

Update in survival hepatocellular carcinoma

Actualidades en la sobrevida del carcinoma hepatocelular

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Abstract

Objective: To offer an update of the literature, including clinical and epidemiological aspects associated with the survival of hepatocellular carcinoma. **Method:** A literature search was conducted using the electronic databases Medline, Embase, Springerlink and PubMed to identify papers published from January 1, 1985, to August 2020. **Results:** This study analyzed the surgical approach and management of hepatocellular carcinoma worldwide, comparing the two main therapeutic strategies that report the highest percentage of global survival. **Conclusions:** According to the protocol of study, a multidisciplinary approach is necessary. Patients with advanced hepatocellular carcinoma would benefit from an individualized multimodal strategy consisting of hepatic resection and, in other cases, liver transplantation.

Key words: Primary liver cancer. Hepatocellular carcinoma. Survival. Accumulated survival.

Resumen

Objetivo: Realizar una revisión de la literatura actualizada, abordando los aspectos clínicos y epidemiológicos más relevantes asociados con la sobrevida del carcinoma hepatocelular y su relación con las estrategias terapéuticas que han demostrado un mejor resultado. **Método:** Se realizó una búsqueda bibliográfica empleando las bases de datos electrónicas Medline, Embase, Springerlink y PubMed para identificar documentos publicados desde el 1 de enero de 1985 hasta agosto de 2020. **Resultados:** Se analizaron el abordaje y el manejo quirúrgico del carcinoma hepatocelular en todo el mundo, comparando las dos principales estrategias terapéuticas que reportan mayor porcentaje de sobrevida global. **Conclusiones:** En el protocolo de estudio del carcinoma hepatocelular es necesario un enfoque multidisciplinario. Los pacientes con carcinoma hepatocelular avanzado se beneficiarían de una estrategia multimodal individualizada que consista en resección y en otros casos con el trasplante hepático.

Palabras clave: Cáncer primario de hígado. Carcinoma hepatocelular. Sobrevida. Supervivencia acumulada.

Introduction

Worldwide, hepatocellular carcinoma (HCC) is the sixth most frequently diagnosed neoplasm and the

fourth leading cause of neoplasm-associated death reported in 2018. Globally, liver cancer ranks seventh in incidence and is reported as the fifth most common neoplasm in males and the ninth in females. Worldwide, a total of 841,000 new cases and 782,000

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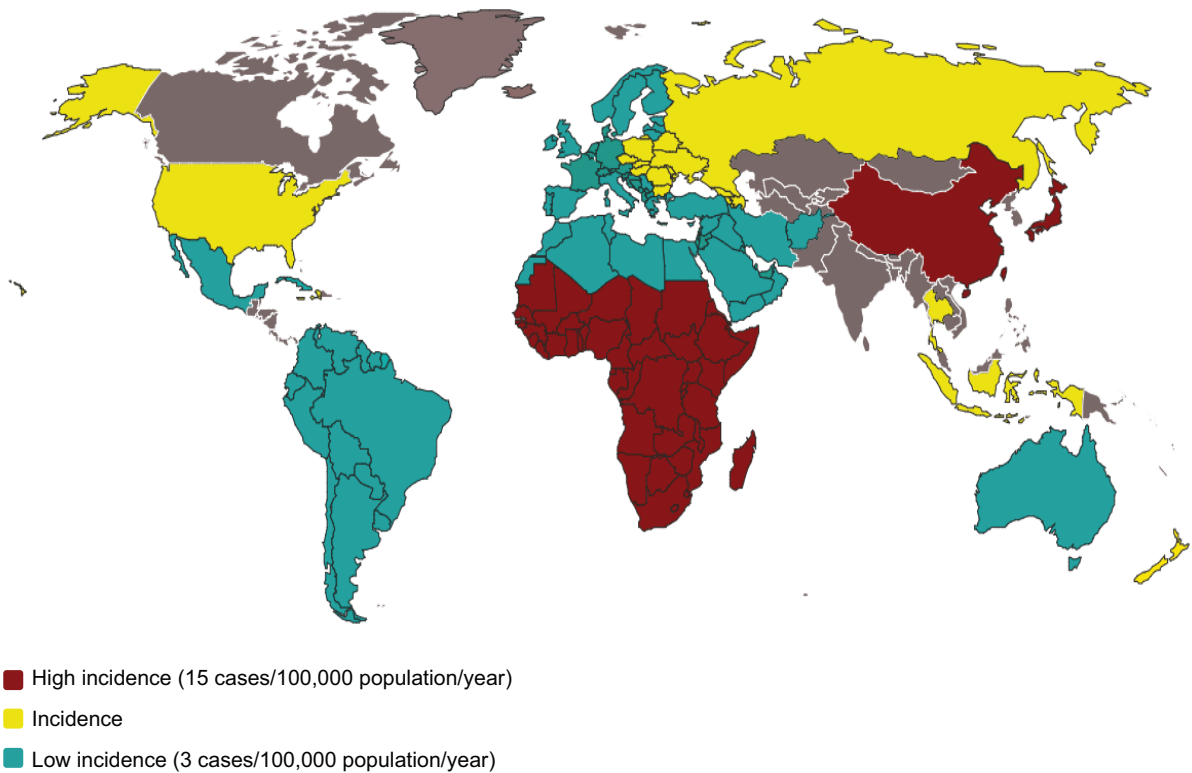


Figure 1. Hepatocellular carcinoma incidence by geographic region. The Pixel Map Generator program (<https://pixelmap.amcharts.com/>) was used to generate the geographic map.

deaths are annually estimated. Recent data indicate that it continues to increase daily throughout the world, with a geographic predominance in Asia and Africa, accounting for 85% of reported cases. Age at presentation varies, with a tendency to progressively increase in all populations, with a predominance for the male gender during the fifth and sixth decades of life^{1,2}. HCC distribution widely varies according to geographical location, ethnic group, and different regions within a single country (Fig. 1). The areas with the highest incidence report more than 15 cases per 100,000 population per year, a figure that corresponds to 40% of total reported cases; for example, in the People's Republic of China, 137,000 cases are recorded every year^{3,4}. In regions with low incidence, there are barely three cases per 100,000 population. In the United States of America, it has significantly increased over the past two decades, especially in the 45-49 age group⁵⁻⁷. As for the behavior of this pathology in Mexico, increases in HCC incidence and mortality have been observed over the past 30 years; however, it is necessary to consider the possibility of under-reporting of cases. The Cortés-Espinosa et al.⁸ research group demonstrated a doubling of said

incidence over a period of 25 years comprised between 1965 and 1990 with a retrospective study carried out in a hospital of Mexico City. More recent data, recorded and analyzed by Méndez-Sánchez et al.⁹, conclude that there was a national increase in HCC mortality of 14% as a specific cause of death, which went from 4.16 to 4.74 deaths per 100,000 population in 6 years. This mortality increase has reached 31% in the same period. In addition, the female gender was found to report the highest mortality, with an increase of 15% vs. 12.5% in the male gender, in comparison with the world population. As for age, the highest mortality was recorded in patients older than 60 years. Data from the National Health Information System (SINAIS – *Sistema Nacional de Información en Salud*) corroborated this elevation, with an increase from 0.4% in the 1980s to 1.3% in 2008.

Worldwide, the survival rate still remains considerably low due to the biological and genetic characteristics of this neoplasm, coupled with the resistance it exhibits against neoadjuvant treatment, mainly to chemotherapeutic agents, and a poor response to radiotherapy.

With the purpose to significantly impact survival of these patients, surgery has been proposed as first-line treatment; however, experts continue to develop new and combined approaches that allow treatment to be individualized in order to provide a better prognosis in the short and long term.

Currently, liver resection is considered the first-line treatment for those patients with single tumors, with a size ≤ 3 cm and preserved liver function; however, its use is limited because most patients, even cases reporting small tumors, have developed pre-surgical liver failure due to late diagnosis at advanced or post-surgical phase of the disease, which significantly affects short-term survival, with a high percentage of cancer recurrence (50%) being recorded¹⁰. Liver transplantation, on the other hand, is considered a potentially “curative” treatment, since it involves infiltrated cancer resection together with damaged liver parenchyma^{11,12}. Candidate patients for this type of liver surgery who meet the Milan criteria, initially described by Mazzaferro et al.¹³, have been accepted and validated by the panel of experts of the 2000 Barcelona Conference, and the Barcelona Clinic Liver Cancer Group classification, as strict selection criteria for hepatocellular carcinoma staging; said criteria are associated with a 4-year survival of 75%. The best approach is undoubtedly surgical, i.e., liver transplantation and liver resection, both aggressive procedures, although with better recorded results: the former, due to the prognosis and survival rate in the short and long term vs. surgical resection, and the latter, for the advantage it provides by “buying time” in case of not having an available donor^{14,15}. The reference is modified by an article that compiles review articles and multicenter analyses and summary reports of recent consensus that strengthens the rationale. The purpose of this review will be solely based on the comparison of liver transplantation vs. liver resection for being the best combined strategy for treating primary liver cancer.

Method

A literature search was carried out using the Medline, Embase, Springerlink and PubMed electronic databases with the purpose to identify documents published from January 1985 to August 2020, using the following MeSH terms: [hepatocarcinoma cellular] [primary liver cancer] [epidemiology] [diagnostic] [treatment] [surgical treatment] [survival] and [follow up]. Fifty-three reference articles were selected. The

Table 1. Risk factors identified to be associated with hepatocellular carcinoma

Age: fifth and sixth decades of life (> 70 years)
Male gender
Ethnicity
Liver cirrhosis
Chronic HBV infection
Chronic HCV infection
Hemochromatosis
Alcoholism
Aflatoxin B1 poisoning
Ionizing radiation
High blood glucose/type 2 diabetes mellitus
Metabolic syndrome/obesity
Hypothyroidism
Fatty liver
Non-alcoholic steatohepatitis
Genetic abnormalities: alpha-1 antitrypsin deficiency, tyrosinemia, galactosemia and hereditary fructose intolerance
Genetic predisposition
Anabolic hormones
Estrogenic contraceptives
Wilson's disease in the presence of cirrhosis

inclusion criteria were: publications from January 1, 1985 to August 2020 related to HCC survival, pathophysiology and world epidemiology available in indexed journals through the *Universidad Nacional Autonoma de Mexico* (UNAM) Faculty of Medicine virtual medical library in English and Spanish. Publications that were not selected were excluded for not meeting the above criteria or because they did not report data of interest on the subject.

Risk factors

Many risk factors are known to be closely related to HCC incidence (Table 1) and mortality increase (Fig. 1).

Ethnic group

With regard to ethnicity, a 2014 study carried out in the United States of America by Setiawan et al.¹⁶, in

which risk factors for liver cancer and other chronic liver diseases were investigated, identified a higher incidence rate in specific ethnic groups, such as Latinos (22.5/100,000), native Hawaiians (21.3/100,000), Japanese Americans (16.8/100,000) and African Americans (16.6/100,000) vs. Caucasians (7.5/100,000), with a marked difference with the former groups being shown.

Age

Age at presentation varies according to geographical location, with a tendency to progressively increase in all populations, with a predominance in males during the fifth and sixth decades of life. Mean age at presentation in Western Europe, Asia and Mexico is around 60 years, while in sub-Saharan Africa there is a marked age decrease down to a mean of 33 years¹⁷.

Food toxins

Aflatoxin B1 toxicity is related to inappropriate storage of grains, and some foods that activate a synergistic effect with underlying chronic inflammatory pathologies of the liver, such as cirrhosis and fibrosis, often associated with infections of viral etiology, or chronic alcoholism, which confer an appropriate microenvironment for them to develop, through a lack of genetic regulation in the cyclic mechanism characterized by hepatocyte necrosis and regeneration.

Gender

As for gender, the regions with the highest reported incidence indicate that the male: female ratio is 5.7:1. The ratio decreases to 2.4:1 in geographical areas with intermediate and low incidence. So far, there is no satisfactory explanation for this phenomenon. There has been speculation about the role of estrogens and androgens as hepatocarcinogenesis modulators¹⁸.

Hepatitis B and C virus infection

Hepatitis B virus (HBV) infection in areas with poor vaccination coverage and hepatitis C virus (HCV) infection in underdeveloped countries are recognized as the main risk factors. The geographical areas with the highest incidence exhibit this infectious pattern, almost endemic, which is associated with chronic liver disease and HCC consequent development. In

America and Europe, the prevalence is much lower owing to the vaccination policies. For this reason, the association between chronic viral liver disease and HCC drives preventive strategies that include universal hepatitis B vaccination at birth and programs aimed at stopping hepatitis B and C transmission and at early eradication^{19,20}.

Pathophysiology

Knowledge of the molecular mechanisms involved in the biology of hepatocarcinogenesis is still incomplete. The different biochemical and genetic signaling pathways that give rise to HCC initially involve a modified hepatic microenvironment related to a chronic liver inflammation that is accompanied by massive fibrosis, both causative of an accumulation of genetic alterations in normal liver cells. Hepatocytes undergo a dysplastic structural modification that gives rise to early carcinoma, which progresses to HCC. This cancer is characterized for being heterogeneous and solid²¹. An intense angiogenic activity in the liver during HCV infection contributes to the high risk these patients have for developing HCC, in comparison with HBV infection, which is related to a chronic inflammatory state that generates oxidative stress mediated by two pathways: one, dependent on HBVx or NS5 transforming proteins, and another dependent on core proteins that are able to modify hepatocytes^{22,23}. From the molecular point of view, HCC is a complex disease that shows heterogeneity between the different tumor nodules that are formed in a single patient.

Clinical aspects

At its initial phase, HCC usually has an asymptomatic clinical presentation, which can linger as such for months and even years; this means that HCC should always be considered within the differential diagnosis of all chronic liver pathologies, even if their occurrence is not linked to a history of liver viral infection or cirrhosis.

When symptomatic, there are different forms of clinical presentation; for example, in sub-Saharan Africa, the most common form of clinical presentation is the appearance of large lesions, palpable on physical examination, located at the upper right quadrant of the abdomen, with liver parenchyma compromise that usually occurs with no evidence of extrahepatic disease despite its dimensions. On the other hand, an acute presentation with hemoperitoneum

secondary to a burst of lesions has been described. In patients with an underlying inflammatory pathology, such as cirrhosis, HCC occurs with ascites, encephalopathy, jaundice or bleeding of varicose origin²⁴. Patients with no previous history of viral infection or cirrhosis generally experience a severe form of the disease, with rapid evolution and a high mortality rate. At the time of diagnosis, most these patients are at an advanced stage of cancer with intrahepatic and extrahepatic compromise that completely contraindicates surgical approach.

Staging

There is no universal consensus on which of all staging systems is the best for classifying this pathology. Currently, the Barcelona Clinic Liver Cancer (BCLC) staging system is the most commonly used due to the criteria it considers for patient evaluation, tumor characteristics and liver function. The system classifies patients at very early stage, early stage, intermediate stage, advanced stage and terminal stage, according to tumor size, vascular invasion, number of tumor nodules and presence of metastasis. This system offers an algorithm for patient management according to the stage the disease is classified at. Patients who are at very early or early stages are considered candidates for curative treatment, which includes liver resection, liver transplant, or local ablation therapy, which reduces the tumor by a percentage for subsequent resection. Patients at intermediate stage, mainly those with multiple nodules with diameters > 10 cm, are not considered candidates for surgical treatment, but they are considered for an approach with potential control of angiogenic and tumor activity through trans-arterial chemoembolization, which seeks to reduce cell mutation and bleeding risk. For those patients who are at confirmed terminal stage, with portal vein invasion or distant metastases, the use of systemic chemotherapeutic agents, such as sorafenib, is considered, or they are enrolled in clinical trials that offer experimental drugs and combination therapies. Despite its reference standard, the BCLC classification system remains controversial due to its limitations in exceptional scenarios^{25,26}.

Auxiliary diagnostic tools

The use of different imaging techniques, such as ultrasound, computed tomography and magnetic resonance imaging, has the purpose to help confirm

the diagnosis, while histopathology is considered the reference method for diagnosis.

Ultrasound

Ultrasound is considered the first screening method for the detection and evaluation of malignant nodules in patients on follow-up for chronic liver disease or with a risk condition, since it is economically accessible and available almost anywhere in the world. Ultrasound effectiveness for detecting any form of HCC is high (94%), but its sensitivity decreases when the target lesion is too small (63%). Ultrasound establishes a 6-month interval as surveillance period for the process of development and evolution of lesions.

Despite the prevention and early detection strategies health systems have tried to implement, once the diagnosis is established, 5-year survival is lower than 10%, partly due to resistance to chemotherapeutic agents and the high rate of recurrence of this cancer²⁷.

Conventional radiological procedures sensitivity and specificity offer a diagnostic and therapeutic use that allows providing a guideline for treatment²⁸.

Survival

HCC mean survival is related to patient risk factors, tumor characteristics and staging, and liver function, i.e., whether it is preserved or there is clinically verifiable liver impairment or failure. A timely initial approach accompanied by an early stage of the carcinoma is the ideal scenario associated with a better prognosis. However, as previously mentioned, once the diagnosis is established, most patients face an advanced stage of the disease that significantly reduces the percentage of survival in the short and very short term²⁹. If we analyze the therapeutic approaches, both surgical intervention modalities, liver resection and liver transplant, are so far the procedures that have been shown to be the best alternatives at almost any stage, offering the patient a mean survival of up to 44.7 months, in comparison with trans-arterial chemoembolization, which offers a mean survival of barely 23.7 months³⁰. Poor prognostic factors have been described, which increase the risk of mortality in populations and that, of course, directly impact survival in the short and long term (Table 2).

Liver resection

Liver resection is reported to be one of the two therapeutic strategies with the greatest benefit to the

Table 2. Factors related to a poorer prognosis and high mortality associated with hepatocellular carcinoma

Age $\geq$ 60 years
Tumor size $\geq$ 10 cm
Number of nodules or tumors $\geq$ 3
Serum alpha fetoprotein concentrations $\geq$ 400 ng/mL
Serum alanine aminotransferase concentrations $\geq$ 80 U/L
Serum total bilirubin $\geq$ 1.2 mg/dL

patient at an early clinical stage. Comparative analyses over the past few decades (Fig. 2) demonstrate a good prognosis in the short and medium term³¹⁻³⁴. In 2014, a group of patients with advanced HCC and preserved liver function was reported, in whom liver resection was observed to reach a cumulative survival rate at 1, 3 and 5 years' follow-up of 88%, 62% and 39%, respectively³³. Another retrospective study, carried out in 2016, analyzed the associations between the BCLC staging system and 5-year mean survival after liver resection in tumors not meeting the Milan criteria, which corresponded to 72.4% for stage 0, 66.3% for stage A, 36.9% for stage B and 28.9% for stage C; this represents an encouraging scenario for those patients who have a single tumor or multiple nodules of very large dimensions who have the opportunity to undergo surgical approach as a potentially curative treatment^{35,36}. The risk of recurrence is explained by the possibility of developing intrahepatic metastases or HCC de novo occurrence in patients with remnant cirrhotic tissue; fortunately, these patients continue to be candidates for transplantation and can undergo trans-arterial chemoembolization while waiting for transplantation. In patients with recurrent HCC with confirmed microvascular invasion, surgical treatment continues to be recommended as first-line, since a second liver resection offers a mean survival of 49 months, and without microvascular invasion, it increases to up to 61 months, in comparison with those patients who did not undergo a second liver resection and were only treated with trans-arterial chemoembolization, with a survival of barely 32 months being reported after recurrence³⁷. Mean survival after liver resection is determined by the "minimum remnant liver volume", a term that refers to the minimum percentage accepted for undertaking this approach and having a better long-term result. Generally, this percentage corresponds to 40% of total parenchyma, but in most patients it represents a poor prognostic factor

because said remnant has a cirrhotic inflammatory component that favors recurrence of this disease.

Some authors propose new surgical techniques based on anatomical sub-segmentation, which allows liver resection to be carried out in a more organized form. This technique has been shown to be able to decrease the risk of intrahepatic metastases through the portal vein in comparison with non-anatomical minor hepatectomy in patients with HCC lesions of between 2 and 5 cm in diameter. In cases with smaller neoplasms, minor non-anatomical hepatectomy is accepted, since the risk of portal dissemination is minimal³⁸.

Liver transplantation

Orthotopic liver transplantation is considered the treatment of choice for patients with Child-Turcotte-Pugh class B or C classification, cirrhosis or early-stage HCC diagnosis³⁹. In patients with preserved liver function and early-stage HCC, it offers a survival of 87% at 1 year, 69% at 3 years and 60% at 5 years. HCC recurrence after liver resection is common, which is why reserving "rescue" liver transplantation as the next step is proposed in the treatment algorithm, since it offers a second opportunity in these cases⁴⁰.

A significant proportion of cases that exceed the Milan criteria is recognized, but different authors have reported a survival rate higher than 70% at 5 years of follow-up in patients who exceed these criteria, which is why broadening them and making them more flexible has been sought for patients with larger tumors or tumors that have been reduced by neoadjuvant treatments such as trans-arterial chemoembolization or local radiofrequency ablation therapy⁴¹.

From this moment on, we can observe that the treatment of a patient with HCC demands to be strictly individualized and requires to be subjected to close surveillance due to the high risk of recurrence there is with this type of cancer. The possibility of broadening the liver transplantation indication for HCC has been proposed in order to include any solitary tumor < 6.5 cm, three or fewer nodules within a larger lesion not exceeding 4.5 cm and total tumor diameter < 8 cm. A comparative analysis of the excellent results obtained over the past few decades allows to identify mean overall survival in the follow-up of patients with HCC who underwent liver transplantation, markedly outperforming liver resection (Fig. 3). Liver transplantation, whether from a living or cadaveric donor, is the cornerstone in

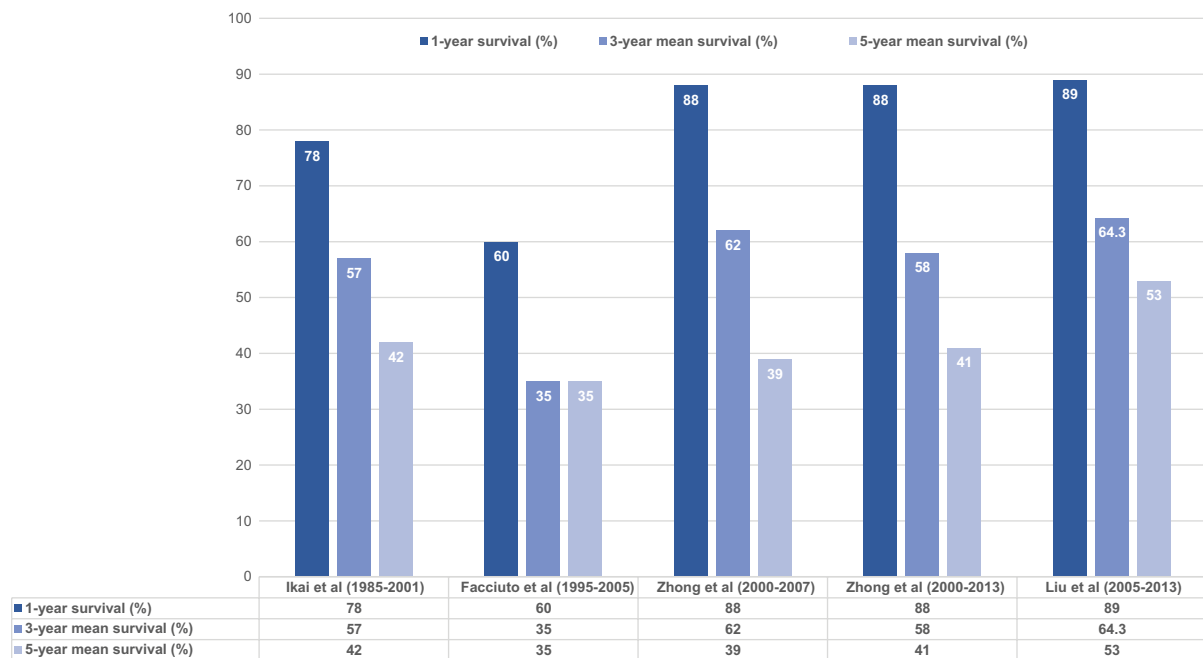


Figure 2. Overall survival comparative analysis by decade in patients with hepatocellular carcinoma who underwent liver resection.

HCC treatment, since mean survival is higher compared to liver resection, and 5-year recurrence rate is lower⁴²⁻⁴⁵.

New therapeutic proposals

There is growing clinical interest in the use of statins for a series of chronic diseases, beyond their traditional indications for cardiovascular disease. Recently, the use of statins, such as simvastatin, has been pointed at as a preventive treatment for HCC. Statins have shown anti-inflammatory, anti-fibrotic and regenerative properties, which makes of them an interesting therapeutic option for chronic liver diseases. Initially, there was concern related to the safety of this drug in patients with liver failure, but documented evidence has provided solid proof that statins are safe and potentially beneficial in patients with ailments characterized as pre-cirrhotic and cirrhotic⁴⁶.

Findings have been described that suggest that the use of statins after HCC diagnosis is associated with a lower risk of death for patients. In 2019, a group of researchers demonstrated that HCC patients who used statins after cancer diagnosis had 15% lower risk of cancer-specific and 11% lower risk of all-cause mortality in comparison with the group of patients diagnosed with HCC who did not use statins. Further studies, with larger patient series and specific clinical endpoints, are

needed before the use of statins can be recommended in patients with chronic liver disease⁴⁷.

Globally, a considerably low survival rate is reported, which is explained by the biological and genetic nature of HCC, and by resistance to chemotherapeutic agents and poor response to adjuvant therapy, such as radiotherapy. With the purpose to significantly improve survival of these patients, first-line treatment was found to correspond to aggressive surgical interventions involving liver resection, even when tumor clinical staging limits its performance, in combination with liver transplantation, when this resource is available.

New and different strategies are being developed to diagnose and treat HCC in order to improve patient survival. Among the diagnostic methods, ultrasound, owing to its sensitivity and specificity, continues to be first choice for surveillance, while histopathology, an invasive method, is considered a standard procedure for definitive diagnosis. For the treating physician it represents a challenge, since diagnosis is generally established late, which considerably reduces patient overall survival. In addition, owing to the high rate of regression/relapse, it is considered a pathology that is hardly "curable", and hence the different therapeutic strategies that have been developed in recent years have their advantages and disadvantages. Liver resection and radiofrequency ablation therapy are considered potentially curative treatments, but there is

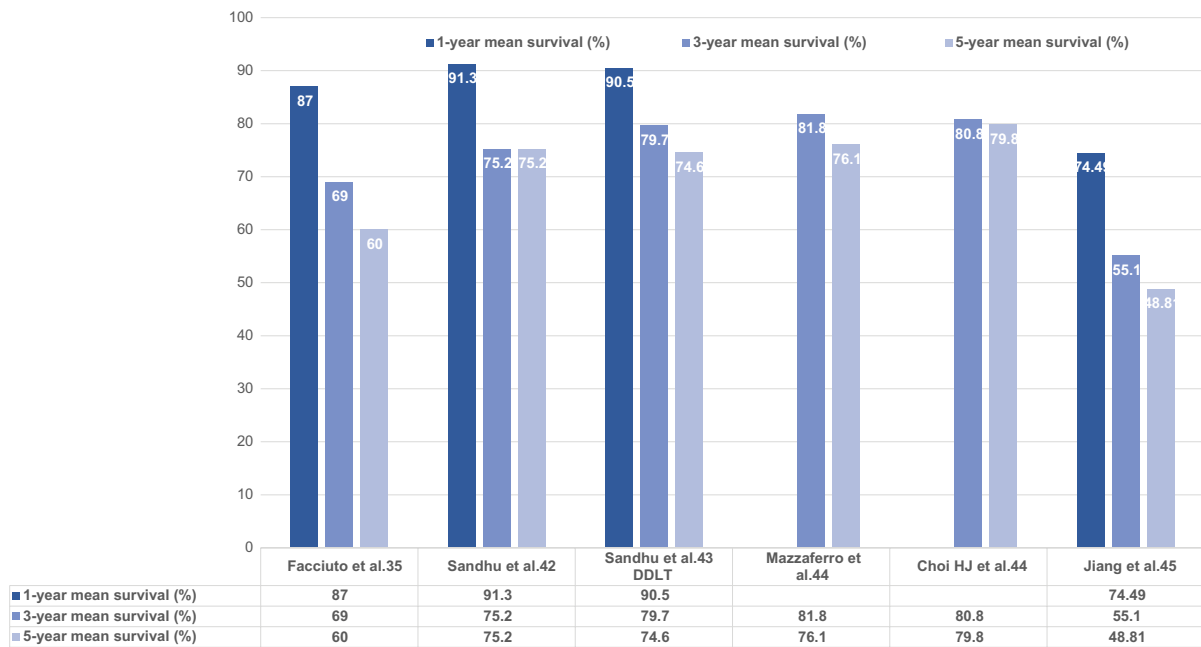


Figure 3. Mean survival comparative analysis in the follow-up of patients with hepatocellular carcinoma who underwent liver transplantation.

recurrence in approximately 50% of cases within the first 3 years after resection, and in more than 70%, within the first 5 years after the procedure, possibly associated with intrahepatic metastases. The results of various retrospective analyses and meta-analyses reveal that liver transplantation, according to the Milan criteria, is associated with longer survival than liver resection. Unfortunately, availability of donors is a major constraint, and around 10% of patients enlisted for this procedure die while waiting. Partial hepatectomy is the optimal treatment for patients with appropriate liver function with no evidence of portal hypertension or vascular invasion, and liver transplantation is potentially curative for patients at early stages, but with inappropriate liver function; however, most patients present with advanced stages, at which they are no longer candidates for said treatment. Thus, chemoembolization by arterial catheterization and chemotherapy are indicated as palliative procedures, with discouraging results.

Discussion

HCC is the third most aggressive cancer all over the world, in both genders, after lung and colon cancer⁴⁸. Many risk factors closely related to an increased number of cases and deaths have been identified, among which HBV and HCV infections stand out, which give rise to different and complex cellular and

molecular interactions that alter the hepatic microenvironment; this risk factor determines, in most patients, the prognosis and treatment response⁴⁹.

Staging of the tumor plays a decisive role in the therapeutic approach, and in making clinical decisions that best suit patient survival. Much evidence is currently available that questions the strict criteria for undergoing liver resection or liver transplantation, and this is often a subject of discussion for the surgeon and his multidisciplinary group: what to do when a patient does not meet the Milan criteria? We should bear in mind that these procedures are considered the only two options with real curative potential that result in lower recurrence and mortality rates⁵⁰.

Treatment can be classified in two main categories: approaches that are potentially curative and approaches that are palliative. Surgical treatment continues to be the mainstay of the options available for HCC management, among which liver resection and transplantation are at top of the list, but it should be borne in mind that the best treatment option will always depend on the patient and his medical history, specifically on liver function, presence of cirrhosis, HBV or HCV infection, portal hypertension, tumor size and location, as well as patient general health conditions. The decision to carry out a liver transplantation or surgical resection is mainly determined by four factors: presence of portal

hypertension, cirrhosis degree, liver function and availability of a donor, associated with the risk of post-transplant recurrence⁵¹.

A new approach to treating patients with HCC consists of more actively using a liver resection and transplantation combined strategy. That is, in patients with preserved liver function and early-stage HCC, a strategy that involves liver resection and transplantation in a staggered manner has been described, which has shown good results that offer the patient a better possibility of survival⁵².

The problem generated by the approach and management of HCC is a subject of discussion all over the world. Currently, the lines of research in relation to HCC recommend following the most current reported guidelines and, at the same time, individualizing treatment, adjusting it to the clinical and histopathological characteristics of each patient⁵³.

Conclusions

The incidence and distribution of HCC largely vary depending on ethnicity, gender, age and, especially, geographical distribution, since it predominates in Southeast Asia and Africa. The incidence reported in Mexico is low, but we do not know if this is due to underreporting of cases.

Patients with high-risk factors for HCC, such as liver cirrhosis, chronic HBV or HCV infection, alcoholic liver disease and steatohepatitis, with presence of visible lesions on ultrasound or triphasic dynamic contrast-enhanced computed tomography, should be considered highly suspicious of HCC. The association between viral liver disease prevention by vaccination and HCC explains why it is considered a preventable neoplasm.

Improvements in epidemiological surveillance of this pathology should be promoted in order to better understand its behavior and distribution, since the Mexican population meets several risk factors associated with the development of primary liver cancer.

Before making a therapeutic decision, liver function should be evaluated in order to identify which approach is best suited to the patient, as well as immediate prognosis, in the post-surgical period, and in the short and long term, for patient overall survival. For liver function clinical evaluation, the Child-Pugh and Model for End-stage Liver Disease (MELD) scales can be used, according to which the registration of low scores allows liver resection, orthotopic transplant from a living or cadaveric donor to be carried out, or else offer the patient neoadjuvant therapy when tumor dimensions preclude surgical approach.

As previously mentioned, the choice of one surgical approach over another will mainly depend on the presence of portal hypertension, liver function and availability of a donor, since transplantation should be prioritized over all available neoadjuvant therapies and even over liver resection itself, given the good prognosis it has in the long term. Liver transplantation is regarded as the solution by “killing two birds with one stone”, since it eliminates the cirrhotic parenchyma and the tumor in its entirety; however, the patient must meet specific criteria that prevent life-threatening post-surgical decompensation. Liver resection, in comparison, has not such a favorable mean survival due to the high percentage of relapse, and thus it can be considered an intermediate strategy that seeks to “buy time” if a donor is not immediately available, when the patient is on waiting list. Alternatively, adjuvant therapies such as trans-arterial chemoembolization or radiofrequency ablation therapy can also be resorted to in order to reduce tumor size and angiogenic activity. One of the biggest challenges a surgeon is faced with is decision making with regard to surgical approach; for this reason, treatment should adhere to internationally established guidelines, but at the same time, it should be individualized and aimed at achieving the highest percentage of survival in the long term.

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Conflicts of interest

None of the authors declares having any conflicts of interest.

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