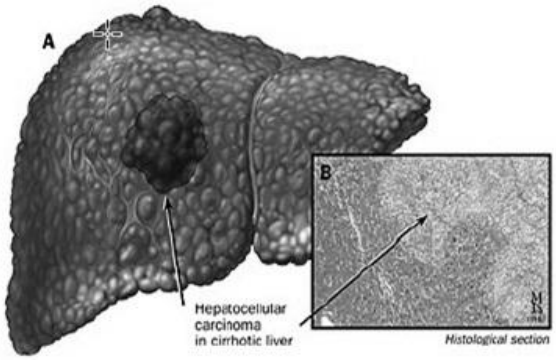

Figure 2: A- Cirrhotic liver with focal tumor; B- histological appearance.

HEPATOCELLULAR CARCINOMA (LIVER CANCER): ANATOMY

The liver is the largest organ in the abdominal cavity and the most complex. It consists of a myriad of individual microscopic functional units call lobules. The liver performs a variety of functions including the removal of endogenous and exogenous materials from the blood, complex metabolic processes including bile production, carbohydrate homeostasis , lipid metabolism, urea formation, and immune functions. The liver arises from the ventral mesogastrium and only the upper posterior surface is outside of that structure. The ligamentum teres and falciform ligament connect the liver to the anterior body wall. [3,4] The lesser omentum connects it to the stomach and the coronary and triangular ligaments to the diaphragm. The liver is smooth and featureless on the diaphragmatic surface and presents with a series of indentations on the visceral surface where it meets the right kidney, adrenal gland, inferior vena cava, hepatoduodenal ligament and stomach. The liver can be considered in terms of blood supply hepatocytes, Kupffer cells and biliary passages. The liver receives its blood supply from the portal vein andhepatic artery, the former providing about 75% of the total 1500 ml/min flow. Small branches from each vessel the terminal portal venule and the terminal hepatic arteriol enter each acinus at the portal triad. Pooled blood then flows through sinusoids between plates and hepatocytes in order to exchange nutrients [4].

The hepatic vein carries efferent blood into the inferior vena cava and a supply of lymphatic vessels drains the liver. Parenchymal cells or hepatocytes comprise the bulk of the organ and carry out complex metabolic processes. Hepatocytes are responsible for the liver's central role in metabolism (Figure no 3). These cells are responsible for the formation and excretion of bile; regulation of carbohydrate homeostasis; lipid synthesis and secretion of plasma lipoproteins; control of cholesterol metabolism; and formation of urea, serum albumin, clotting factors, enzymes, and numerous proteins. The liver also aids in the metabolism and detoxification of drugs and other foreign substances [4]

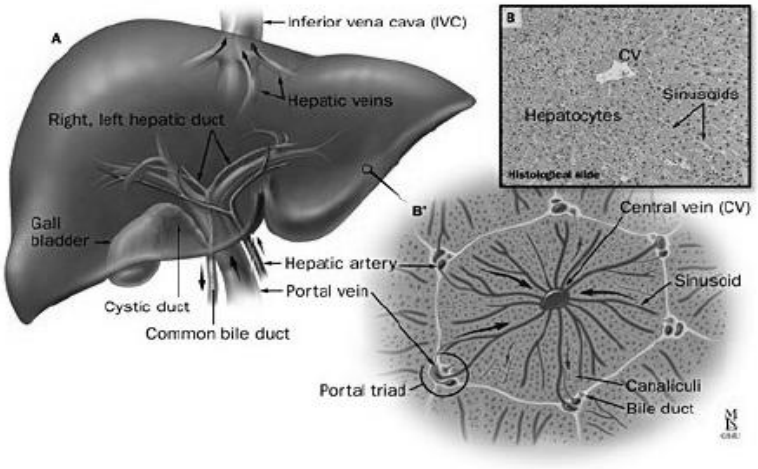

Figure 3: A-Normal gross anatomy of a liver; B, histological slide; B'-histological view.

Kupffer cells line the hepatic sinusoids and are part of the reticuloendothelial system, filtering out minute foreign particles, bacteria, and gut-derived toxins. They also play a role in immune processes that involve the liver. Biliary passages begin as tiny bile canaliculi formed by hepatocytes. These microvilli -lined structures progress into ductules, interlobular bile ducts, and larger hepatic ducts. Outside the porta hepatis, the main hepatic duct joins the cystic duct from the gallbladder to form the common bile duct, which drains into the duodenum. HCC cases are associated to cirrhosis secondary to chronic infection with either hepatitis B or C viruses[4].

PATHOLOGY OF LUNG CANCER

HCC may present as a unifocal, multifocal, or diffusely infiltrative tumor [5]. All patterns demonstrate broad potential for vascular invasion. When associated with cirrhosis, HCC usually arises from malignant transformation of a regenerative nodule.

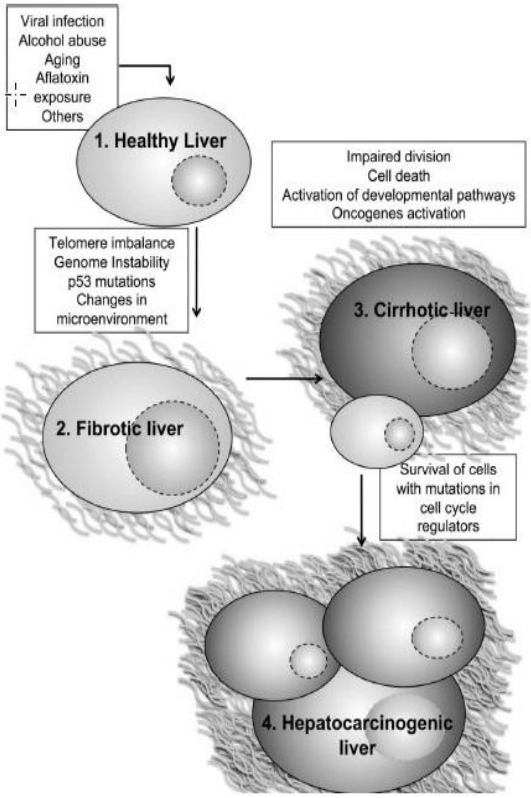

Figure 4: Development of liver tumors and their evolution to HCC

There is stimulation to angiogenesis, and the tumor receives abundant arterial vascularization. The mean tumor duplication time is about 200 days [6]. This time decreases as tumor increases. With up to 3 cm in size, HCC is generally well differentiated, encapsulated, and has low potential for blood vessel invasion. When it reaches approximately 5 cm in size, the nodule begins to loose differentiation and to exhibit microscopic vascular invasion, acquiring capacity to generate metastases [7,8]

SIGN AND SYMPTOMS OF LIVER CANCER

Signs and symptoms of liver cancer often do not show up until the later stages of the disease, but sometimes they may show up sooner. If you go to your doctor when you first notice symptoms, your cancer might be diagnosed earlier, when treatment is most likely to be helpful. Some of the most common symptoms of liver cancer are:

- Weight loss (without trying)
- Loss of appetite
- Feeling very full after a small meal
- Nausea or vomiting
- An enlarged liver, felt as a mass under the ribs on the right side
- An enlarged spleen, felt as a mass under the ribs on the left side
- Pain in the abdomen or near the right shoulder blade
- Swelling or fluid build-up in the abdomen
- Itching
- Yellowing of the skin and eyes (jaundice) Some other symptoms can include fever, enlarged veins on the belly that can be seen through the skin, and abnormal bruising or bleeding [7,8].

HEPATOCELLULAR CARCINOMA (LIVER CANCER): CAUSES [9,10,11]

Hepatitis B and C

The two most important etiological factors contributing to hepatocelluar carcinoma are hepatitis B and hepatitis C (Figure 5). In parts of China and Taiwan, 80% of hepatocellular carcinoma is due to hepatitis B. In the United States and Europe, hepatitis C and hepatitis B contribute equally to disease cases. In Japan, where the prevalence of hepatitis B and hepatitis C is similar, the incidence of hepatocellular carcinoma is higher in patients with hepatitis C compared to hepatitis B (10.4% vs. 3.9%). The pathogenesis of hepatocellular carcinoma in the presence of hepatitis B virus may be due to increased cell turnover from chronic liver disease, or a combination of processes specific to the hepatitis B virus. These may include integration of the hepatitis B DNA genome into the host genome, thereby disrupting the regulatory elements of cell cycling, or via transactivation of host oncogenes by either HBx protein or a truncated protein derived from pre-S2/S region of hepatitis B genome. The pathogenesis of hepatocellular carcinoma in hepatitis C is less understood. It is possible that some of these patients had previous exposure to hepatitis B virus.

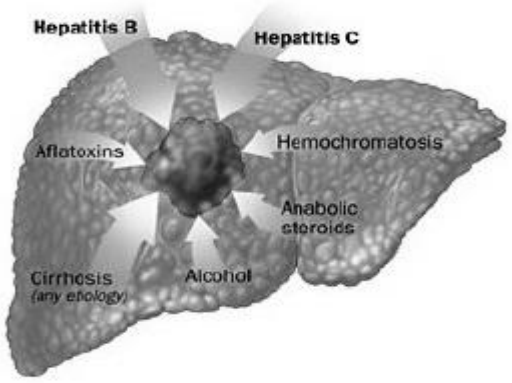

Figure **5:** Causes of hepatocellular carcinoma

Cirrhosis

Cirrhosis, irrespective of its etiology , is a risk factor for the development of hepatocellular carcinoma. The risk is 3–4 times higher in patients with cirrhosis compared to those with chronic hepatitis in a given population. An increase in hepatocellular proliferation may lead to the activation of oncogenes and mutation of tumor suppressor genes. These changes, in turn, may initiate hepatocarcinogeneses .

Other Factors

Other etiological factors affecting disease incidence include aflatoxins, alcohol, hemochromatosis , and anabolic steroid use.

HEPATOCELLULAR CARCINOMA (LIVER CANCER): DIAGNOSIS

Clinical Features

The classic clinical features of HCC include right upper quadrant pain and weight loss. Other clinical scenarios that

suggest this diagnosis include worsening liver function in a patient known to have cirrhosis, acute abdominal catastrophe from rupture of a liver tumor with intra-abdominal bleeding, and some rare extrahepatic manifestations [12].

Alpha-Fetoprotein (AFP)

Alpha-fetoprotein levels may be assessed by a blood test. Alpha-fetoprotein (AFP) is a tumor marker that is elevated in 60–70% of patients with hepatocellular carcinoma. Normally, levels of AFP are below 10 ng/ml, but marginal elevations (10–100) are common in patients with chronic hepatitis. However, all patients with elevated AFP should be screened (abdominal ultrasound, CT scan or MRI) for hepatocellular carcinoma, especially if there has been an increase from baseline levels. In our experience, a steadily rising AFP is almost diagnostic of hepatocellular carcinoma. The specificity of AFP is very high when the levels are above 400 ng/ml. Undifferentiated teratocarcinoma and embryonal cell carcinoma of the testis or ovary may give false-positive results and should be considered in the differential diagnosis of elevated AFP [13].

Radiographic Diagnosis

The diagnostic accuracy of ultrasound, CT, magnetic resonance imaging (MRI) and angiography is dependent on a number of variables: expertise of the operator (especially with ultrasound), sophistication of equipment and technique, presence of cirrhosis and, most importantly, experience of the interpreter [14,15].

HEPATOCELLULAR CARCINOMA (LIVER CANCER): THERAPY

HCC recently appeared as a potentially curable disease with many treatment options that depend on patient factors as the performance status and operability, and tumor related factors like size, location and the presence or absence of extratumoral spread.

- ***Herbal Remedy For Liver Cancer*** Herbal drugs have become increasingly popular and their use is wide-spread. Herbal medicines have been used in the treatment of liver diseases for a long time so the maintenance of a healthy liver is essential for the overall well being of an individual. [16] Liver injury induced by toxins is more common nowadays. Herbal remedies are focused in the pharmaceutical industry to evolve a safe route for liver disorders. Therefore, hepatoprotective natural products are *Andrographic paniculata, Chamomile capitula , Silybum marianum, Coccinia grandis, Flacourtia indica, Wedelia calendulacea, Annona squamosa, Prostechea michuacana, Ficus carica, Lepidium sativum, Sargassum polycystum, Solanum nigrum, swertia chirata, Phyllanthus emblica, Curcuma longa, Picrorhiza kurroa* [17].

- ***Liver Resection.*** Orthotopic liver transplantation (OLT) is the curative options in which both the tumor and the underlying liver disease are removed. Therefore, it is the treatment of choice for patients with hepatic cirrhosisrelated hepatocellular carcinoma.[18].

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 (near major blood vessels) precludes it from being safely removed without compromising function of the remainder of the liver, 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 [19]. Excessive blood loss during liver resection not only increases the need for blood transfusion, with its associated problems, but increases the risk of structural injury and suboptimal tumor margin clearance by obscuring the surgical field. Newer surgical techniques of vascular isolation, as well as the use of intraoperative ultrasonography, have significantly reduced the need for blood transfusions and blood products in modern liver surgery.

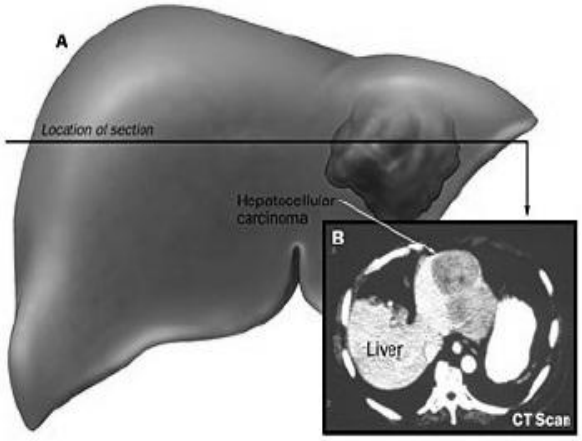

Figure 6: A-Hepatocellular carcinoma in healthy liver; B-corresponding computed tomography (CT) scan.

- ***Radiofrequency Ablation*** Percutaneous ablation with percutaneous ethanol injection (PEI) or radiofrequency ablation (RF) achieves complete responses in more than 80% of tumours smaller than 3 cm in diameter and provide 5-year survival rates of 40–70%. new technique that makes use of a “heating” probe to destroy tumors within the liver.

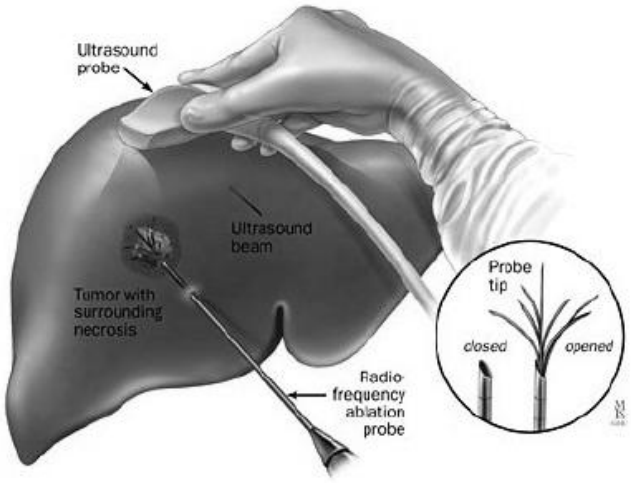

Figure 7: Radiofrequency ablation (RFA) in hepatocellular carcinoma.

A thin probe is placed within the tumor, typically under ultrasound guidance. After deploying the tip array, an electrical current is applied, generating heat (80–100°C) that destroys the tumorThe best outcomes have been reported in Child–Pugh A patients with small single tumours, commonly less than 2 cm in diameter [20,21].

- ***Palliative Therapy***. Due to the implementation of prevention programs for HCC, patients are usually diagnosed in early stage. Nevertheless, some are detectable at an intermediate or advanced stage with

preserved liver function or not, multinodular disease exceeding the Milan criteria, with or without symptoms or extrahepatic spread manifested by absence of portal/node invasion or distant metastasis. For these patients, palliative therapies are proposed to reduce symptoms related to disease progression and improve survival. The general principle of palliative treatment is to prevent the blood supply to the HCC by blockage of the arterial system of liver[22]. These treatments include transarterial embolization (TAE), transarterial chemoembolization (TACE), intra-artery chemotherapy (IACT), and radiotherapy (external and internal). They can be usedas bridge to liver transplantation [23].

- ***Cryosurgery*** Although surgical resection may afford the only potential for cure for patients with liver tumors, many patients may not be surgical candidates for a variety of reasons. Novel methods for local ablation have been developed with the goal of increasing the number of patients eligible for surgical therapy. Hepatic cryosurgery is one such interstitial therapy that has gained popularity in recent years. This technique relies on the in situ destruction of a defined area within the liver using liquid nitrogen at subzero temperatures. Although cryosurgery has been used in the past for the treatment of a variety of surface malignancies, recent advances in the ability to deliver liquid nitrogen deep within tissue using a closed-circuit insulated probe system, as well as improvements in intraoperative imaging using intraoperative ultrasound, have provided the capability for safe hepatic cryoablation [24].

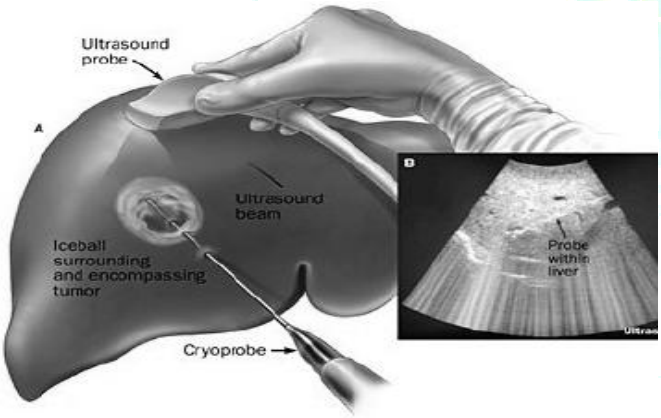

Figure 8: Cryosurgery of hepatocellular hematoma; B, corresponding ultrasoundshowing the probe in the tumor.

Cryosurgery is a technique utilizing subzero temperatures to destroy tumors. In most cases, the tumor is destroyed but not removed. The technique involves the placement of one or more probes (cryoprobe) into the tumor using ultrasound to guide the placement. Liquid nitrogen, at -190°C, is circulated in a closed system through the end of the probe creating an ice ball at the tip. The ice ball is allowed to encompass the tumor and approximately one-half-inch margin around it the tumor is frozen and thawed twice, potentially taking up to 30 minutes. Following completion of the procedure, patients are monitored in the Intensive Care Unit overnight and remain in the hospital for 3–5 days. Cryosurgery is an operative procedure requiring general anesthesia. It may be performed alone or in conjunction with a liver resection[25, 30].

- ***Systemic Therapies***. Parallel to the development of research concerning pathological and histological pathways leading to HCC, many drugs and hormonal therapy have been tested as agents inhibiting important signaling pathways in tumor cells and also angiogenesis in systemic therapy for HCC. Patients in intermediate or advanced stage who do not undergo curative surgical treatment and ablative techniques are candidates for these therapies. Systemic therapies have not unfortunately provided benefit effect or increased survival for patients with advanced HCC. Several clinical trials have been conducted on these agents searching an optimal therapy against advanced HCC, but there is no currently defined as a standard formula effective against advanced HCC. They can be used as single or combined hormonal or chemotherapy. The most used is the multikinase inhibitor sorafenib that was approved by the European Medicines Agency (EMEA) and the US Food and Drug Administration(FDA). These promising benefits in patients with metastaticdisease need further evaluation. Other therapeutic agentssuch as doxorubicin, epirubicin, mitoxantrone, cisplatin, gemcitabine, capecitabine, 5-Flu, Tamoxifen, and placebo.have been also used as single agent against advanced HCC.Some combined agents against HCC have been investigated,and the most known are cisplatin, doxorubicin, 5-Flu, and interferon-α (PIAF), gemcitabine and oxaliplatin (GEMOX), oxaliplatin and 5-Flu/leucovorin (FOLFOX), capecitabine and oxaliplatin (XELOX). The results vary depending on the research groups, countries, and characteristics of the patients tested [26].
- ***Liver Transplantation*** In patients with small tumors and advanced cirrhosis (Child B or Child C) the treatment of choice is liver transplantation. The 5-year survival in patients with small tumors (a single tumor less than 5 cm, or two tumors less than 3 cm) is 50–60%. Poorly differentiated tumors that show vascular invasion, and large tumors have a poor prognosis.

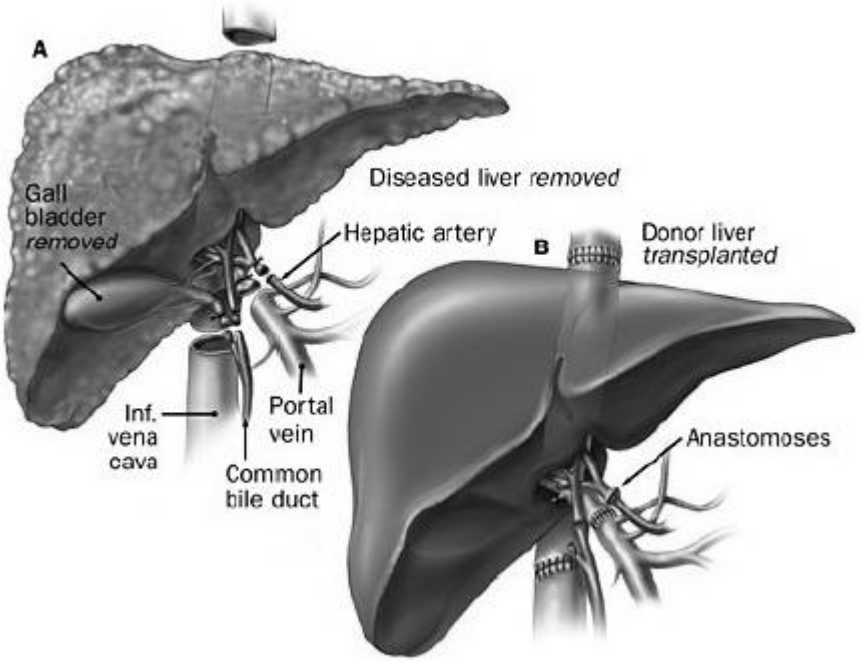

Figure 9: Liver transplantation; A, before, diseased liver; B, after, donor liver in place.

Although the presence of tumors of both lobes was at one time considered a poor prognosis after livertransplantation, a recent study demonstrated that patients with bilobar disease have the same survival rates as patients with unilobar disease [27]

- ***Interventional Radiological Therapy Hepatic*** artery chemoradiation is by far the most commonly performed procedure in the treatment of unresectable liver tumors (i.e., those that are inoperable). 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 has several theoretical advantages over intravenous pump infusion therapy because it delivers highly concentrated drugs to the tumor itself and arrests blood flow, the latter prolonging contact time within the tumor.

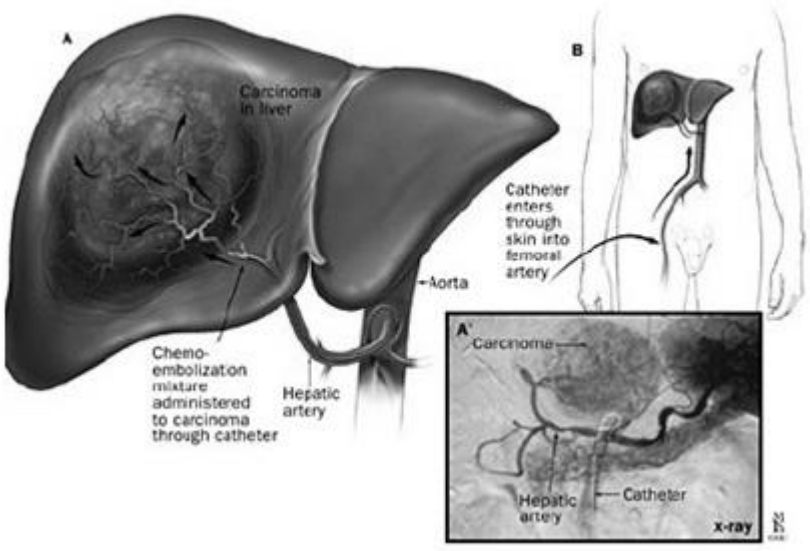

Figure 10: A, B, Hepatic artery chemoembolization; A', with corresponding angiogram.

This technique deprives the tumor of its oxygen supply while achieving a drug concentration in the tumor 10–25 times greater than that which can be achieved by infusion alone. In addition, the "dwell time" for the drug is markedly prolonged, with measurable drug levels present as long as a month after chemoembolization [28, 30].

- ***Percutaneous Ethanol Injection*** Ultrasound-guided percutaneous ethanol injection in hepatic tumors was first described in 1983.

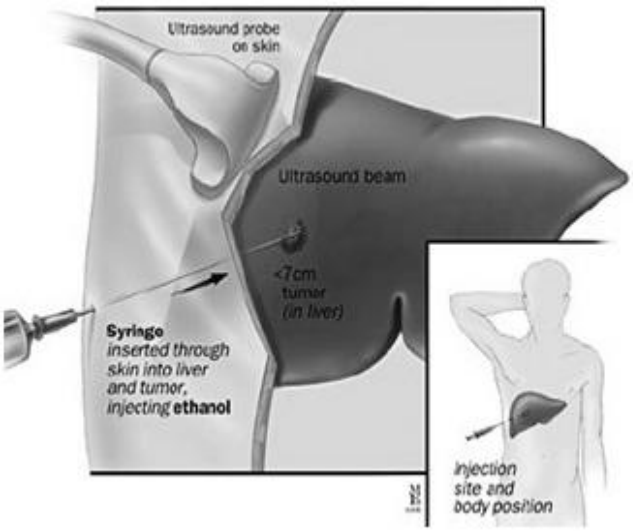

Figure 11: Percutaneous ethanol injection

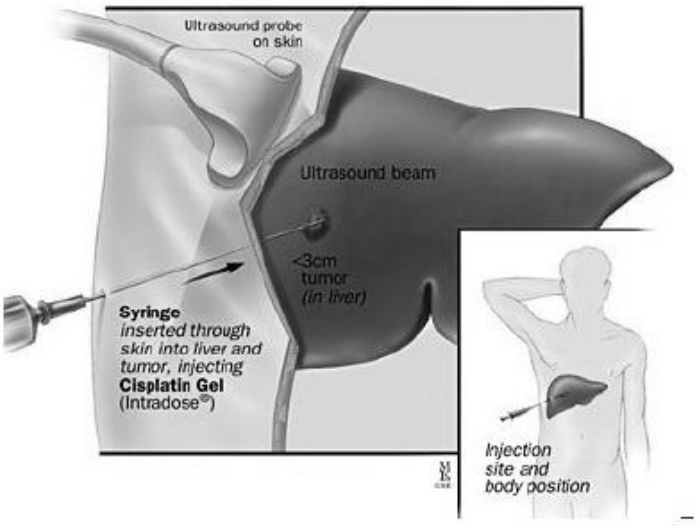

Figure 12: Percutaneous cisplatin gel infusion.

Percutaneous ethanol injection has been used primarily to treat tumors less than 5 cm in diameter and patients with less than three lesions. It has been demonstrated that ethanol injection is more effective against hepatoma lesions than against metastatic lesions. The procedure is performed under ultrasound guidance. A small needle is inserted into the posterior aspect of the tumor, and ethanol is slowly injected into the lesion.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 [29,30].

- ***Cisplatin Gel Infusion*** Percutaneous cispatin gel infusion is a new and promising therapeutic option for the treatment of unresectable liver tumors. This technique was recently developed and is currently undergoing clinical trials in the United States. It is similar to percutaneous ethanol injection in that it is performed under ultrasound guidance.

A small needle is inserted directly into the deepest aspect of the tumor and the cisplatin gel is infused. The gel slowly diffuses throughout the tumor and acts as a carrier of the chemotherapeutic drug. Because this treatment method is undergoing initial clinical trials, strict enrollment criteria have been defined. Tumors greater than 7 cm cannot be treated using this technique [30].

CONCLUSION

The HCC remains a malignant disease leading to death.Significant progress has been made in the management of the disease. Because of its complexity, a multidisciplinary approach must be implemented to support the different aspects in HCC. A better control of epidemiology should better sit prevention programs in at-risk populations. A better understanding of the molecular and histological responsible for the occurrence of the disease should allow the development of new diagnostics and treatments more effective in the treatment of HCC.

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