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NEW THERAPEUTICS OF HEPATOCELLULAR CANCER

REVIEW ARTICLE

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Acronym List

ADH – Acetate dehydrogenase

AFP – α -fetoprotein

ALDH – Aldehyde dehydrogenase

EBRT – External Beam Radiation Therapy

EGFR – Epidermal growth factor receptor

HCC – Hepatocellular carcinoma

HBV – Hepatitis B virus

HCV – Hepatitis C virus

IMRT – Intensity modulated radiation therapy

PEI – Percutaneous ethanol injection

PIVKA II – Protein-induced by vitamin K absence or antagonist II

PDGFR – Platelet-derived growth factor receptor

ROS – Reactive oxygen species

TACE – Transarterial Chemoembolization

cTACE – conventional Transarterial Chemoembolization

RFA – radiofrequency ablation

VEGFR – Vascular Endothelial Growth Factor Receptor

Abstract

Hepatocellular carcinoma is the 6th largest cause of death due to malignant neoplasia worldwide. In addition to being related to a high mortality rate, it is also related to a high morbidity rate, despite the means spent on disease prevention and surveillance.

This pathology relates to numerous risk factors, from eating habits, contact with occupational chemicals, infections, viruses and fungi and individual genetics, that can be manipulated in a way that reduces the likelihood of disease development and affects its course.

Hepatic resection remains the traditional choice in the treatment of hepatocellular carcinoma. However, advances in molecular biology, the knowledge of the molecular mechanisms involved and the development of percutaneous intervention techniques have paved the way for other treatments to present options with features more appropriate to a variety of disease scenarios.

The objective of this study is to review the new treatments available against hepatocellular carcinoma integrated in the frame of current knowledge about the disease.

Resumo

O carcinoma hepatocellular constitui a 6^o maior causa de morte por neoplasia maligna a nível mundial. Para além de estar relacionado com uma elevada taxa de mortalidade está também relacionado com uma elevada taxa de morbilidade, apesar dos meios despendidos na prevenção e vigilância da doença.

Esta patologia relaciona-se com inúmeros fatores, desde os hábitos alimentares, contacto com químicos na carreira profissional, causas infecciosas viral ou fúngica e a genética individual que podem ser manipulados de forma a reduzir a probabilidade de desenvolvimento da doença e afetar o seu curso.

A resseção hepática continua a ser a opção tradicional no tratamento do carcinoma hepatocelular. Contudo, avanços na biologia molecular e em técnicas de intervenção percutânea abriram um caminho para que outros tratamentos apresentem opções com características mais apropriadas a uma variedade de cenários de doença.

O objetivo deste estudo é rever os novos tratamentos disponíveis contra o carcinoma hepatocelular integrados no campo do conhecimento corrente da doença.

Keywords

- Hepatocellular carcinoma
- Etiopathogeny
- Cell signaling pathways
- Hepatocellular carcinoma therapies

Introduction

The hepatocellular carcinoma (HCC) is one of the most frequent malign neoplasia in the world. It is associated to a high mortality and morbidity.

Its treatment and prognosis depends of its stage at the moment of diagnosis and of the early treatment. Liver transplantation is the only known curative treatment.

However, other therapeutic strategies are used, such as quimioembolization, systemic quimiotherapy, radiotherapy, percutaneous ablation, surgical resection. This treatment's efficacy is dependent on various factors.

This makes the research and development an absolute need in order to treat the disease and better the prognostic of the sick.

Methods and Materials

The studies collected to perform this revision were selected from the internet database PubMed. This revision was limited to the studies published from the year 2000 to 2017 and the keywords used were “hepatocelular carcinoma / pathophysiology”, “hepatocelular carcinoma therapy”, “hepatocelular carcinoma/surgery” and “liver transpant”.

The research was also limited to the English and Portuguese languages.

The recovered studies and articles served as the basis for this article. Each one of them was read and its results crossed with reference books for verification and integration purposes.

Chapter 1 – Hepatocellular carcinoma

HCC definition

Hepatocellular carcinoma is a primary malignant solid cancer of the liver and one of the most responsible for cancer related deaths. It is the most common type of cancer and exists in almost every community in the world, affecting developed and in developing countries and is related to common pathologies such as hepatitis and alcoholism.

Epidemiology

The HCC is the fifth most common cause of cancer in the male gender and the seventh in women in the whole world. It is the most common cancer in Africa and Asia.

HCC's presence is correlated to the rate of infection of viral hepatitis (HBV mainly). This disease is most frequent in areas with this pathology such as sub-Saharan Africa and Eastern Asia in which the incidence reaches 20 per 100000 individuals. Approximately 85% of all liver cancers appear in these areas and China is responsible for 50%.^[1]

In Italy, Greece, France, Switzerland and Spain the incidence is of 20-20 per 10000 and in North and South America the incidence is less than 5 per 100,000 individuals.

The global ratio of incidence between men and women is 2-3:1. The areas that don't follow this pattern are central Europe, where there is the biggest discrepancy (4:1) and certain countries like Harare, Zimbabwe, Cali, Costa Rica, Colombia, South Karachi and Pakistan where the ratio is closer to 1:1. The difference in incidence between males and females is presumably related with sex specific risk factors like chronic infection with HBV and aflatoxin intake.

Race also influences the incidence of HCC. The highest incidence is found on Asian / Pacific Island descendants (11.7/100,000). They are followed by Hispanics (8.0/100,000), African descendants (7.0/100,000) and American Indians / Alaskan Natives (6.6/100,000). Caucasians have the lowest race related incidence (3.9/100000). Figure 1 illustrates the rate variation of HCC around the world.

It is also the third major responsible for liver cancer-related deaths in the world.

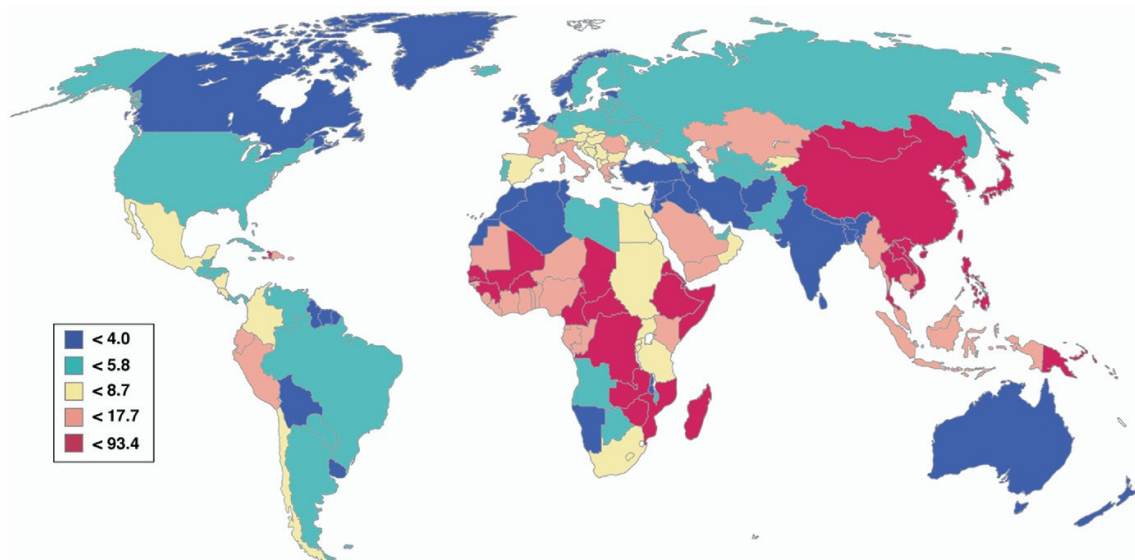


Figure 1 – Age adjusted mortality rate variation by 100000 individuals around the world. From [2]

Etiology and Risk Factors

The vast majority of the major risk factors of the HCC is known. The most relevant of those is the previous occurrence of cirrhosis.

In Asiatic and African countries the ingestion of aliments with aflatoxin B and the infection with hepatitis B virus (HBV) are the most common causes.[3]

In countries in development the moment of infection is the moment of birth or early in life. HCC itself appears in individuals aged at 40 years. If the virus can occult itself

persistently it increases its oncogenic relevance. For instance if the virus is acquired in adulthood the risk of HCC decreases but chronic carriers of HBV have 100 more times of developing the disease than non-carriers. The presence of cirrhosis further amplifies this risk of developing HCC. This progression of events can be thwarted by vaccination on infants. This not only prevents infection on the vaccinated population but also in the non-vaccinated by preventing the number of infections.

Aflatoxin B, a chemical substance produced as a secondary metabolite by the ubiquitous molds *Aspergillus flavus* and *Aspergillus parasiticus*, In developing countries this cause is brought forth by the deficient storing of rice, corn, wheat, peanuts and sunflower seeds.[4] Temperatures between 24 and 35°C and moisture content of 7% (10 with ventilation) are conditions of fungus development. It can affect the body by transcutaneous way but its primary way inside the organism is the ingestion of aliments that contain the mold. The poisoning with this substance results in liver necrosis, bile duct proliferation and edema. It increases the risk of HCC by 3 times. Moreover there has been noted a synergy between aflatoxins and the HBV and HCV. The liver destruction provoked by the virus lead to a reduced rate of toxin expulsion form the organism leading to more liver damage. Aflatoxin is 30 times more potent in HBV antigen positive patients. A patient with only HBV has a 5 times increased risk of HCC but if we consider a previous aflatoxin poisoning this risk raises to 60 times. Aflatoxin also decreases the efficacy of vaccination against these viruses compromising the treatment.[4]

In Japan and western countries, the most common factor of HCC predisposition is the infection with hepatitis C virus (HCV) or ethylic habits.[3]

Alcohol is one of the most recognized factors in HCC developing. The incidence of HCC is higher among alcoholics even after abstinence, due to persistent alterations in cell

regeneration. Alcohol itself is not a carcinogen. This was proved through animal experiments in which the administration of alcohol only provoked cancer when in concert with partial hepatectomy or a diet with low methyl donors or carbohydrates. The rate of intake is also important. Alcohol causes a deficiency of intake in nutrition. If alcohol was administered with drinking water, it can affect the absorption of nutrients causing deficiency in its intake. If ethanol is administered as liquid diet, it provides adequate nutrition.[5]

The enzymes involved in the metabolism of ethanol are also responsible for potentiate carcinogens such as those resulting from cytochrome P450 2E1. This enzyme and alcohol dehydrogenase (ADH) act together in the liver to form acetaldehyde. Acetaldehyde is a mutagenic and carcinogenic substance, stimulating apoptosis, sister chromatids exchange and enhanced cellular lesion, which stimulates hyper regeneration. Following this process, acetaldehyde is subjected to the action of aldehyde acetate. This reaction is especially relevant in the Asian population in which the alleles ALDH2*2 and ADH3*1 codify an enzyme with higher capacity for acetaldehyde (AA) production. Preliminary studies show that despite no direct relation between these alleles and HCC, there is a higher prevalence of ADH3*1 in HCC patients. CYP 2E1 is an ethanol oxidizing system induced by alcohol and other chemicals foreign to the organism. Its induction is correlated with the production of reactive oxygen species, which have a known role in carcinogenesis. This process raises the conversion rate of procarcinogens such as AFB1, vinyl chloride and dimethylhydrazine to carcinogen status.

Alcohol diminishes the absorption of various macro and micronutrients but not of iron. This metal is absorbed by the gut in increased quantities and accumulates itself in the liver, synergizing with ethanol's action on the ROS production. This synergy raises ROS' concentration to levels too high to be managed by the natural processes of detoxification of the organism.

Tobacco influence is not deeply studied, though an association with it seems certain. The results vary between no association or a positive one. The association of smoking and heavy alcohol consumption is associated even strongly with HCC.[6] However the results that the combined effect of tobacco and alcohol only found it in cases were infection with HCV or HBV was simultaneous. Besides, its effect seemed to be interactive with HBV and multiplicative with HCV.[7]

Oral contraceptives are another factor of dubious contribution to the development of HCC. A meta-analysis of 14 retrospective case-control and 3 cohort studies that studied users against non-users suggests that there is no positive association between the use of these drugs and the onset of disease. However, a subgroup analysis by geographic region and a study design in North America found a positive association but not in a cohort studies from other continents. In spite of these results, it was observed that the incidence of HCC rises with age. Oral contraceptives are generally used only in reproductive age and although the risk of liver cancer rises with the duration of its use, this rise does not have statistical significance. This result is helped by the fact that the concentration of estrogens in contraceptives has decreased and a wider variety of progestins is used since the first production of pills which reduces its adverse effects.[8]

The effects of coffee in the creation and development of hepatocellular carcinoma are still not studied in deep, but evidence suggests that it has a protective effect against this pathology, by protecting against cirrhosis. Bravi *et al.* found in a meta-analysis that coffee consumption reduced HCC risk in 41%. This results were found in results from widely different populations ranging from Europe to Japan. They attribute this effect to caffeine which stimulates γ -glutamyltransferase and aminotransferase activities and other liver

enzymes and to other substances present in the drink such as kahweol, cafestol and diterpenes that have a detoxifying effect. However, despite the inverse relation ascertaining correlation is not easy. Although recalling of coffee intake is fairly correct, it is not an exact method of measuring.[9]

Among the genetic and familiar causes, hereditary hemochromatosis and the deficiency in alpha-1-antitrypsin are the most frequent.

Hereditary hemochromatosis is an autosomal recessive inheritance disease greatly associated with the HFE gene in chromosome 6 and two of its common mutations C282Y and H36D. In heterozygotes these mutations cause symptoms in 15 to 25% of subjects. In homozygotes this causes a malfunction of cellular communication making transferrin continually absorb iron from the ingested food. This accumulation of iron generates disseminated organ damage, and the liver as a natural reservoir of iron is one of the most affected. Cirrhosis and liver cancer are the result of this damage. Prevalence of cancer in concert with this pathology is 18,5% higher in patients with this disease than in patients without it.[10]

Deficiency in alpha-1-antitrypsin is the other genetic condition related to hepatocellular carcinoma. This pathology is associated with homozygosity for the α 1ATZ allele and it is considered autosomal codominant..

α 1ATZ is a glycoprotein that rises in the occurrence of inflammation and tissue injury. It appears in 1 in 1800 newborns. Homozygotes suffer from premature emphysema because the absence of the molecule allows increased damage to the connective tissue matrix. In liver it results in the anomalous polymerization of the molecule and causes accumulation in the

endoplasmic reticulum. However there are studies that contest polymerization as the cause of ER accumulation. The mutation is also associated with mitochondrial injury in liver cells. Mitochondrial lesion may be caused directly by the altered ER or by the increased autophagy by macrophages and proteasomes that is stimulated by the altered ER. ER accumulation did not activate UPR but it led to the activation of caspase 4 in human cells as well as the activation of BAP31, an integral membrane that appears to mediate pro-apoptotic signals and NF- κ B from the ER to the mitochondria. However, animal's studies have not shown an increased apoptosis. These findings lead the investigators to conclude that the ER bloated with α 1ATZ activates NF- κ B, autophagy and the caspase pathway, but this last one is blocked in its late stages. This puts the cells in a sick but not dead state, tilting the balance of proliferation/cell death to the side of proliferation. This proliferation is more pronounced in liver cells with a not too high number of PAS stained intracellular globules.[11]

Fisiopathology

Pathogenesis

Cancer pathogenesis is a complex process. Studies show that cancer is the result of cumulative alterations in the DNA of somatic cells or inherited mutations on germline cells. These alterations affect primarily two types of genes: tumor suppressor genes and protooncogenes.

The risk factors already presented produce a state of chronic inflammation and increased oxidative stress that favors mutation of genes and DNA repairing proteins. X.W. Wang *et al.* (2002) have found that in patients with Wilson's disease and hemochromatosis the frequency of p53-mutated alleles in non-tumorous liver tissue is higher than in non-tumorous

tissue form healthy subjects. In the same vein, alcohol and tobacco produce continuous aggression and inflammation that activate mutations of similar effect (Figure 2).[12]

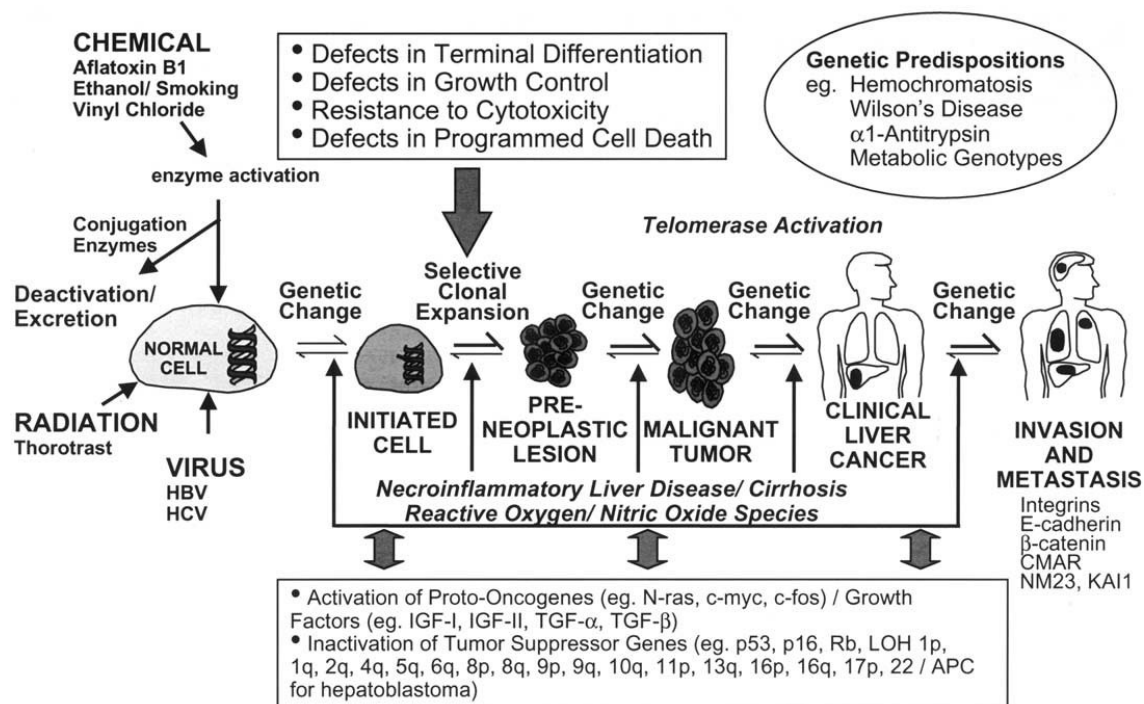


Figure 2 – Hepatocarcinogenesis multiple mechanisms and evolution. A normal hepatic cell is subjected to multiple stimuli that induce alterations in growth differentiation and cell death. A progressively more aggressive environment leads to cancer and finally metastasis. From [12].

However three specific conditions produce by means that afford a more deep study. These conditions are HBV infection, HCV infection and aflatoxin B intoxication.

HBV mediated Pathogenesis

HBV is the pathology more associated with HCC. At least three mechanisms have been pointed has an explanation of the pathogenic process.

The first one is the chromosomal instability that results from the fusion of exogenous genetic material to the nucleus of a mature cell. The second one may activate endogenous retinoic acid β -receptor like, cyclin A and TRAP1 genes. The integration of the HBx in

proximity with parts of the genome that regulate cell division and growth would contribute to the carcinogenesis process.

The third mechanism focuses on the role of the HBx gene which is identified as a major factor in malignization. This viral gene regulates the expression of class 3 promoters, proto-oncogenes, HBV enhancers and other viral genes. It also transactivates NF-kB which indirectly up-regulates IL-6, and the induction of nitric oxide synthetase and FAS ligand, which causes resistance to apoptosis. It binds itself with p53 in its C-terminus, forming a non-working complex. IL-8, TNF, TGF-B1 and EGFR are promoters of cell proliferation that are affected by HBx transactivation. HBx also activates JAK/STAT pathway.[13]

HCV mediated Pathogenesis

HCV is an RNA virus that is incapable of integrating its host genome, so a gene based approach to its role in HCC is not considered. Instead of that the focus of research is its proteins, especially the core proteins. This proteins are capable of interacting with p21^{WAF1}, reducing its expression. They also interact with and p53, promoting both apoptosis and cell proliferation, and regulate p73 functions. (Figure 3) A reduction in the expression of DNA mismatch repair gene hPMS2 favors malignization by providing growth advantages. Another mechanism reported is the up-regulation of WNT-1 that promotes proliferation.[13]

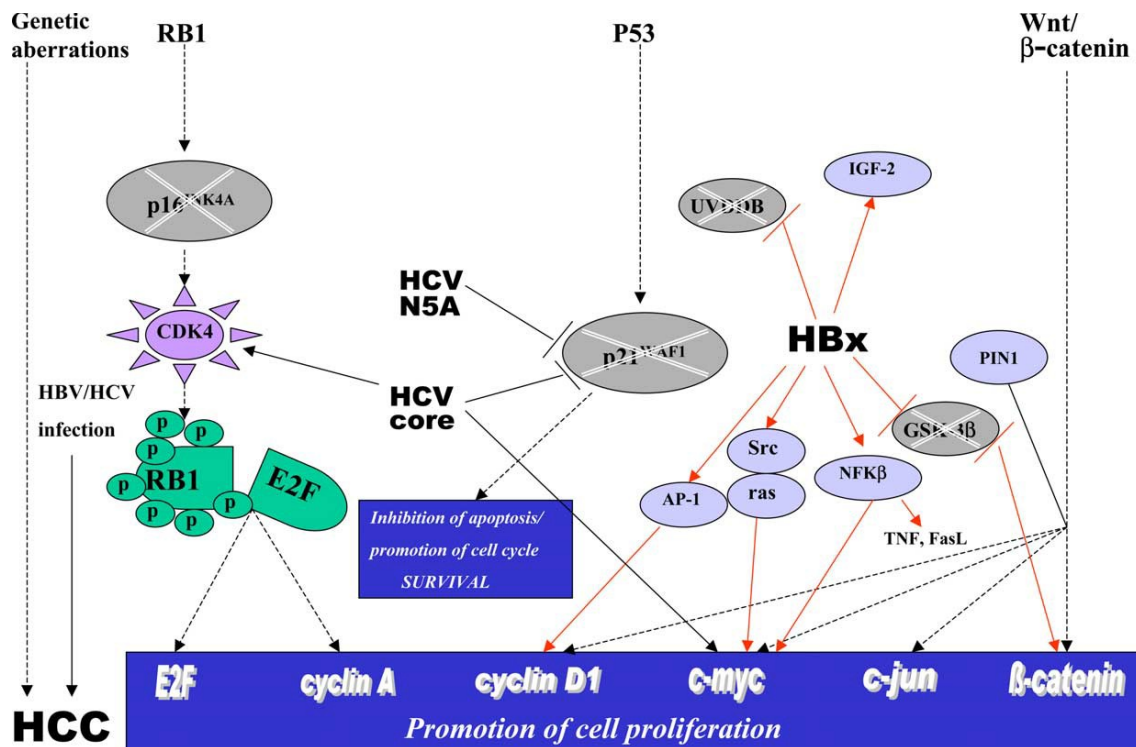


Figure 3 – Molecular pathways involved in hepatocarcinogenesis that are affected by hepatitis virus. From [13]

Aflatoxin B mediated Pathogenesis

Aflatoxin B is the most frequently noted phenomena associated with HCC. It causes a G»T mutation of the p53 gene at codon 249 which results in its inactivation. However, in cases where the p53 mutation is not detected, but aflatoxin B intoxication is present, there is the suggestion that this mutation is not enough to provoke cancer. The simultaneity in various cases of intoxication and HBV infection suggests that this process is the result of the synergy between this two aggressions.[13]

Clinical Features and Natural History

HCC is a pathology with a heterogeneous presentation. At the time of the diagnostic, approximately 40% of patients present no symptoms. In the other 60%, 91 in 100 present pain in the right superior quadrant of the abdomen, which reflects damage to Glisson's capsule.

Since cirrhosis is the basis for the development of a great number of cases, hepatic insufficiency is often seen. Its signals and symptoms include:

- Anorexia
- Jaundice (40%)
- Loss of weight
- Abdominal Discomfort
- Hepatomegaly (90%)
- Splenomegaly (65%)
- Ascites (52%)
- Fever (38%)

Other findings include:

- Erythrocytosis
- Diarrhea
- Increased production of gonadotrophins

Carcinoma in situ is the earliest stage of HCC. It is defined as a well-differentiated cancer with ill-defined nodular appearance, that contains bile ducts and portal veins and no structure invasion. A classification divided these tumors into 2 types: an indistinct type, that has a size from 1 to 2cm, has no local invasive capacity, appears in the CT, first as hypovascular,

then as hypervascular, and a distinct type that possesses local invasiveness and whose size ranges from 1 to 6 cm.

Very early stage HCC is a carcinoma in situ in a liver with preserved function. This tumors present the best outcomes and haven't a tendency to reappear after treatment. Molecular studies are the best tool to ascertain their malignancy but it is expected that neoplastic invasion can perform the same function in the future.

Early HCC is defined empirically has the presence of 2 to 3 hepatic nodules smaller than 3 cm. This stage responds incredibly well to liver transplantation. It has a poorly understood progression history since all individuals are treated. A decade ago, the best survival rate was reserved to patients with just one tumor and classified as a Child-Pugh A. It was 65% at 3 years. This has since become 50-70% of 5 year survival.

Patients with a Child-Pugh score A and submitted to resection have a best chance of survival if they don't have a notable portal hypertension (hepatic venous pressure gradient <10 mmHg), clearance of indocyanine-green clearance at 15 min below 20%, and bilirubin concentrations <17.1 mol/L.

Intermediate and advanced HCC is the stage were most patients are diagnosed for the first time. Twenty years ago the maximum survival expectancy was only 1 year.

End stage HCC is most common in Africa or Asia, where it is detected by its symptoms. Treatment does not provide benefits in relation to survival and life expectancy is 6 months. Patients with a Child-Pugh class 6, Okuda stage III or a performance test score of 3-4 have a cancer classified as such.

Metastasis

Like other tumors there are 3 main paths used by HCC to spread outside the liver: physical contact, blood vessels and lymphatic vessels.

Physical contact can be achieved through two ways: HCC rupture and HCC direct contact with surrounding organs and tissues. Rupture can cause the tumor to spread its cells over the spillaged zone. This is a method of invasion when occupying the peritoneum and the omentum. For direct contact, HCC uses the falciform ligament and is capable of reaching the pancreatoduodenal area and the anterior abdominal wall through it. The peritoneum is invaded in 11% of the cases and the adrenal glands in 11%.

As for the blood vessels, HCC prefers to invade the portal, hepatic, inferior vena cava and other, in that order. From these vessels, the metastasis invade the other organs. The most frequently invaded organ by this mechanism is the lung (55% of extrahepatic metastases sites). HCC cells spread through the capillary network of the lungs and stay in the lower lobe of the lungs to generate non-calcified nodules of tissue. This method of metastasis is also used when invading the heart despite this being significantly rarer.

The second most invaded site is the lymphatic system (53% of extrahepatic metastases). The nodes most invaded are those in the mediastinum. When lymphadenectomy is associated with hepatitis or cirrhosis it is commonly reactive.

The bone is the third site of metastasis most invaded in 28% of the cases. The metastasis are generally lytic, expansile and hypervascular. Collapse of the vertebral bodies is a complication of thoracic and spine invasion and it results in cord compression.[13]

Immunologic Resistance of HCC

HCC cells produce PDL-1, a molecule that binds with T-cells, inhibiting its signaling mechanism and inducing apoptosis. Besides, the production of CTLA-4 causes two inhibition processes: induction of regulatory T cells and reduces T cell activation by reducing a co-stimulatory signal.

Immune activation is the beneficial response to the patient. Cytotoxic CD4⁺ and CD8⁺ T cells are activated and target HCC cells. This happens thanks to immune checkpoint inhibitors, agents that increase antitumoral activity by counteracting the action of immune inhibitors like PD-1 and CTLA-4.[14]

Immune tolerance is the immunosuppression caused by HCC by stimulating regulatory T cells and suppressing T cell activation.

Prevention

The prevention of HCC is divided on primary and secondary. Primary prevention intends to prevent the appearance of HCC in patient with chronic liver disease, and the secondary prevention aims at the prevention of the resurgence in treated HCC patients.[15]

Primary prevention is achieved mostly by the prevention of its risk factors. It is divided in four stages:

Stage 1 consists in the prevention of liver disease. Aflatoxin poisoning is prevented by a significant investment in timely harvests and management of the conservation status of

crops as contamination can start even before the harvest. An adequate drying process that diminishes the moisture to values under 10% is required as is required an elimination of insects and inert atmospheres. In the processing of the crops, efforts must be made in the dilution, decontamination and separation of the contaminated material. Dilution mixes crops of less regulated origin with crops of heavily regulated material (this procedure is ineffective if there is a high percentage of contaminated crops and should only be used when other procedures are inexistent). Avoidance of other liver toxins and drugs, such as alcohol, is an essential step. The avoidance of HBV and HCV is paramount, by hygienic measures or the use of vaccination. For HBV prevention, anti-surface antigen (Anti-HBsAg) is the vaccine of choice. This strategy has proven its worth in the incidence reduction of HCC in Taiwan after a universal vaccination program was implemented. Other HBV vaccines are being developed such as an epidermal powder immunization, triple recombinant vaccine or oral immunization. No vaccine for HCV exists at the moment, but it is expected that one will be produced in the future.

Stage 2 consists on interventions designed to treat early stages of liver disease with the intent of stopping the progression of the disease to cirrhosis and from that to HCC. . An early treatment of acute HCV infection is suggested to stop the progression to chronic hepatitis C.

Stage 3 is based on interventions that prevent the development of cirrhosis. It consists of avoiding aflatoxins, steroids and high-dose androgens and the treatment of chronic hepatitis infection with interferon alpha or nucleoside analogs.

Stage 4 concentrates on impeding the molecular changes that transform liver cirrhosis in HCC.

Secondary prevention of HCC focuses on preventing the resurgence of liver cancer on treated patients. After 3 years of successful treatment the probability of recurrence is 50%. Liver transplantation is the only “definitive cure” for HCC. The administration of polyprenic acid, and iodine labeled lipiodol are being evaluated for control after resection.[15]

Diagnosis

Imagiological Diagnosis

To confirm the existence of HCC one of two conditions that must be fulfilled:

1. A mass bigger in diameter than 2 cm is identified in the liver with contrast enhancement features on the arterial phase with venous washout;
2. A biopsy with relevant characteristics of a hepatic mass in non-cirrhotic liver is performed.

Diagnostic methods must be chosen in accordance with the manifestations of the disease.

In cases where the focal mass diameter is more than 2 cm and the patient already exhibits cirrhosis, non-invasive methods have priority.

In cases where the diameter of the mass is inferior or equal to 2 cm or in tumor that do not fit any of the above criteria it is assumed that nodules are HCC if they show typical vascularity and washout on 2 imaging modalities.

A biopsy should be performed if it is atypical and its vascular profile is not the same with different techniques.

If the nodule has a diameter smaller than 1 cm, regular screening must be performed in intervals from 3 to 6 months. If in 2 years no growth is observed then routine vigilance can proceed at 6 months intervals.

Different methods of complementary diagnostic have different traits and applications. For HCC the preferred method of imaging is the triple phase dynamic contrast enhanced magnetic resonance imaging (MRI), supplanting hepatic angiography. HCC is denounced in this imaging method and CT by the presence of arterial enhancement followed by hypointensity in the portal washout, as figure 4 shows.

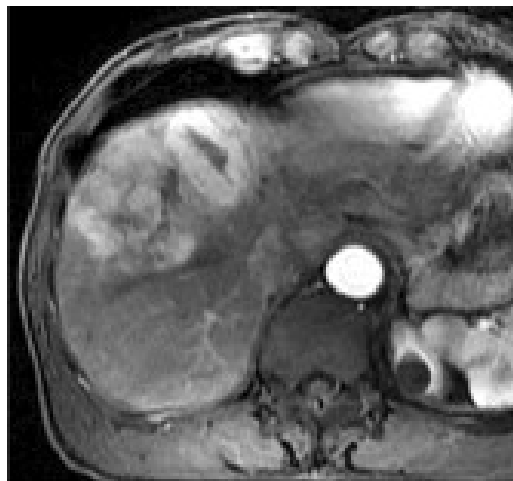


Figure 4 – Hyperenhancement in late hepatic arterial phase in an MRI image of a 64

These findings have a specificity of 95% and a sensibility of 90%. Studies that use the explanted liver show that MRI is slightly better than CT in the study of HCC, although both methods are more accurate the bigger the tumor is.[16]

Molecular Diagnosis

Early HCC lacks an increased arterial supply, typical histological alterations, AFP or PIVKA II elevated concentrations. However HSP70 is upregulated in this stage and does not appear in non-malignant lesions or other benign lesions so it is a possible marker for the condition. CAP 2 is another molecule that fulfills these conditions and highlights stromal invasion. Glypican-3 is a plasma membrane sulfate proteoglycan that appears in fetal but not adult liver and is a widely recognized marker for HCC and malignization. In spite of this it also appears in inflamed tissue. Glutamine synthetase is an enzyme that accelerates the conversion of glutamate and ammonia in glutamine, an energy source to tumor cells and it is a target of WNT/beta-catenin pathway. Its rising concentration may be a signal of hepatocarcinogenesis process. BMI-1 is another molecule with such potential, since it contributes to the immortalization of liver cells through induction of telomerase. It also inhibits tumor suppressor genes p16 and p19.[17]

Advanced HCC is characterized by the presence of p53 mutations in the inner advance nodules but not in outer ones. AFP serum levels rise above 200 ng/mL, and this concentration is highly specific of liver cancer in cirrhotic patients, although its sensitivity is much lower, with only a third of patients with AFP levels above 100 ng/mL. [15] Beta-catenin mutation is another feature of this stage, but its correlation with prognosis is not clear, being associated with good and bad outcomes. The marker CK7 or CK19 as well as TGFBR2 have been found to be more frequent in poorly differentiated cells. CK7 is also related with the possibility of metastasis, being positive in many cases of intrahepatic metastasis. TGF- β is correlated with a decrease in patient survival.[17]

Differential Diagnosis

The main differential diagnostics of HCC are closely related to this pathology. The most common in the western world is cirrhosis due to similar modifications of liver architecture and the relation the two diseases have.

Intracellular Cholangiocarcinoma is also an important differential diagnosis since its incidence is increasing worldwide and it presents a vascular pattern to HCC in imagiology studies.[18]

Staging

Since HCC is a pathology with such importance various systems of staging and recommendations based on its development and other factors have been created to serve as tools in the combat against the disease.

Asian systems are particularly numerous. In this review, only the most commonly used will be explained in detail.

Child-Pugh Score

Though not specific for HCC, the Child-Pugh score is a very useful tool in the study of this disease since it measures liver performance (Table 1). It was one of the first tools with such use and has proved itself very robust.

Table 1: Child-Pugh score 2.From [19]

Measure	1 point	2 points	3 points
Total bilirubin, $\mu\text{mol/L}$ (mg/dL)	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin, g/dL	>3.5	2.8–3.5	<2.8
Prothrombin time, prolongation (s)	<4.0	4.0–6.0	> 6.0
Ascites	None	Mild (or suppressed with medication)	Moderate to Severe (or refractory)
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

TMN Score

Developed by the American Joint Committee on Cancer this staging system focuses on primary tumor size (T), lymph node involvement extension (N) and presence of extrahepatic metastasis (M). It is one of the most commonly used but is very generic and unspecific.[20]

- **T** classifies size or direct extent of the primary tumour

Tx: The tumour cannot be evaluated

Tis: There is a carcinoma in situ

T0: There are no signs of tumour

T1, T2, T3, T4: Used to classify the size and invasion of the primary tumour in crescent order.

- **N** classifies the degree of spread to regional lymph nodes

Nx: Lymph nodes could not be evaluated

N0: Tumour cells are absent from regional lymph nodes

N1: Metastasis of Regional lymph node is present; at some sites, tumour spread to closest or small number of regional lymph nodes

N2: Used when the extension is between N1 and N3 (N2 is not used at all sites)

N3: The tumour spread to more distant or numerous regional lymph nodes. The N3 classification is not universal.

- **M classifies** the presence of distant metastasis.

M0: There are no distant metastasis

M1: There is metastasis to distant organs

TMN score and Child-Pugh scores have demonstrated a greater predictive ability for survival prediction in multivariable analysis.

French Staging

This staging system defines 3 categories each with a different prognosis. Stage A has a higher survival rate compared to B which has a higher survival rate than stage C (Table 2).

Table 2: French Staging. From [21]

Parameter	0	1	2	3
Karnofsky Index	≥ 80			< 80
Serum bilirubin	< 50			≥ 50
Serum alkaline phosphatase	< 2		≥ 2	
Serum AFP	< 35		≥ 35	
Portal Obstruction	No	Yes		

Results	Stage
0	A
1-5	B
≥ 6	C

Barcelona Clinic Liver Cancer (BCLC) Staging System

Initially developed for patients subjected to a resection following HCC, this staging system is used to decide which clinical options are most useful in relation to the stage of the cancer, and was good for predicting survival post-surgery (Figure 5).

Stage A may opt for a liver transplant or a curative treatment since the tumors are inferior in size to 5 centimeters or are limited to 3 nodules of less than 3 cm. This results in a survival of 5 years.

Stage B has a 50% chance of 3 year survival.

Stage C have a 10% chance of survival at 3 years due to extrahepatic and vascular invasion joined by poor performance.

Stage D is the worst stage and the only way to treat the patient is by means for a liver transplant.

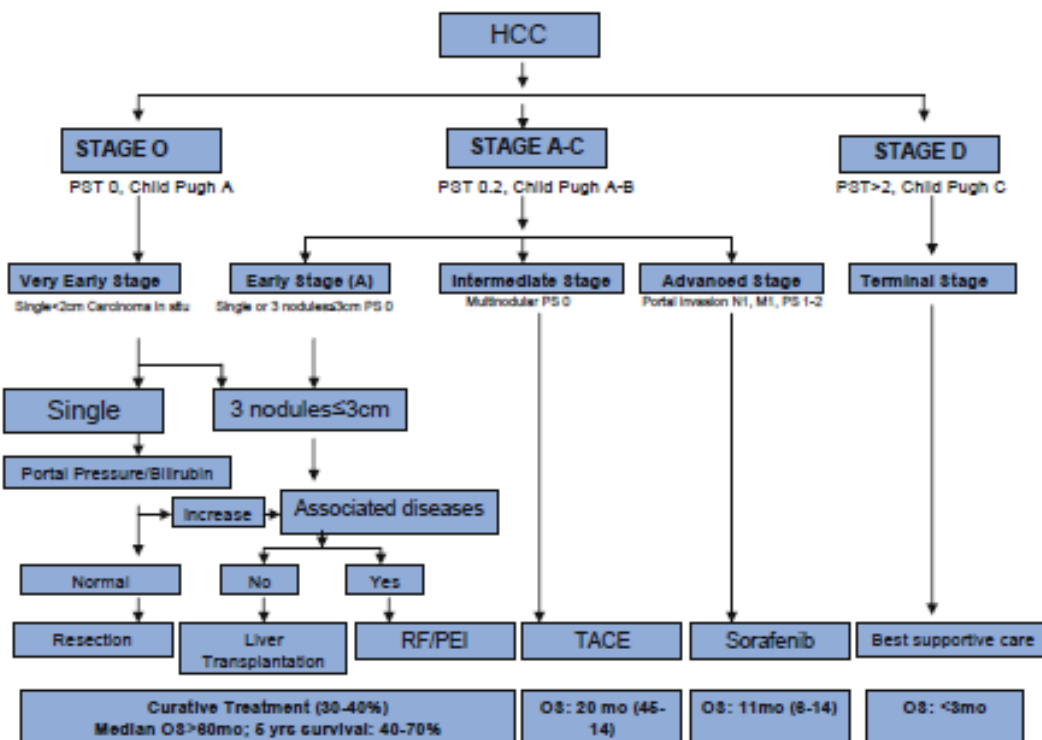


Figure 5 – BCLC Staging System with treatment options and overall survival. Figure from [21]

Okuda Staging of HCC

Okuda Staging system was one of the first systems to join tumor characteristics like tumor size, with liver function to assess the patient in a more complete way (Table 3). Stage I patients have a median survival of 8.3 months while stage II last only 2. Stage III is the worst classification with a median survival of only 0.7 months.

The Okuda system, while good at classifying tumors in advanced or intermediate stage is incapable of distinguishing between early and advanced tumors, due to not considering the tumor's vascularity, extrahepatic invasion and centrality.

Despite this flaws it remains as the standardized staging system for HCC in Western Countries.[21]

Table 3: Okuda Staging System and score. Tables from [21]

	+	-
Tumor Size	>50%	<50%
Ascite	Present	Absent
Albumin (mg/dL)	<3	>3
Bilirubin (mg/dL)	>3	<3

Results	Stage
4 (-)	I
1 or 2 (+)	II
3 or 4 (+)	III

CUPI

Together with CLIP, this system is considered one of the best in terms of discriminative ability, monotonicity and homogeneity.[21] However CUPI (Table 4) is best at predicting the survival at the 3 month mark and CLIP at the 6 and 12 month mark.[21]

Table 4: Chinese University Prognostic Index. Table from [22]

Variable		Weight
TMN Stage	I / II	-3
	IIIa / IIIb	-1
	IVa / IVb	0
Asymptomatic disease on presentation		-4
Ascites		3
AFP \geq 500 ng/mL		2
TB (μ mol/L)	<34	0
	34-51	3
	\geq 52	4
ALP \geq 200 IU/L		3

Japan Integrated System

The Japan Integrated System for liver cancer uses the Child-Pugh score for ascertaining liver function and the LCSGJ TMN score for classifying the neoplasia (Table 5). Each score is correlated with a number. Then these two numbers are added to give a score from 0 to 5. This allows a more precise classification but, due to its complexity, it is not well integrated in clinical practice and has a poor prognostic power.

Table 5: TMN stage used by liver Cancer Study Group of Japan criteria. From [19]

Score	0	1	2	3
Child-Pugh	A	B	C	
Score				
TMN Stage by LCSGJ	I	II	III	IV

Table 6: TMN stage used by liver Cancer Study Group of Japan criteria (cont.). From [19]

Factors	I. Single	II. Size 2cm	III. No vessel invasion
T1	Fulfilling three factors		
T2	Fulfilling two factors		
T3	Fulfilling one factor		
T4	Fulfilling 0 factors		
Stage I	T1 N0 M0		
Stage II	T2 N0 M0		
Stage III	T3 N0 M0		
Stage IV-A	T4 N0 M0 or T1-T4N M0		
Stage IV-B	T1-T4, N0 or N1, M+		

CLIP Staging of HCC

This is the youngest amongst staging systems, being developed in Italy in 1998.[23] It takes in consideration, liver performance (by using the Child-Pugh Score), tumor morphology, the AFP concentrations and the vascular state of the cancer by means of portal vein thrombosis (Table 6). The higher a patient's score in this system the worse the prognosis is.[21]

Table 7: CLIP Staging of HCC. Table extracted from [21]

	0	1	2
Child-Pugh Score	A	B	C
Tumor Morphology	Uninodular and extension $\leq 50\%$	Multinodular and extension $\leq 50\%$	Massive and extension $> 50\%$
AFP	< 400	≥ 400	
Portal vein thrombosis	Yes	No	

Studies in Italy, France, Canada, Germany, United States, Canada and Tokyo have established the good prognostic value of the test when used in advance stages, especially when compared with other systems. Furthermore, it has shown a superior predicative power, even independently of the tumor stage or treatment used.

Hong Kong Liver Cancer Staging System

Developed in 2014 by a Hong Kong research group, based on a cohort study of 3865 HCC patients this system proposes four major prognostic factors: liver tumor status, Child-Pugh Score, ECGOS PS and metastasis/extrahepatic vascular invasion (Figure 6).

This system has better prognostic value than BCLC classification but has the bias of being based on a group of patients that were predominantly affected with a viral associated cancer (HBV was present in 80% of the cohort). Also, eastern populations are fundamentally different from Western ones so conclusion must be validated for these populations.[20]

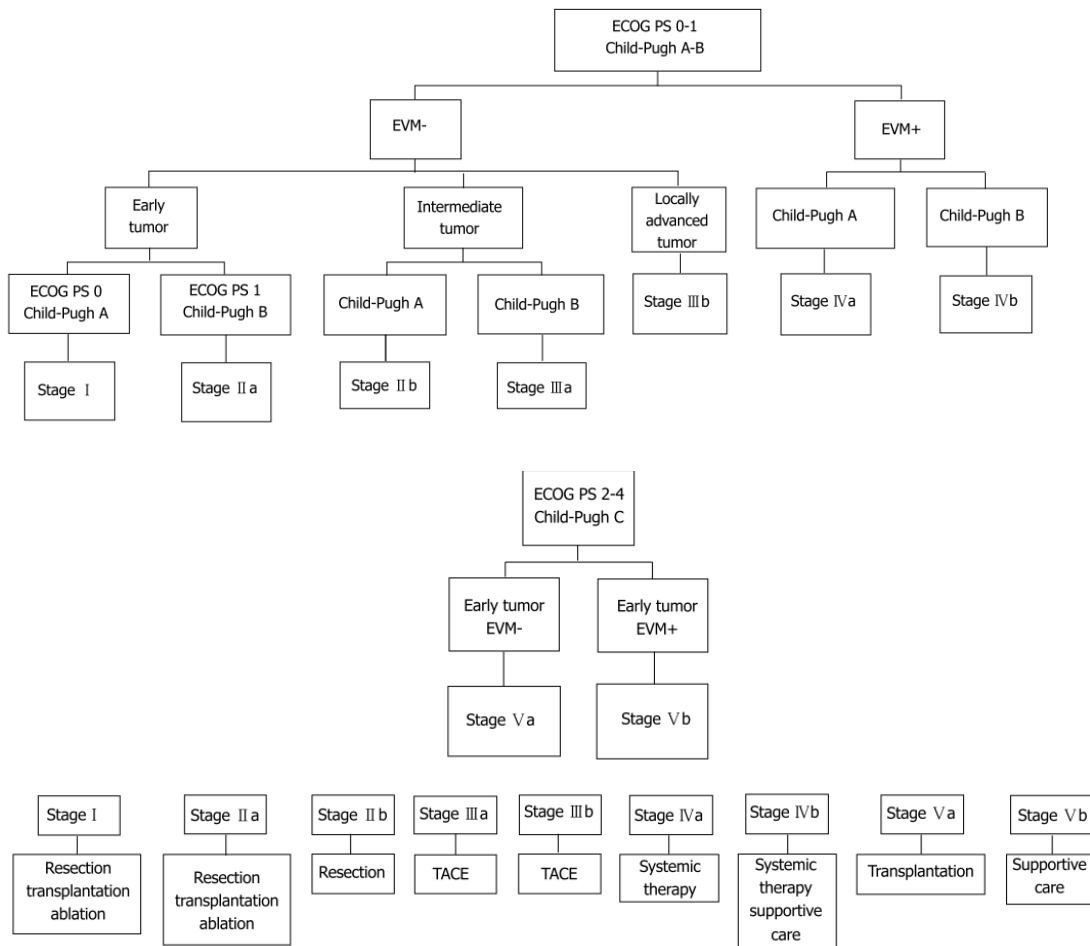


Figure 6 – Prognostic and Treatment of Liver cancer according to the HKLC staging system. Image from [20]

Chapter 2 – New Therapeutics of the Hepatocellular carcinoma

Therapies for HCC can be divided into four categories, by ascending aggressiveness:

- Pharmacological, genetic or immune therapy;
- Percutaneous interventions, which includes ethanol injection, radiofrequency and thermal ablation;
- Transarterial interventions like embolization, chemoperfusion, or chemoembolization;
- Surgery, which includes tumor resection and liver transplantation.[15]

Established Treatments

Medical Treatment

Cytotoxic chemotherapy and hormonal therapy have not been found to be helpful in improving the survival of HCC patients. Chemotherapy presents responses rates no bigger than 25%, and patients usually need it because liver cirrhosis difficults the administration of drugs.

Conventional Chemotherapy

Chemotherapy is a somewhat ineffective choice when treating HCC since cirrhosis prevents to some extent hepatic metabolism. Ascites, portal venous thrombosis poor performance status and serum bilirubin are other conditions that difficult drug treatment and can nullify chemotherapy.

However, if intrahepatic disease and ascites are absent chemotherapy can still be effective and bring benefits to treatment.[24]

Sorafenib

Sorafenib, an inhibitor of tyrosine-kinases, is the standard drug in the treatment of advanced stage HCC. It is also the control arm of other studies that involve drugs.[25].

Studies have shown that sorafenib raises the survival rate of patients suffering from HCC in advanced stages, suggesting an important role of the pathways of cellular signaling mediated by growth factors in the etiopathogeny of this cancer. Among these, VEGFR2, PDGFR, RAF-1, B-RAF and c-KIT receptors are the mainly affected molecules. In vitro, sorafenib induces apoptosis of HCC cells. Phase II studies showed sorafenib's potential benefits and phase III studies showed that sorafenib presented and overall median survival of 10,7 months.[25]

Percutaneous Intervention

Percutaneous Ethanol Injection (PEI)

This method consists in repeated injections of ethanol on separate 4 days with guidance from ultrasound image methods. Ethanol induces necrosis of tumor cells, blood vessel ischemia and dehydration. It is especially effective in tumors with less than 3 cm in diameter, in which it reaches remission in 70% of cases.

Percutaneous Acetic Acid Injection uses the same principle but uses another toxic substance. These methods are comparable in both post-act survival and posterior recurrence. However it can cause pain, and fever or facial flushing.

These two methods are contra indicated in cases where the normal structure of the liver is compromised such as cirrhosis in Child C, extensive ascites and complete portal vein thrombosis.

These methods show no significant difference with surgery when applied in early stages of cancer.

Radiofrequency thermoablation

This treatment is indicated in in early stage HCC, especially in lesions with less than 3 cm in diameter. This therapeutic strategy uses frictional heat to incite tumor necrosis. This heat is generated by a radiofrequency waves emitted from a probe, guided by ultrasound generated images (Figure 6). Patients included in the Milan criteria have a 5-year survival rate of 40 to 75%. Between 60 to 87% survive the next 3 and 97% survive for at least an year. It is more effective than PEI and PAI, achieving survival without recurrence and with less sessions of therapy.[26]

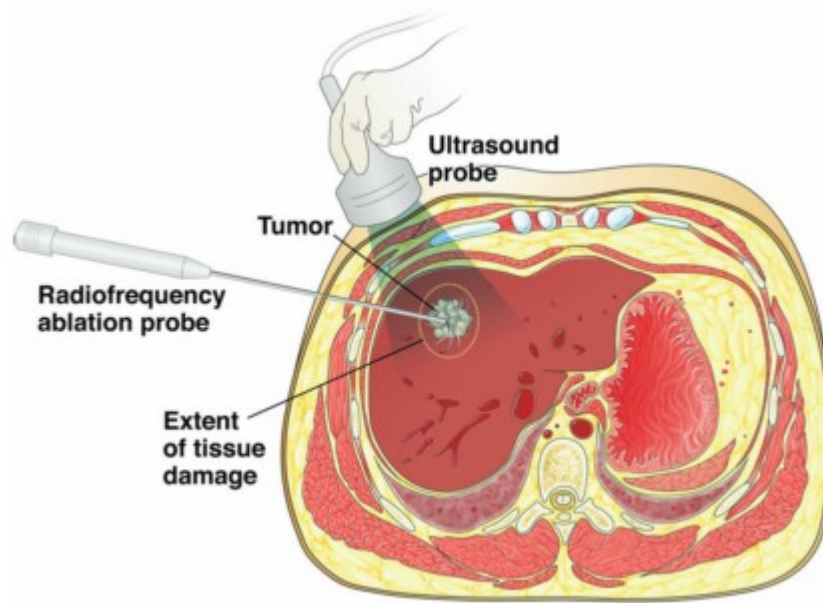


Figure 7 – Percutaneous Radiofrequency ablation of HCC [16]

Transarterial Intervention

TACE

When resection is impossible to perform, transarterial chemoembolization (TACE) has been proved to improve HCC patient survival.

The liver possesses two means of blood influx: the hepatic artery and the portal vein. This makes it one of the organs with dual vascular supply. One of the advantages of this anatomy detail is the unique advantage it provides to embolotherapy and imaging.

The purpose of embolization is dual: to induce necrosis by blocking the arterial supply of oxygen and other nutrients and to slow the washout of drugs in circulation so they can have a more potent localized effect. This minimizes systemic effects and maximizes local effects. [27]

Not all patients are eligible for such a procedure (Table 6). Since embolotherapy is used as a middle step between medical treatment and liver resection or transplantation. According to the BCLC staging system it should be used in intermediate stage HCC and the

Child-Pugh score considered perfect for the intervention is the class A. This treatment only benefits patients with unresectable cancer.[27]

Table 8: Contraindications to cTACE.[27]

Relative Contraindication	Absolute Contraindications
AST and ALT >5 x upper limit of normal	Hepatic encephalopathy
Severe thrombocytopenia (<50,000/IL)	Active systemic infection
Recent variceal bleeding	Uncorrectable bleeding disorder
Intractable arteriovenous fistula	Uncorrectable contrast medium sensitivity
Right-to-left cardiopulmonary shunting	Renal insufficiency (glomerular filtration rate <30 mL/min)
Severe thrombocytopenia (<50,000/ μ L)	Severely reduced portal flow by branch or main PVT
Biliary obstruction	ECOG performance status >2
Segmental or branch PVT	Leucopenia (white blood cell count <1000/IL)
Extrahepatic metastases	
Ascites	
Diffuse tumor burden involving >50% of liver	
Lactate dehydrogenase >425 U/L	
Serum bilirubin >3 ng/dL	

Transarterial chemo-embolization (cTACE) is performed by infusing a water-in-oil emulsion intra-arterially. The oil part of the emulsion is composed of Lipiodol, an iodinated poppy seed lipidic medium, a micro-embolic agent with the function of tumor seeking. The water part is composed of a chemotherapeutic mixture. Lipiodol is integrated by the tumor cell membrane and disables its transferring pumps by hypoxia. It is retained by tumor cell for 8 to 12 months but only 4 weeks on cirrhotic or non-altered liver cells.[27]

[32] C. P. I. Development, J. Lee, and C. B. Sirlin, "CT and MR Imaging Diagnosis and Staging of Hepatocellular," vol. 272, no. 3, pp. 635–654, 2014.

However in HCC, resection is still a high-risk procedure. The procedure is considered when the functional part of the liver drops below 40% of the total volume. This surgery demands a careful interdisciplinary study in pre-operative, intra-operative and post-operative times. Special attention must be given to portal hypertension, functional evaluation and patient selection. A good study may be complemented with radiographic planning and neoadjuvant tumor reduction. A pre-operative portal vein embolization may increase the functioning liver volume post-resection.

Nowadays, liver resection perioperative mortality in cirrhotic patients is 5% (a reduction of 10% since the 1980s). The Barcelona center managed to reach a perioperative mortality of 0% in 100 patients with a single nodule of HCC and without portal hypertension.

One of the principal concerns post-operation is tumor recurrence. It is estimated that in 2 years 10 to 50% of patients recidivate as well as 70% in 5 years. The main causes for this recurrence are remaining cancer tissue that the resection could not remove or intrahepatic metastasis.

Liver transplantation

Liver transplantation consists in the removal of the damaged tissue and the implantation of a new organ. This method removes cirrhotic tissue like resection but the effects of the removal are often accompanied by an increased progression of the cancer in other organs.

Patients are chosen for transplantation using the Milan criteria an extension of the criteria for treatment in HCC. Basically they consist of two conditions that If fulfilled predict a bad prognostic. The conditions are:

- One single nodule of HCC with less than 5 cm;
- Up to three nodules with size less than 3 cm.

Patients who are selected using these criteria in major units achieve 70% survival at 5 years with a recurrence below 15%.[28]

Recent Treatments

Medical Treatment

Various drugs are being developed that can be used on the treatment of hepatocellular carcinoma (Figure 8).

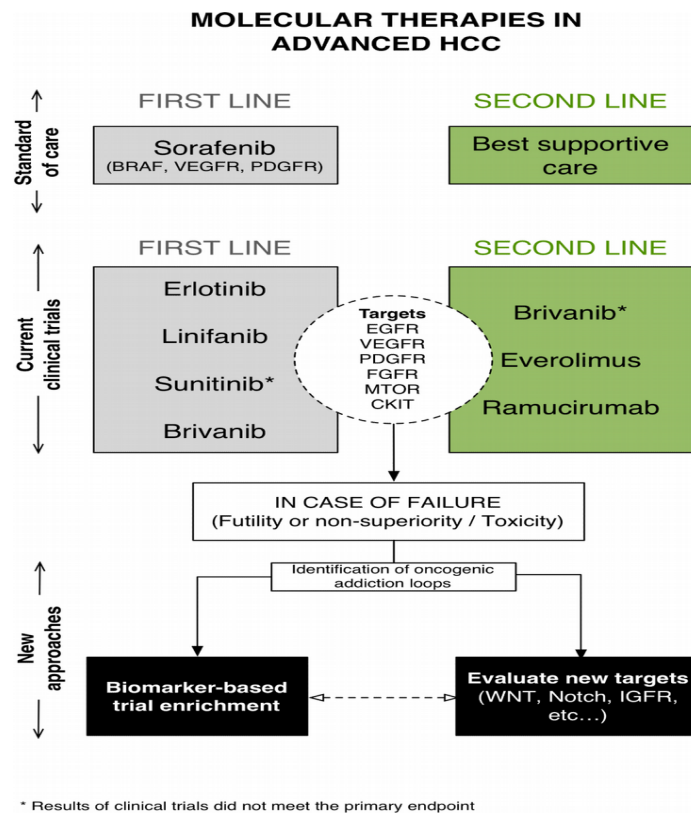


Figure 8 – Standard and New molecular therapeutic approaches to treat HCC. From [31]

Sorafenib-Regorafenib Sequential Therapy

Sorafenib is already indicated for the treatment of BCLC stage C and unresectable HCC as the standard treatment. It is also used as the treatment in intermediate stage HCC when TACE does not produce results. Since sorafenib is associated with a certain toxicity, it was suggested that a sequence treatment would be tested. When HCC starts to be refractory to TACE, the treatment would change to sorafenib and when the toxicity of sorafenib starts to be

prejudicial it would change to regorafenib. A RESORCE study showed that the median overall survival with regorafenib was 10,6 months and that patients with Child-Pugh scores of 5 responded better to treatment than patients with a score of 6.[29]

VEGFR and PDGFR are not the only targets of the angiogenic function of this type of cancer, though the alternatives did not receive much attention.[30]

The maturation of blood vessel is regulated by the angiopoietin-Tie system. This group of proteins is formed by two tyrosine kinase receptors, Tie1 and Tie 2 and 4 ligands Ang-1 to Ang-4. Studies have found that a high ratio of Ang-2/Ang-1 or even just elevated expression of Ang-2 is a predicting factor of inferior prognosis and is indicating of high microvessel density. Two compounds are being studied as agents for targeted these mechanisms: regorafenib (fluoro-sorafenib, BAY73-4506) and AMG-386. The first inhibits Tie2, C-KIT, FLT-3 and RAF kinases as well as VEGFR2 and VEGFR3. The second is an antiangiopoietin peptibody that acts as an inhibitor of the link between Tie2 receptor and Ang-1 and Ang-2. [30]

Heparan sulfate mimetics molecules are inhibitors of heparanase. Heparanase is a molecule that remodels the extracellular matrix and is expressed in large quantities in human tumors.[30]

Sunitinib is a multikinase inhibitor with antiangiogenic activity. It is an oral small molecule. Besides targeting VEGFR and PDGFR it also targets c-KIT, inhibiting cell growth. The efficacy of sunitinib was evaluated by CT tumor perfusion and 48% of the study participants showed tumor necrosis. Its adverse effects include fatigue, rash, nausea,

myelosuppression and transaminase elevation but in general these effects were well tolerated.
[25]

Bevacizumab is an anti-VEGF humanized monoclonal antibody. Trials in unresectable cancer patients have shown a tendency to toxicity and blood vessel damage. In 20% of cases, in Malka study, there was variceal bleeding, and there was 1 case of hemorrhagic ascites, 1 case of severe proteinuria and 1 case of ischemic attack.[25]

Erlotinib is another agent that has efficacy against HCC. The adverse reactions included common drug side effects (dry skin, nausea, pruritus, vomit) and anemia, altered liver function and thrombocytopenia.

This drug has also been tested in combination with bevacizumab and has shown results in pretreated HCC which is impressive since this type of cancer is notoriously refractory against therapy. However the toxic effects are significant with one documented death by uncontrolled variceal bleeding and diverse.

Cetuximab is a specific EGFR antibody. It is classified as a chimeric (human/mouse) monoclonal IgG1 antibody. It has shown activity dose dependent growth inhibition and activity against the HepG2 cell line.[25]

mTOR inhibitors are another drug class worth considering in the treatment of HCC. Everolimus and sirolimus are two substances used in the prevention of the organ transplant rejection. They achieve this by inhibition of the serine/ threonine protein kinase mTOR that regulates protein transcription and synthesis and cell growth and motility. Everolimus is an effective radiosensitizer, especially in high linear transfer particles RT but its association with

sorafenib has not demonstrated an increase in survival in first-line treatments. NVP-BEZ235 and Antroquinonol have demonstrated antitumor activity against HCC cells in vitro. Saisarib, a dissociator of the mTOR-raptor complex has shown potential in the prevention and treatment of the disease.[30]

C-KIT, or CD117 is a protein that acts as a stem cell growth factor receptor with tyrosine kinase activity. Dasatanib, clasatanib and imatinib are tyrosine kinase inhibitors that act by targeting this protein. The last drug seems to act as a radiosensitizer as well, but it is not yet extensively studied.

Immune cell system modulation is another modality of treatment explored in the therapy of HCC. It is composed of various methods to strengthen and engage the immune system more aggressively in the fight against HCC. These treatments by definition include vaccination and antivirals but here it will only be discussed drugs that modulate the host. The most preponderant drugs in this field are thymopentin, bavituximab and tremelimumab.[30]

Thymopentin is an immunoestimulant. This thymic polypeptide interacts with T cells and it is being tested in viral diseases and immune deficiencies. The most studied applications of this drug are in post resection therapy and transcatheter arterial embolization.

Bavituximab is an enhancer of antitumoral response. This chimeric immunoglobulin G1-phosphatidylserine-targeting monoclonal antibody can also be used in combination with sorafenib thanks to its well tolerated nature.

Tremelimumab is monoclonal antibody that acts as an immune checkpoint inhibitors by binding itself with CTLA-4 on the surface of activated T lymphocytes. This results in the inhibition of 7-CTLA4-mediated downregulation of T-cell activation. Nivolumab is an anti-PD1 antibody that acts in a similar way. Despite presenting good results, when used in clinical

trials in combination with RT, none of these substances is currently used in clinical practice.
[30]

Lenvatinib is a multi-tyrosine kinase inhibitor used in the treatment of radioactive iodine refractory thyroid cancer. It affects FGFR 1-4, PGFR α , VEGF receptors 1-3 and KIT and RET-oncogenes. A phase II study, using a comparison of the objective response rate, has shown that lenvatinib may induce a similar level of tumor necrosis to TACE.[29]

Stem Cell research

Cancer stem cell is a relatively new area in experimental oncology. These cells would be resistant to common cell quiescence and renewal and to conventional treatments, such as chemotherapy and radiotherapy. If this hypothesis is confirmed it would reveal a new target for a specialized therapy. Stem cell markers as CD133, CD44, and EpCAM and pathways as WNT/ β -catenin, AKT, and IL-6 are thought to be vital to cancer stem cell signaling and may reveal themselves to be interesting targets of therapy.[30]

Chemotherapy

HCC is highly refractory to chemotherapy due to high rates of drug-resistant genes. Chemotherapy can be divided in two modes: Single-agent Chemotherapy and Combination chemotherapy.

Single-agent chemotherapy with 5-fluoracil was shown to have low toxicity, reasonable effectiveness even with liver dysfunction and broad anti-cancer activity. This treatment shows a

higher overall survival when the patient had not undergone previous treatment with sorafenib (OS of 14.5 months vs OS of 9.8 months).

Doxorubicin is another drug of single agent chemotherapy but few studies have shown a improvement of OS with monohterapy.

Combination chemotherapy uses two or more drugs at the same time to improve outcomes. Fol-FOX4 had better results than doxorubicin but also presented an increased rate of neuropathy.[24]

Transarterial treatment

Transarterial radioembolization (TARE) is a recent treatment for HCC. It seeks to induce tumor necrosis using beads that incorporate radioactive material, by introducing them in selected arteries. The most common beads are made of resin or glass and coated with yttrium-90. This treatment is not contraindicated in cases of portal vein thrombosis.

Irreversible Electroporation

This treatment uses electrical pulses in order to create pores in the cell membrane that lead to cell death. This method causes minimal damage due to its precision, barely affecting the parenchyma and blood vessels, and makes the therapy very appropriate to lesions in proximity with important structures or less accessible to common interventions

It also presents an excellent response in patients with lesions smaller than 3 cm with 97% of them reaching a complete response, but limited success in lesions bigger than 4 cm. The rate of readmission, elevation of transaminases is lower than that of MWA.

Systemic Radiotherapy

Hepatic sensitivity to radiation was one of the reasons that made EBRT too risky to consider as a treatment. Even a dose of 28-35Gy, too low to be of therapeutic use, has a risk higher than 5% to induce anicteric hepatitis and even liver failure. This therapy can also cause lesions in other organs.

However, the precision of radiotherapy has increased over the years and with the appearance of intensity modulation radiation therapy (IMTR) and 3-dimensional conformal radiotherapy.

3-dimensional conformal radiotherapy enables radiation quantities of 90 Gy to be used on the liver without adverse toxicity. It can reach 90% of response from HCC and better 2-year overall survival.

IMTR can be combined with helical computer tomography to target multiple tumors.

However this methods are heavily dependent of the radiation quantity used and this quantity is limited by HBV infection, PVT, TACE and classes B and C of the Child-Pugh score.[26]

Charged particle radiotherapy consist in using particle beams as the form of radiation to induce necrosis. Since proton beams lose little energy until they reach their target, they are less toxic to surrounding tissues.

This method has shown, in an interim analysis results similar to TACE.[26]

Stereotactic radiotherapy is most effective when used against small lesions and the subject has its liver function well preserved. It shows local response and overall survival similar to RFA but has a delayed response in lesions larger than 2 cm.[26]

Other than the treatments presented, there is promise in the study of epigenetic modifications of HCC, like DNA methyltransferases and microRNAs. Inhibitors of histone deacetylase are also suggested to reduce cell growth and induce apoptosis.

Immunotherapy targeting the immune checkpoint inhibitors is also a new target and tumor antigen-made vaccines are also being considered.

The molecules MEK, MET AND MYC are new targets to molecular therapy.[24]

Discussion and Conclusion

After the conclusion of this work, it becomes evident that HCC study is far from complete, despite being one of the most prevalent cancers worldwide.

The etiopathogeny is the field the study most developed in HCC. This presents a valuable source of information in preventing the conditions necessary for the occurrence of cancer. This studies, when used in combination with a carefully made clinical history and doctor-patient relationship can prevent many cases of this disease.

The selection of patients and its staging is the most diverse but this diversity i a result of the various environments in which this cancer exists. This staging systems are very useful to select therapies to the diseased, making prognostic predictions and establishing priorities among patients.

In terms of treatment, resection surgery with or without posterior transplant is still the curative treatment but is severely limited to patients with a stable liver function. Since HCC is frequently related with a decrease in liver function and cirrhosis, the need for innovative therapies is evident.

These new treatments are intimately related with the progress in chemotherapy and nanomedicine. The discovery of new drugs that affect angiogenesis and cell growth pathways is the most promising field followed closely by innovative localized percutaneous interventions.

To summarize, the research on HCC is progressing but one can never underestimate the gravity of this problem, in both the patient centered view and population centered perspective.

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