Revista de Gastroenterología de México 87 (2022) 216–234

REVISTA DE GASTROENTEROLOGÍA DE MÉXICO

www.elsevier.es/rgmx

GUIDELINES AND CONSENSUS STATEMENTS

The second Mexican consensus on hepatocellular carcinoma. Part I: Epidemiology and diagnosis☆

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Received 4 August 2021; accepted 21 October 2021

KEYWORDS
Hepatocellular carcinoma;

Abstract Hepatocellular carcinoma (HCC) is more frequently manifesting as one of the main complications of cirrhosis of the liver, its principal risk factor. There have been modifications in its incidence over the past decade, related to an epidemiologic transition in the etiology

☆ Please cite this article as: Cisneros-Garza LE, González-Huezo MS, Moctezuma-Velázquez C, Ladrón de Guevara-Cetina L, Vilatobá M, García-Juárez I, et al. II Consenso Mexicano de Carcinoma Hepatocelular. Parte I: Epidemiología y diagnóstico. Rev Gastroenterol Méx. 2022;87:216–234.

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Epidemiology;
Diagnosis;
Risk factors;
Surveillance

of cirrhosis, with a decrease in the prevalence of hepatitis C and an increase in nonalcoholic fatty liver disease (NAFLD) as a cause, as well as the development of HCC in the non-cirrhotic liver due to NAFLD. Genetic markers associated with the disease have been identified, and surveillance and diagnosis have improved. Regarding treatment, surgical techniques, in both resection and transplantation, have advanced and radiologic techniques, at the curative stage of the disease, have enhanced survival in those patients. And finally, there have been radical changes in the systemic approach, with much more optimistic expectations, when compared with the options available a decade ago.

Therefore, the *Asociación Mexicana de Hepatología* decided to carry out the Second Mexican Consensus on Hepatocellular Carcinoma, which is an updated review of the available national and international evidence on the epidemiology, risk factors, surveillance, diagnosis, and treatment of the disease, to offer the Mexican physician current information on the different topics regarding hepatocellular carcinoma.

In this first part of the document, the topics related to epidemiology and diagnosis are presented.

PALABRAS CLAVE
Carcinoma hepatocelular;
Epidemiología;
Diagnóstico;
Factores de riesgo;
Vigilancia

II Consenso Mexicano de Carcinoma Hepatocelular. Parte I: Epidemiología y diagnóstico

Resumen El carcinoma hepatocelular (CHC) se presenta cada vez más frecuentemente como una de las principales complicaciones de cirrosis, su principal factor de riesgo. La última década ha presentado modificaciones en su incidencia, relacionadas con una transición epidemiológica en la etiología de la cirrosis, con disminución en la prevalencia de hepatitis C y aumento en la etiología relacionada con la enfermedad por hígado graso no alcohólico (EHNA), además del desarrollo del CHC en hígado no cirrótico por EHNA. Se han identificado marcadores genéticos asociados a la enfermedad, así como avances en vigilancia y diagnóstico. En relación al tratamiento, el perfeccionamiento de técnicas quirúrgicas, tanto relacionadas con resección como trasplante, y radiológicas en estadios curativos permite mejorar la supervivencia de los pacientes candidatos a este abordaje; finalmente, hay cambios radicales en el abordaje sistémico con expectativas mucho más optimistas cuando se comparan con lo disponible hace una década.

Es por eso que la Asociación Mexicana de Hepatología decidió realizar el II Consenso Mexicano de Carcinoma Hepatocelular, en el cual se hizo una revisión actualizada de la evidencia disponible nacional e internacional sobre la epidemiología, los factores de riesgo, la vigilancia, el diagnóstico y el tratamiento de la enfermedad, con el objetivo de ofrecer al médico mexicano una revisión actualizada sobre los diferentes tópicos de esta enfermedad.

En esta primera parte del documento se presentan los tópicos relacionados con la epidemiología y el diagnóstico.

Introduction

There have been changes in the worldwide incidence of hepatocellular carcinoma (HCC) in recent years that are directly related to its main risk factor, cirrhosis of the liver. In addition, after a decade of not having a wide range of systemic therapeutic options, their development has been exponential in the past few years, broadening the management possibilities of those patients, resulting in more encouraging perspectives. Therefore, the aim of the present consensus was to review the current information available, regarding the main topics related to HCC in Mexico, and the rest of the world, as an update on the disease and its management.

Methodology

Twenty-seven specialists with experience in HCC, from different disciplines, including gastroenterology, hepatology, radiology, surgery, transplantation, oncology, and palliative medicine, were invited to review four main topics related to HCC:

I Epidemiology and risk factors
II Surveillance and diagnosis
III Curative treatment
IV The non-curative approach

Forty-nine statements were formulated on the different topics and distributed into four working groups by the consensus coordinators. A bibliographic search of the past 5 years was previously carried out, utilizing the terms HCC + epidemiology, surveillance, risk factors, diagnosis, treatment, review, guidelines, and meta-analysis, adding the word Mexico, in the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and OVID. References in relation to the Mexican population were also added that were provided by the participating authors, as well as the classic bibliography. All the participants had access to the bibliography.

The 49 statements were made available to the 26 participants, utilizing an online platform (SurveyMonkey). The statements were commented on and approved, utilizing the following options:

- In complete agreement
- In partial agreement
- Uncertain
- In partial disagreement
- In complete disagreement
- Comments

A second round was carried out at a virtual meeting of all the participants, in which the statements were discussed, voted upon, and the comments from the first round were corrected and agreed upon.

In a third round, carried out through email, the final statements were voted upon.

The consensus was worked on, based on the definitive statements. The final statements and voting results are presented below.

I. Epidemiology, risk factors, and trends

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Overall epidemiology

1. HCC accounts for 80-85% of the primary malignant tumors of the liver and occurs in the presence of cirrhosis in 80% *of cases.*

In complete agreement: 100%.

HCC is the most common malignant tumor of the liver, corresponding to 80-85% of the primary malignant neoplasms of that organ, followed by cholangiocarcinoma, and occurs in the presence of cirrhosis in the large majority of cases. The incidence and mortality rates differ worldwide due to multiple factors, the main one being the heterogeneous distribution of risk factors, i.e., the different causes of cirrhosis and its global distribution, as well as the age of exposure to the risk factors. The main causes of cirrhosis worldwide are viral hepatitis (hepatitis B virus [HBV], hepatitis C virus [HCV]), alcohol-related liver disease, and cirrhosis secondary to nonalcoholic fatty liver disease (NAFLD). Exposure to aflatoxins also increases the risk in specific geographic regions. Finally, other factors that contribute to local differences in incidence and mortality rates are predisposing genetic factors, environmental factors, and access of the population to HCC screening.[1–4]

2. HCC holds sixth place in the annual incidence of cancer and fourth place in cancer mortality, making it the second most lethal malignant tumor worldwide.

In complete agreement: 100%.

Even though incidence has changed in recent years, in general terms, HCC holds sixth place in the annual incidence of cancer, with 841,080 new cases every year. The annual age-adjusted incidence rate is 9.3/100,000 inhabitants. HCC holds fourth place in cancer mortality, with 781,631 annual deaths, and is the second most lethal tumor, after cancer of the pancreas, with an age-adjusted rate of 8.5/100,000 inhabitants, a mortality to incidence ratio of 0.93, and a 5-year survival rate of 5-30%.

Asia and Sub-Saharan Africa have the highest incidence and mortality rates of HCC, accounting for 55.6% of cases and 54.7% of deaths across the globe. Age-adjusted incidence in Eastern Asia and Sub-Saharan Africa is 34.1/100,000 inhabitants. Incidence is lower in the West, with 4.4/100,000 in Europe and 4.8/100,000 in the United States, with a recent increase associated with the obesity pandemic and NAFLD. Mongolia has the highest incidence, at 93.7/100,000 inhabitants, and Nepal has the lowest, at 1.2/100,000 inhabitants. According to a recent publication analyzing a span of the past 25 years, the worldwide incidence of HCC has increased by 75%, during that time interval.[4–6]

3. Globally, HCC is more frequent in men, and its incidence and mortality peaks are in the seventh decade of life.

In complete agreement: 96%; in partial agreement: 4%.

The age-adjusted incidence rate for HCC is 14.1 in men and 5.2 in women. Its higher frequency in men than in women has a ratio of 2 to 4:1. It is approximately < 1.5 in Mexico and in some Central American countries, such as Guatemala. The discrepancy regarding sex is not clearly defined and varies geographically, possibly associated with the different risk factors for liver disease. Ethnicity is another important factor, with a higher incidence in Hispanics, compared with other races.

Age-adjusted mortality in men is 14.2/100,000 inhabitants and is higher than the 6.2/100,000 inhabitants for women. The highest incidence and mortality peaks present at the seventh decade of life.[1–6]

Epidemiology in Mexico

4. In Mexico, HCC holds ninth place in the incidence of malignant tumors, and distribution is similar between sexes. It holds third place in cancer mortality and is third in women and fourth in men.

In complete agreement: 92.3%; in partial agreement: 7.7%.

Information on the prevalence, incidence, and risk factors for HCC in Mexico is scarce. An analysis of national death certificates within the time frame of 2000-2006 in Mexico, showed a growing trend. The mortality rate due to specific causes revealed an increase of 14% due to HCC, with a mortality increase from 4.16/100,000 inhabitants in 2000 to 4.74/100,000 inhabitants in 2006. Another study analyzed HCC mortality in Mexico, evaluating the population over 65 years of age from four regions with the highest HCC prevalence (the north, center, center-west, and south), within the time frame of 1998-2012. Mortality was constant in that age group throughout the study period, with the lowest at 6.2/100,000 inhabitants and the highest at 18.9/100,000 inhabitants. Men had the highest national mortality rate, except in the central region. Interestingly, mortality rates in both men and women were highest in the central and southern regions. On the other hand, when HCC was analyzed as the cause of death in the rest of the age groups, there was an increase in mortality throughout the study period, possibly indicating that HCC is presenting in groups under 60 years of age. Another interesting finding that should be underlined was observed in women above 65 years of age, in whom HCC was the most prevalent tumor (14.0/100,000 inhabitants), even surpassing breast cancer and cervical cancer. Regarding age, the seventh decade of life was the most affected group in geographic areas of low prevalence and started at 60 years of age in the regions of high prevalence.[7,8]

Etiology and overall risk factors

5. Cirrhosis is the main risk factor for the development of HCC. Close to one-third of patients with cirrhosis will develop HCC, signifying a 1-8% risk per year, depending on the etiology of the liver disease.

In complete agreement: 96%; in partial agreement: 4%.

Approximately 80% of patients diagnosed with HCC present with underlying cirrhosis of the liver. The annual risk for HCC is higher in patients with cirrhosis of viral etiology (HBV 3-8%/year, HCV 3-5%/year) than due to alcohol (1.3-3.0%/year), primary biliary cholangitis (3-5%/year), and NAFLD (> 1.5%/year). In addition to chronic HBV infection in the absence of cirrhosis, there is recent evidence that NAFLD can also result in HCC in patients with no cirrhosis in approximately 20% of cases. Even though the annual risk for developing HCC due to other causes of liver cirrhosis (such as hemochromatosis, autoimmune hepatitis, or alpha-1 antitrypsin deficiency) is difficult to calculate because of study designs, overall, it is considered to surpass 1.5% per year.[9–14]

6. Other risk factors associated with the development of HCC are smoking, exposure to aflatoxins (AFB1), alcohol consumption, visceral obesity, and type 2 diabetes mellitus. The consumption of animal fats, saturated fats, and processed meats has also been associated with a higher risk for HCC.

In complete agreement: 96%; in partial agreement: 4%.

Regarding the contribution of smoking to the development of HCC, a systematic review of 81 studies on the use of tobacco conferred a cumulative risk for developing HCC of up to 1.90 (95% CI: 1.68 to 2.14; $p < 0.00001$) and a mortality of 1.29 (95% CI: 1.23 to 1.34; $p < 0.00001$), depending on the number of cigarettes a day, maintaining a risk of 1.39 (95% CI: 1.26 to 1.52; $p < 0.00001$), even if smoking had been suspended. A European multicenter study showed that tobacco use contributed to nearly half of the cases of HCC.[13,15]

Alcohol consumption and its associated cirrhosis has been identified as one of the main causal agents of HCC in studies around the world. In Europe, alcohol is considered to contribute to 32 to 53% of the cases of HCC, in Africa from 13 to 40%, in the United States to 37%, and in Latin America to 22%.[6,14,16,17]

The exposure of foods to aflatoxin B1 (AFB1) is an important co-factor for the development of cirrhosis of the liver and HCC, particularly in Asia and Africa. Aflatoxins and mycotoxins contaminate cereals and oilseeds. AFB1, produced by *Aspergillus* spp., is the one most frequently involved in liver carcinogenesis. More than 90% of the Eastern African population is estimated to be exposed to those toxins, whereas said exposure is minimal in the Western countries, which partially explains the development of HCC at early ages in many of the Sub-Saharan African countries. Molecular and epidemiologic studies have shown that AFB1 predominantly causes mutations at codon 249 of the TP53 suppressor gene, resulting in an R249S substitution, which is rarely observed in tumors other than HCC. R249S substitution is found in 50-90% of the TP53 mutations in HCC in regions with high aflatoxin exposure, in contrast to the under 6% of TP53 mutations in HCC in the United States. A synergistic role of AFB1 on HCC, in persons infected with HBV, has been observed.[18–24]

Diabetes mellitus, as an independent factor, was associated with a two to three-times increased risk for developing HCC, in both case-control meta-analyses and cohort studies, in addition to a 1.6 to 2.4-higher risk of death. Insulin resistance and the consequent production of reactive oxygen species can produce hepatic inflammation and are thought to play a role in liver carcinogenesis. Diabetes has also been suggested to further increase the risk for HCC, once the subjects have cirrhosis of the liver, and to be an independent factor for lower overall survival and disease-free survival in subjects with HCC.[25–29]

Obesity predisposes to the development of HCC due to the accumulation of lipids in the hepatocyte, which leads to low-grade chronic inflammation. Obesity has significantly increased worldwide and increases the risk of death from

cancer in general and from HCC. Obese individuals have an increased risk (1.5 to 4.0-times higher) for HCC, compared with non-obese individuals, and men with HCC and a body mass index (BMI) above 35 kg/m^2 have a higher mortality rate. A systematic review showed that the risk for presenting with HCC increased 17% in subjects with overweight (25.0-29.9 kg/m^2) and 89% in obese individuals, compared with normal weight subjects.[30–32]

With respect to different lifestyle habits, in addition to tobacco use and alcohol consumption, animal-origin saturated fat and processed food consumption is associated with an increased risk for HCC. A prospective study utilizing data from a cohort study on nurses (the Nurses' Health Study) and another on healthcare professionals (Health Professionals Follow-up Study) in the United States, examined the effect of meat intake and meat mutagens on the development of HCC, over a follow-up period of 32 years. A total of 163 cases of HCC were reported, finding that greater processed red meat consumption was significantly associated with an 84% increased risk for the development of HCC, whereas greater white meat consumption, mainly poultry and fish, reduced the risk by 39%. That concurs with the findings of a previous meta-analysis, in which a protective effect upon changing to a diet including white meat was suggested. In line with that, observational studies have shown a protective effect regarding the Mediterranean diet.[33–35]

In addition to the above, genetic studies have consistently identified single nucleotide polymorphisms (SNPs) associated with liver injury and the development of HCC. Two of them are the GG genotype of the rs738409 polymorphism (C > G; p. I148 M) of the patatin-like phospholipase domain-containing 3 (PNPLA3) gene and the transmembrane 6 superfamily member 2 (TM6SF2) rs58542926 (C > T; p. E167 K) SNP, both of which are involved in lipid metabolism and associated with the development of NAFLD. A recent study that included 1,022 subjects with HCC, 2,021 controls with chronic liver disease, and 2,484 healthy subjects found a strong association of the PNPLA3 and TM6SF2 genes with HCC (OR 1.67, 95% CI 1.16-2.40; p = 0.005; and OR 1.45, 95% CI 1.08-1.94; p = 0.01) after adjustments for fibrosis, age, sex, and etiology. The PNPLA3 and TM6SF2 variants were independently associated with HCC in alcohol-related liver disease (OR 3.91, 95% CI 2.52-6.06). However, there was no association with other etiologies. Interestingly, the PNPLA3 SNPs were associated with the appearance of HCC in non-cirrhotic subjects, suggesting a potential carcinogenic influence, through the modification of the protein function, without altering gene expression.

A Mexican case-control study on 92 patients with HCC and 372 controls confirmed that the presence of the GG variant of the PNPLA3 rs7384099 polymorphism and the GG homozygote variant of the PNPLA3 rs2294918 polymorphism was associated with a significant increase in HCC (OR 2.6, 95% CI 1.6-4.11; p = 0.00002 and OR 1.8, 95% CI 1.1-3.1; p = 0.01, respectively), finding no significant differences, in relation to the NCAN or TM6SF2 genes. Those data showed that the presence of the G allele of the rs738409 and rs2294918 polymorphisms of the PNPLA3 gene makes them independent genetic risk factors highly associated with HCC.[36–38]

7. The most common cause of HCC worldwide is chronic HBV infection, followed by HCV infection. HBV and NAFLD can cause HCC, even in the absence of cirrhosis.

In complete agreement: 100%.

Approximately 54% of cases of HCC worldwide can be attributed to HBV infection, and they are mainly concentrated in Asia and Africa. In that context, the Asian region is characterized by a high prevalence of HBV infection that varies from 20% in Taiwan to 5% in India. China is one of the countries with a larger contribution of HCC due to its almost 18% prevalence of chronic HBV infection and its huge population. In Africa, the prevalence of HBV fluctuates between 27% in the North and 49% in the Sub-Saharan region. Twenty million deaths between 2015 and 2030 are estimated to be attributable to acute hepatitis, chronic hepatitis, cirrhosis, and HCC caused by HBV, with 5 million from HCC. In comparison, in Western countries as a group, 20% of HCC cases can be attributed to HBV.[6,39]

Regarding HCC associated with chronic HBV infection, independent predictive factors for its development have been identified, among which are: positivity for the ''e'' antigen, a high viral load, the B and C genotypes, serum surface antigen levels > 1,000 IU/mL, the presence of the precore mutation, fibrosis grade, and coinfection due to other viruses, such as HCV or HIV. Added to those is the multiplying factor of large quantities of tobacco and alcohol, increasing the risk for HCC by 9 times. A family history of HCC has been identified as another important factor. One spectrum of HBV infection is the so-called ''occult infection'', defined as the presence of HBV DNA in the liver, with undetectable serum surface antigen. In several studies conducted on patients with cryptogenic HCC, in either the presence or absence of cirrhosis, occult HBV infection has been posited to be a cause, and so it should be searched for.[40–46]

HCV infection is the most important viral cause of HCC in Europe, North America, Latin America, Japan, Central Asia, the Middle East, and North Africa, especially Egypt. The main risk factor for developing HCC in patients with HCV is cirrhosis of the liver. Other risk factors are male sex, advanced age, HBV or HIV coinfection, and genotype 3. In the current setting, in which there are effective treatments for HCV, the main risk factors for HCC are the presence of cirrhosis and non-sustained viral response (SVR) status.[3,4,47–49]

NAFLD is increasing across the globe as a cause of HCC. The main risk factor for the development of HCC is the presence of cirrhosis, with an incidence ranging from 0.2% in women to 2.4% in older-age Hispanics with cirrhosis. The majority of the calculations for HCC in the different subgroups of age, sex, and ethnicity are near or above 1% yearly. Unlike other etiologies of HCC, NAFLD is characterized by a higher frequency of HCC in the absence of cirrhosis. In addition, the risk for HCC in NAFLD shares the PNPLA3 and TM6SF2 genetic variants, as previously described.[4,12,36–38]

Cirrhosis of the liver related to excess alcohol consumption continues to be an important factor for developing HCC worldwide, with a constant 20 to 25% of cases of HCC in the United States. It is considered the second most frequently related factor in Europe. A retrospective cohort study that included 450 patients with alcohol-related cirrhosis showed that older age (< 55 years) and thrombocytopenia (< 125,000 per mm^3) were independent factors for developing HCC.[2,50,51]

Finally, it is important to underline that even though the majority of cases of HCC appear in the context of liver cirrhosis, it can also develop in the non-cirrhotic liver. Therefore, HCC associated with chronic HBV infection in the absence of cirrhosis is thought to occur in 30 to 50% of cases in endemic areas, such as Asian and African countries. Regarding hepatitis C, the HALT-C study showed a yearly incidence of HCC of 0.8% in non-cirrhotic patients. NAFLD-associated HCC frequently occurs in subjects with no cirrhosis, as suggested in multiple studies, with prevalences ranging from 27 to 38%.[52–54]

Risk factors in Mexico

8. In Mexico, HCV is the most common etiology of HCC, followed by alcohol use and NAFLD.

In complete agreement: 92.3%; in partial agreement: 7.7%.

The main risk factor associated with the development of HCC is cirrhosis. Epidemiologic studies conducted in Mexico have provided us with information on the main causes of cirrhosis. In 2004, a study was published that included 1,486 patients from 8 healthcare institutions in different geographic areas of the country. Alcohol was the main cause of cirrhosis in 587 (39.5%) patients, HCV was the cause in 544 (36.6%) patients, 154 (10.4%) patients presented with cryptogenic cirrhosis, primary biliary cholangitis was the cause in 84 (5.7) patients, HBV in 75 (5.0%), and 42 (2.8%) patients had other causes. No statistically significant differences between alcohol and HCV were observed and the cryptogenic cause was probably related to NAFLD. In 2018, another article was published that included a total of 1,210 patients seen at 8 different institutions in different geographic areas of Mexico. In that study, the most frequent causes of cirrhosis were HCV (36.2%), alcohol (31.2%), NAFLD (23.2%), HBV (1.1%), autoimmune disorders (7.3%), and other conditions (1.0%). Finally, a 2020 study presented as an abstract that included 4,862 individuals from 5 hospitals in the center of Mexico reported the epidemiologic transition of the main causes of cirrhosis spanning the last 20 years, with NAFLD/cryptogenic disease as the first cause (29%), alcohol in 23% patients, HCV in 22%, and autoimmune liver diseases in 16%.

Finally, a study with 148 cases of HCC in Mexico documented during 2008 to 2014 at 2 centers in the north and central region of the country reported alcohol as the main cause of HCC in 29%, followed by HCV (25%), and in third place, NAFLD (13%). Thus, the conclusion is that the main causes of HCC in Mexico are alcohol-associated chronic liver disease, HCV, and NAFLD.

Regarding the effect of aflatoxins in the Mexican population, the presence of that type of carcinogen was reported in foods, such as corn and certain cereals, oilseed, and processed foods. AFB1 is the main aflatoxin and is synthesized during the secondary metabolism of certain strains of *Aspergillus flavus*, *A. parasiticus*, *A. nomius*, and *A. pseudotamarii*. Fortunately, it is found in low concentrations in the abovementioned foods, and so may not necessarily be a primary risk factor for the development of HCC in the Mexican population.

With respect to smoking as a risk factor, the 2016-2017 National Survey on Drugs, Alcohol, and Tobacco in Mexico reported a 17.6% prevalence of smokers in the population between 12 and 65 years of age, i.e., 14.9 million smokers. Due to that considerable number in Mexico, tobacco is expected to act as a cofactor for the development of HCC.

Therefore, we can say that the risk factors for HCC are alcohol, HCV, and NAFLD in Mexico.[55–63]

Protective factors and prevention

9. Primary prevention should focus on measures for the opportune prevention, diagnosis, and treatment of HCV, HBV, NAFLD, and alcohol-related liver disease.

In complete agreement: 92.3%; in partial agreement: 7.7%.

HCC prevention policies should be directed at preventing its main risk factor, cirrhosis, encompassing at the primary healthcare level: the promotion of a healthy lifestyle that enables the control of diseases that are a risk for the development of cirrhosis, such as hazardous alcohol consumption and NAFLD; the prevention of risk conditions related to the acquisition of chronic hepatitis viruses; the opportune diagnosis and treatment of risk conditions, such as diabetes mellitus, obesity, and metabolic syndrome; screening for alcohol use disorder; the favoring of strategies for promoting and achieving universal vaccination against HBV; the review and adequate processing of blood derivatives before transfusion; the use of disposable syringes; the sterilization of surgical and dental material; the use of condoms; liver damage control programs; opportune HBV detection in individuals with risk factors; and the implementation of the National Plan for the Elimination of Viral Hepatitis, administering the currently available and highly effective drugs to HBV-positive individuals, for their treatment.[64–71]

10. Effective antiviral treatment for HBV, the sustained virologic response in HCV, and alcohol abstinence reduce the risk for HCC.

In complete agreement: 96%; in partial agreement: 4%.

Chronic hepatitis B (cHB). It is well established that viral replication and the grade of liver injury are the two most relevant factors related to the development of HCC in patients

with cHB, and epidemiologic studies have shown that HBV DNA levels correlate with the risk for the development of HCC.

Treatment with nucleos(t)ide analogues (NAs) and long-term sustained suppression of the viral load in patients with cHB have been shown to significantly reduce the incidence of HCC; the NAs of choice, which have a high barrier to resistance, are: entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF). Hosaka et al. found that the 5-year cumulative incidence of HCC was significantly lower in patients with cHB that received ETV, compared with untreated patients (3.7% vs. 13.7%; $p < 0.001$), with a 60% reduced risk for HCC (adjusted HR 0.37; $p = 0.03$). In that same study, the reduced risk for the development of HCC was more apparent in the subgroup that received ETV and also presented with cirrhosis, compared with the untreated patients (a 5-year cumulative incidence of 7.0% vs. 38.9%; $p < 0.001$). In a cohort study with a 4-year follow-up, Su et al. reported that treatment with ETV was also associated with a 60% reduced risk for the development of HCC (HR 0.40, 95% CI 0.28-0.57). In addition, advanced age, male sex, HBeAg positivity, and an alpha-fetoprotein (AFP) value $\geq$ 7 ng/mL, before starting treatment with ETV, were also factors related to the development of HCC. In an observational study, treated patients received ETV (46.9%), TDF (22.2%), other types of NAs (30.8%), or pegylated interferon (pegIFN) (0.1%); Lin et al. found that receiving treatment was associated with a significantly reduced risk for developing HCC in patients with cHB.[41,72–78]

Chronic hepatitis C. The SVR showed a 76% decrease in the development of HCC in patients treated with pegINF. With the advent of the direct-acting antivirals (DAAs), achieving SVR has been shown to reduce the incidence of HCC and there is no evidence that DAAs promote the development of HCC. In a study that included 22,500 patients treated with DAAs (19,518 with SVR and 2,982 non-SVR), there were 271 new cases of HCC. Patients with SVR had a significantly reduced risk for developing HCC (0.90 vs. 3.45 HCC/100 person-years; adjusted HR = 0.28, 95% CI: 0.22-0.36), compared with the non-SVR patients. In addition to a non-SVR status, the presence of cirrhosis was the most important risk factor for developing HCC, in which the annual incidence of said tumor was comparatively higher in the cirrhotic patients vs. the non-cirrhotic patients (1.82 vs. 0.34/100 person-years; HR 4.73, 95% CI 3.34-6.68). In conclusion, the SVR reduces the risk for the development of HCC in those patients. In the presence of cirrhosis, the risk is also reduced, but does not disappear.[79–84]

Alcohol. A meta-analysis published in 2011 showed that abstinence from alcohol can reduce the risk for HCC by 6-7% annually and approximately 24 years are needed to reach the average risk for the general population.[67]

11. The use of lipophilic statins, aspirin, metformin, adequate vitamin D levels, coffee intake, and whole grain consumption have been associated with a reduced risk for the development of HCC.

In complete agreement: 88%; in partial agreement: 8%; uncertain: 4%.

Statins. Some observational studies have reported an association between the administration of statins and a lower risk for the development of HCC. Kim et al.[85] compared the characteristics of patients diagnosed with HCC versus controls paired by age and sex and found statin use to be a protective factor, with respect to the development of HCC (adjusted odds ratio [aOR] 0.44, 95% CI 0.33-0.58). In a large cohort of 260,864 patients with cHC, Tsan et al.[86] also found that the use of statins prevented the development of HCC. In that study, there were 27,883 cases of HCC during the follow-up period, which was the equivalent of 2,792,016.6 person-years. Of the 35,023 patients using statins (equal to or greater than 28 cumulative defined daily doses [cDDDs], 1,378 had HCC. Of the 225,841 patients not taking statins (< 28 cDDDs), 26,505 were diagnosed with HCC. There was a dose-response relationship regarding statin use and HCC prevention, in which the adjusted HRs were: 0.66 (95% CI 0.59 to 0.74), 0.47 (95% CI 0.40 to 0.56), and 0.33 (95% CI 0.25 to 0.42) in patients with 28 to 89, 90 to 180, and > 180 cDDDs per year, respectively, in contrast to the patients that did not receive statins. According to a systematic review with a meta-analysis conducted by Zhou et al.,[87] atorvastatin use (OR 0.63, 95% CI 0.45-0.89) and fluvastatin use (OR 0.58, 95% CI 0.40-0.85) were associated with a lower risk for developing HCC.

Aspirin. In observational studies, regular long-term (5 years of more) aspirin use, in a cumulative dose-dependent relationship, has been suggested to reduce the risk for HCC and said association has not been demonstrated with other nonsteroidal anti-inflammatory drugs (NSAIDs). In a cohort of patients with cHC and cHB and a median 7.9-year follow-up, Simon et al.[88,89] recently reported that the incidence of HCC between aspirin users was 4%, compared with 8.3% in aspirin nonusers (adjusted HR 0.69, 95% CI 0.62-0.76). The protective effect of aspirin once again had a cumulative dose-dependent relationship: from one to 3 years of use, the adjusted HR was 0.90 (95% CI 0.76-1.06); from 3 to 5 years of use, the HR was 0.66 (95% CI 0.56-0.78), and for more than 5 years of use, the HR was 0.57 (95% CI 0.42-0.70). Liver disease-related mortality at 10 years of follow-up was also lower in the aspirin users (11.0% versus 17.9%); adjusted HR 0.73 (95% CI 0.67-0.81). There was no difference between aspirin users and nonusers, with respect to the frequency of gastrointestinal bleeding events.

Metformin. Metformin, as an AMP-activated protein kinase activator, can promote autophagy, which is one of the proposed antitumor mechanisms by which it can prevent the development of HCC. Tseng et al. found that metformin use was associated with a lower risk for developing HCC in patients with type 2 diabetes. A protective synergistic effect was observed in the patients that, in addition to metformin, received statins or aspirin. Chan et al. reported a protective effect, in relation to HCC recurrence, in diabetic patients taking metformin that survived the initial two years

after liver resection (HR 0.65, 95% CI 0.60-0.72; p < 0.05). Overall survival was also better in patients that received metformin (HR 0.79; 95% CI 0.72-0.88; p < 0.05), compared with patients that did not.[90–92]

Vitamin D. In an epidemiologic study on European populations that included 520,000 participants that compared the lowest tertile versus the highest tertile, the patients with the highest vitamin D levels were associated with having a 49% reduced risk for HCC. That protective effect was sustained, even after adjusting the multivariate analysis for different factors, such as biomarkers for preexisting liver injury, HBV infection, HCV infection, body weight, or smoking. Vitamin D inhibits HCC progression by lowering histone deacetylase 2 (HDAC2) expression, which is an enzyme involved in tumorigenesis.[93,94]

Coffee. Several observational studies have shown that regular coffee intake has a protective effect, with respect to the development of HCC, regardless of the etiology conditioning the chronic liver disease, or whether the coffee consumed is caffeinated or decaffeinated. In general, the protective effect occurs with the consumption of 2 to 3 cups of coffee per day. However, the quality of evidence is low, given that the majority of studies lack the appropriate adjustment for potential confounding factors, requiring better quality evidence on the theme. Nevertheless, the European guidelines on HCC management have formally recommended its use.[10,95–98]

Consumption of fiber derived from whole grains. Very few studies have evaluated the impact of diet on the risk for developing HCC. However, dietary quality can have an impact by modulating or regulating the risk conditions involved in hepatocarcinogenesis, such as metabolic diseases. The consumption of whole grain fiber is suggested to reduce the risk for metabolic diseases, improve gut barrier integrity, and improve the composition of the gut microbiota. A 2019 study by Yang et al., with a mean follow-up period of 24.2 years, included 125,455 participants, 141 of whom presented with HCC, and those authors found that whole grain fiber consumption was associated with a reduced risk for the development of HCC.[99–101]

Trends

12. The worldwide incidence of cases of HCC has increased over the years, but the age-adjusted incidence has decreased. The incidence of HCC attributed to HBV has decreased, the incidence associated with HCV and NAFLD has increased, and the incidence related to alcohol has remained relatively constant.

In complete agreement: 96%; in partial agreement: 4%.

For years, the incidence of HCC cases has been increasing worldwide. Between 1990 and 2015, new cases of liver cancer have been reported to have increased by 75 to 114%, describing 471,000 cases in 1990 and 1,007,800 cases in 2016. That increase in the incidence of HCC is largely due to demographic growth and the aging of the population. Nevertheless, the age-adjusted incidence rate has decreased, going from 10.8/100,000 in 2008 to 9.3/100,000 in 2018. The incidence of HCC attributed to HBV has gone down because of universal vaccination programs, among other things, but the incidence of HCC associated with HCV and NAFLD has increased, whereas the incidence of alcohol-related HCC has remained relatively constant. Consequently, a reduction in age-adjusted incidence has been seen in Asia but it has increased in the West, albeit that increase has been slowing down in recent years, most likely as a result of treatment for HCV.[2,6,102,103]

13. In Mexico, the incidence and mortality of HCC are on the rise.

In complete agreement: 92.3%; in partial agreement: 7.7%.

In 2015, the age-adjusted mortality rate in Mexico was reported at 5.2/100,000, compared with 4.1/100,000 in 2000 and 4.7/100,000 in 2006, signifying a 14% increase in the time interval evaluated. In Mexico, HCC accounts for more than 90% of the primary liver tumors and they develop mainly in patients with cirrhosis. The most frequent underlying causes related to HCC in the country are HCV and alcohol, and according to a 2050 projection carried out by Méndez-Sánchez et al.,[104] HCC is calculated to continue on the rise, being the third cause of liver disease-related mortality in Mexico.

In a recent study conducted by Cisneros-Garza et al.[58] that analyzed the characteristics of Mexican patients with HCC, the disease was predominant in men in the sixth decade of life and was associated with pre-existing liver disease in up to 87% of the cases. The most frequent etiology was alcohol-related cirrhosis, followed by HCV and NAFLD. Factors found in that study that can explain a poor prognosis in the Mexican population were diagnosis at advanced stages of the disease and treatment related to availability, given that international guidelines were followed in only 45.3% of cases, impacting survival.[7,105]

II. Surveillance and diagnosis

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Surveillance

14. Adult patients with cirrhosis are at higher risk for the development of HCC and should enter surveillance programs.

In complete agreement: 96.15%; in partial agreement: 3.85%.

The level of risk for the development of HCC is the determining factor for incorporating a patient into a surveillance program, taking into account life expectancy, functional capacity, and the will and ability of the patient to commit to a surveillance and treatment program. Cirrhosis is the

main recognized risk factor, which, regardless of etiology, is present in 80% of the cases of HCC in the Western world. In studies on the incidence of HCC in cirrhosis, a risk higher than 1.5% yearly is considered the minimum risk for justifying a surveillance strategy. Another position is that, if by making the diagnosis, the patient is expected to survive for more than 100 days, surveillance is an adequate strategy for diagnosis and opportune treatment.

As stated above, the main causes of cirrhosis are those that determine the epidemiology of HCC worldwide. Thus, 20 to 25% of all cases of HCC are attributable to alcohol consumption, figures that have remained stable over time. There is a preponderance of cirrhosis secondary to HCV infection as a risk factor for HCC in the West, unlike that which occurs in Asian countries. In Asia and Africa, information on the age of diagnosis of HCC and viral status showed that patients with HCC associated with HBV were younger than the HCC patients with HCV-associated disease, possibly related to the vertical transmission of HBV in those areas. In other countries, said difference in the age at diagnosis of HCC related to HBV or HCV was not found, which was related to the horizontal transmission of those viral infections.

Importantly, at least 20% of the adult patients that develop HCC do not have cirrhosis, and include patients with HBV infection, patients with advanced fibrosis (F3 METAVIR score) in the context of hepatitis C, and individuals with NAFLD.[13,106–113]

An attempt to define HCC risk prediction models for clinical application has been made, but so far, only those developed by Ioannouo et al. appear to be useful. They are based on cohorts of veterans and validated for predicting the development of HCC over a 3-year period in cases of cirrhosis related to NAFLD, alcohol, and hepatitis C. For the HCV model, a sample of 48,151 patients with HCV was analyzed, whereas for the NAFLD and alcohol models, 62,030 patients with cirrhosis were initially identified. Patients are stratified as low-risk, intermediate-risk, and high-risk, theoretically enabling priority to be given to patients with an increased risk, as well as providing screening and personalized surveillance in clinical daily practice.[12,114–118]

15. Even though there is a reduced risk for the development of HCC after treatment with direct-acting antivirals for hepatitis C and the sustained virologic response is lower, the risk is not eliminated, and so patients with advanced fibrosis (F3/F4) should remain under surveillance.

In complete agreement: 100%.

Case series suggest that there is a risk below 1% annually for persons with no cirrhosis and with no advanced fibrosis. The risk increases with the development of cirrhosis, with figures between 2 and 8% yearly. Risk decreases in patients with SVR after treatment with interferon but does not disappear. There is also evidence that current treatment based on DAAs reduces the risk for HCC by 71%. However, in patients with cirrhosis, the risk persists even after 10 years of SVR. Patients with bridging fibrosis (METAVIR F3) are at risk of being misclassified, given that few physicians employ techniques, such as elastography, for establishing the grade of fibrosis, as well as the fact that the transition from F3 to F4 (cirrhosis) cannot be completely defined during surveillance and the customary clinical follow-up.[79,119]

16. Type 2 diabetes mellitus, obesity, and NAFLD are important risk factors for the development of HCC. Individuals with advanced fibrosis (F3/F4) are recommended to undergo surveillance.

In complete agreement: 96.3%; uncertain: 3.7%.

As stated above, diabetes mellitus, as an independent factor, has been shown to increase the risk for HCC by 2 to 2.5 times, compared with controls. Its association was independent from alcohol use or viral hepatitis, but few studies have examined factors, such as obesity or diet. In a meta-analysis that analyzed 10 cohort studies (more than 90 million person-years) and three case-control studies, there was a positive association between obesity (BMI $\geq 30\,kg/m^2$) and the risk for developing HCC, with an increase in the relative risk (RR) from 1.4 to 4.1. NAFLD-associated HCC also presented in patients with no cirrhosis, and importantly, both HCC and NAFLD share risk factors, such as DM2, obesity, and metabolic syndrome. Establishing NAFLD as an independent risk factor has been made very difficult, precisely because of those associations. In the absence of advanced fibrosis (F1-F2), the risk for presenting with HCC has been found to be low and periodic surveillance is not recommended. However, in the presence of advanced fibrosis (F3 and F4), the risk increases, making surveillance necessary for identifying early lesions that can be treated. The incidence risk for HCC in cirrhosis due to NAFLD varies from 1 to 3%. A US Veterans Health Administration study estimated that the risk for NAFLD varies, with an annual rate of 1.06%, but reaching a yearly rate of 2.4% in Hispanics with cirrhosis.[12,25,27,32,120]

17. Ultrasound imaging is recommended for surveillance because it is a noninvasive method, is widely available, and has good sensitivity and specificity for detecting suspicious nodules.

In complete agreement: 92.6%; in partial agreement: 3.7%; in partial disagreement: 3.7%.

Ultrasound (US) is a noninvasive and accessible imaging method for the surveillance of patients with risk factors for developing HCC, and thus is the study of choice in all the guidelines from the different international medical societies, such as the American Association for the Study of Liver Diseases, The European Association for the Study of the Liver, the Asian-Pacific Association for the Study of the Liver, and the KLCSG-NCC Korea practice guidelines.[9,10,121,122]

The sensitivity of US for detecting nodules suspicious for HCC is dependent on the operator, as well as on the characteristics of the patient. At high-volume centers with experience, sensitivity reaches 80%, whereas at conventional centers sensitivity is 65%. Nevertheless, that strategy is less effective for the detection of HCC in early disease stages, with a sensitivity of 63%. In general terms, computed axial tomography (CAT) and magnetic

resonance imaging (MRI) are not routinely recommended for surveillance, but they can be useful in patients in whom US is limited due to obesity or technical factors, as well as in patients at very high risk for developing HCC.[1,9,123–125]

Once there is evidence of an alteration through US, there are defined algorithms to follow, and the size of the detected nodule determines the strategy. Generally, it is unlikely that nodules with a diameter $\leq$ 1 cm correspond to HCC. Nodules > 1 cm should be evaluated through multiphase contrast CAT or MRI to confirm or rule out the typical contrast uptake pattern in the arterial phase, followed by washout of the contrast during the later phases. In nodules of 1-2 cm, the typical dynamic imaging characteristics have a specificity and positive predictive value (PPV) close to 100% and a sensitivity that can reach 71%.[9,10,126]

18. The sensitivity of ultrasound imaging for detecting hepatocellular carcinoma in the at-risk population varies from 60 to 80%. *The combination of ultrasound and serum alpha-fetoprotein (AFP) determination increases the diagnostic yield by an approximate additional* 10%.

In complete agreement: 100%.

According to evidence from systematic reviews, current guidelines recommend liver US as the screening method of choice, with or without AFP determination, every 6 months. Approximately 20% of US imaging studies are classified as inadequate, making it necessary to establish other reporting and evaluation strategies, particularly in cases of obesity, NAFLD, and alcohol-related cirrhosis. In the current system, the study is considered negative, if there are no focal abnormalities or there are only benign lesions, such as cysts. A study is considered non-diagnostic, if there are nodules smaller than 10 mm, and diagnostic, if lesions are larger than 10 mm. The 10-mm diameter has been established as a discriminatory value, given that there is scant possibility that a smaller nodule would be malignant, and the patient should continue to be under the customary surveillance, to have adequate follow-up. In contrast, any nodule larger than 10 mm can be malignant and there is an important risk for delaying the diagnosis, if the established algorithms are not followed. According to the receiver operating characteristic (ROC) curve, the sensitivity and specificity threshold for those lesions is 60% and 90%, respectively. When the AFP level is above 20 ng/dl and in sites with a 5% prevalence of HCC, a PPV of 25% is expected. Adding AFP measurement to surveillance through US is believed to increase sensitivity, albeit the precise increase is not known. Several algorithms based on the etiology of the cirrhosis and changes in AFP have been suggested, to improve the precision of the follow-up strategy value. In a meta-analysis that included 32 studies comparing the sensitivity of US, with and without AFP, for the detection of HCC in patients with cirrhosis, US detected HCC with 84% sensitivity (95% CI 76%-92%), but sensitivity decreased to 47% (95% CI 33%-61%) in cases of early-stage HCC. In studies comparing HCC, with and without AFP, US detected HCC in any stage, with a lower level of sensitivity than the combination of US + AFP (RR 0.88, 95% CI 0.83-0.93). However, US alone detected HCC with a higher specificity level than US + AFP (RR 1.08, 95% CI 1.05-1.09). US, with or without AFP, detected early-stage HCC with 63% sensitivity (95% CI 48%-75%) and 45% specificity (95% CI 30%-62%), respectively (p = 0.02). Only 4 studies evaluated CAT or MRI as screening methods, detecting HCC with 84% sensitivity (95% CI 70%-92%).[127–131]

19. Surveillance of HCC through ultrasound imaging every 6 months is recommended.

In complete agreement: 88.89%; uncertain: 3.7%; in partial disagreement: 7.4%.

Two characteristics have been considered in choosing the ideal surveillance interval for HCC: the rhythm of tumor growth enabling its detection through screening methods and the incidence of HCC in the at-risk population. Based on the knowledge of tumor biology, approximately 6 months has been established as the time it takes for a hepatic nodule to double in size. That is a moderate interval, given that strategies, such as those performed every 3 months, do not reflect greater detection, and tumors detected in strategies every 12 months have less possibility to be treated, resulting in lower survival. In addition, cost-benefit studies show improved life expectancy and quality of life, at a reasonable cost, with semestral strategies. A 6-monthly surveillance regimen is strongly recommended in individuals with conserved liver function, i.e., Child-Pugh class A/B, because regardless of the tumor characteristics, advanced liver dysfunction (Child-Pugh class C) is not susceptible to any therapeutic intervention, unless the individual is on the waiting list for a liver transplantation.[10,132–136]

Diagnosis

20. Upon finding a suspicious nodule larger than one cm through ultrasound, a multiphase contrast-enhanced study is recommended: computed tomography or magnetic resonance imaging, enhanced with liver-specific contrast agents.

In complete agreement: 96.15%; in partial disagreement: 3.85%.

Once a focal lesion is identified through US, multiphase contrasted CAT or MRI is the gold standard for characterizing small nodules in the cirrhotic liver. All guidelines currently support dynamic CAT and MRI as first-line modalities for diagnosis.[9,121,122,137,138]

CAT performed with commercially available extracellular contrast media enables HCC diagnosis, based on physiologic changes in the intralesional blood flow that accompany hepatocarcinogenesis, evaluated in the multiphase studies through pre-contrast images and then dynamically, after contrast agent administration. In general, the contrast medium should be infused at a speed of 4-6 ml/sec and a dose of 1.5 to 2 ml/kg of weight. There are three phases: late hepatic arterial phase, portal venous phase, and delayed phase. The late arterial phase is characterized by complete enhancement of the hepatic artery and its branches, as well as of the portal vein. That phase coincides with maximum arterial perfusion and enhancement of the liver tumors and is essential for the detection and characteriza-

tion of hypervascular HCC. The portal vein phase coincides with maximum parenchymal uptake, characterized by the enhancement of the hepatic veins, as well as the portal veins, that is acquired approximately 60-80 s after contrast medium injection, and the delayed phase is acquired in 3-5 minutes. Those last phases are essential for characterizing the immediate washout and the presence of the tumor capsule.[139–141]

Apart from their diagnostic role, imaging studies can aid in identifying several characteristics that serve as prognostic factors. Large tumors, the presence of multiple nodules, irregular hyperenhancement of the tumor contour in the arterial phase, macrovascular invasion, and most importantly, the presence of vascular microinvasion. Microvascular invasion can be predicted if there are irregular tumor contours, an absent or incomplete capsule, the presence of intratumoral arteries, extranodular growth, multiple confluent nodules, and peritumoral enhancement in the arterial phase. When the diagnosis is made through imaging criteria, confirmation biopsy is not necessary, and the additional information provided by the histopathologic diagnosis is not relevant in the conventional setting because it does not change patient management.[142–144]

Regarding MRI, the main findings that suggest HCC are similar to those observed in CAT, and so they include the behavior of the lesion with the intravenous contrast agent: hypervascularity in the arterial phase and/or arterial/venous phase (early portal phase), and washout in the late venous phase, i.e., if a hypointense lesion is observed in relation to the rest of the parenchyma. In that context, the performance is similar regarding specificity (CAT 92% vs. MRI 91%) and PPV (CAT 8.1 vs. MRI 8.8), but with better sensitivity and negative predictive value (NPV) for MRI (CAT 66%/0.37 vs. MRI 82%/0.2, respectively).[126,139,145–149]

Nevertheless, unlike CAT, evaluation through MRI not only provides information on the behavior of the intravenously contrast-enhanced lesion, but also tends to be multiparametric. The multisequence analysis provides additional signs of HCC that include lesion hyperintensity in the T2-weighted sequences, the appearance of a ''capsule'' in the venous phase, the presence of intralesional fat in T1-weighted out-of-phase sequences, and more recently, restricted diffusion (seen on diffusion-weighted imaging [DWI]) and the hypointense appearance with the use of liver-specific contrast agents.[150–156]

Finally, 18F-fluorodeoxyglucose uptake in positron emission tomography/computed tomography (18F-FDG PET/CT) offers no additional information for the early diagnosis of HCC due to its low diagnostic precision, especially in well-differentiated HCC. It only has a potential value in the detection of extrahepatic metastatic disease in advanced tumors, albeit the advantages are scarce, given the high diagnostic precision of CAT and MRI in that setting. At present, the added value of PET-CT in the evaluation of HCC must be confirmed through additional prospective studies.[10]

21. If a contrast-enhanced study performed due to abnormal findings in a surveillance ultrasound study is not conclusive, the performance of another multiphase contrast-enhanced study is recommended (contrast-enhanced CAT, MRI, US).

In complete agreement: 100%.

During the characterization of nodules in the cirrhotic liver, almost all HCC tumors and certain high-grade dysplastic nodules show a hypointense signal in the hepatobiliary phase. Therefore, images during the hepatobiliary phase improve the detection of precancerous lesions and early-stage HCC that still tends to present hypovascular or isovascular characteristics during the arterial phase, in both tomography and MRI, signifying a diagnostic challenge. However, some low-grade dysplastic nodules and regeneration nodules may also appear hypointense during the hepatobiliary phase. Longitudinal follow-up studies on non-hypervascular nodules that appear hypointense during the hepatobiliary phase have shown that within a year of their finding, the risk for their becoming hypervascular increases with their size. Said risk is estimated at 37.6% for nodules > 1 cm and 77% for nodules > 1.5 cm. In another study on atypical nodules < 2 cm, the use of liver-specific contrast agents improved the diagnostic performance (sensitivity, specificity, diagnostic accuracy, PPV, and NPV) of the multiphase MRI in the characterization of the nodules (88.4-99.4%, 88-95%, 88-98.5%, 97-99%, and 65-97.5%, respectively). A hypervascular nodule in a cirrhotic liver that is > 1 cm in size, without washout in the portal or venous phase, and hypointense during the hepatobiliary phase, is highly suggestive of HCC or a high-grade dysplastic nodule. In contrast, the high intensity of the signal (greater than that of the adjacent parenchyma) during the hepatobiliary phase is a strong indicator of a benign lesion.[149,157,158]

Nevertheless, it is advisable to proceed with caution: even though images during the hepatobiliary phase considerably improve the sensitivity of HCC detection (approximately 11%), their specificity continues to be limited. The sign of hypointensity observed during the hepatobiliary phase does not have the same level of specificity as the portal and/or venous washout (3-5 min), and so does not have the same diagnostic value. Many non-visible regeneration nodules and non-visible low-grade dysplastic nodules can appear as hypointense nodules during the hepatobiliary phase, especially if they are > 2 cm in size, and the specificity of their images in the hepatobiliary phase for diagnosing HCC only reaches 33%. It bears remembering that any lesion composed of cells that lack the OATP1 transporter, i.e., without hepatocytes, are also hypointense in the hepatobiliary phase, including cholangiocarcinoma, hepatocholangiocarcinoma, and hepatic hemangioma. Thus, the detailed analysis of the characteristics of the nodule in other MRI sequences continues to be essential, before making the diagnosis.[152,154,159]

Another ancillary sign through MRI is the presence of restricted molecular diffusion in primary malignant lesions. DWI has become a vital part of liver images due to its high sensitivity for detecting benign and malignant hepatic

lesions. The diffusion sequence is utilized to calculate the apparent diffusion coefficient (ADC) of each voxel in the image. The ADC reflects the mobility of protons in water, thus indirectly providing information on tissue cellularity, necrosis, vascularization, and fibrosis. One of the main limitations of the technique is, again, the relative lack of specificity, and there is a certain overlapping of ADC values between benign and malignant lesions. Several studies examining the use of DWI for diagnosing HCC have shown an inverse correlation between the ADC value and the grade of HCC, with a lower ADC value in poorly differentiated high-grade HCC, compared with well-differentiated low-grade HCC. Nevertheless, the use of DWI has not yet been clearly defined in the international guidelines, which is possibly due to the lack of standardized ADC measurements, despite the fact that many authors have striven to provide unified criteria for its use. Currently, the Liver Imaging-Reporting and Data System (LI-RADS) is the only classification system that includes high signal intensity on DWI (or restricted diffusion on ADC maps) as an ancillary feature focused on the diagnosis of HCC.[126,160–163]

22. Characterizing lesions according to the LI-RADS classification is strongly recommended.

In complete agreement: 96.15%; in partial disagreement: 3.85%.

The American College of Radiology proposed a system for standardizing interpretation reports and data collection of US, contrast-enhanced US (CEUS), CAT, and MRI studies of the liver in patients at risk for HCC. Known as LI-RADS, it stratifies lesions into 5 main categories, from lesions that are definitely benign (LR 1) to lesions that are definitely HCC (LR 5), so that physicians can evaluate the benefits and risks of proceeding with a more invasive treatment or simply carry out lesion follow-up. The prospective evaluation through MRI of nodules smaller than 2 cm, detected through sonography during surveillance, has shown that 25% of LR 2 lesions and 69% of LR 3 lesions were HCC and that there is 98.2% specificity in LR 4 for diagnosing HCC. Therefore, distinguishing between LR4 and LR 5 in nodules detected through sonography has no clinical value. Traditionally, diagnostic criteria are considered arterial enhancement, venous washout, and hyperintensity in T2, with specificity values > 95%, but low sensitivity (45-65%) in lesions of 1-2 cm in size, whereas in the LI-RAD system, the only main criterion is enhancement in the arterial phase. However, the final LI-RADS category depends on lesion size (< 10 mm, 10-19 mm, and > 20 mm), as well as the presence of one or more of the following 3 findings: venous washout, the appearance of a capsule, and interval growth. In the LI-RADS system, the behavior of the lesion after liver-specific contrast medium administration, particularly gadoxetic acid, is an ancillary sign. The gadoxetic acid enters the cell through a specific transporter (OATP1) present in normal functioning hepatocytes, before being excreted in approximately equal amounts, by the hepatobiliary and renal systems. The main advantage of gadoxetic acid is in the analysis of its uptake by hepatocytes during the delayed phase, also known as the hepatobiliary phase, that is generally evaluated 20 min after its administration. During that phase, the functioning hepatocytes uptake the gadoxetic acid and increase their signal intensity, whereas the non-hepatocytic cells and the tumor cells do not, and so they appear hypointense. Several studies describe the added value of liver-specific contrast media for the improved detection of metastasis and in the characterization of benign focal lesions and primary malignant lesions.[126,145,155,164,165]

23. Histologic diagnosis is necessary in non-cirrhotic patients suspected of presenting with hepatocellular carcinoma or if imaging studies are inconclusive for making the diagnosis.

In complete agreement: 100%.

Liver biopsy as the diagnostic method of choice in HCC has been substituted by imaging studies in patients with cirrhosis. In fact, in the diagnostic algorithm for the tumor, biopsy, which has 93% sensitivity and 100% specificity, is resorted to when imaging studies are inconclusive or there is controversy. Biopsy is essential in individuals with a healthy liver and suspected HCC. The risk of complications, such as neoplastic cell seeding and bleeding, as well as inadequate sampling, has further limited the use of liver biopsy in the diagnosis of HCC in patients with underlying liver disease.

Liver biopsy is useful in other scenarios: 1) the differential diagnosis, 2) clinical trials, and 3) stratification for prognostic purposes. The main differential diagnoses are benign lesions of indeterminate outcome (high-grade dysplastic nodule and incipient HCC). In those patients, the immunohistochemical markers of glypican-3 (GPC3), heat shock protein 70 (HSP70), and glutamine synthetase (GS), which guarantee 72% sensitivity and 100% specificity, are resorted to for the diagnosis. It is also possible to differentiate HCC from other primary and metastatic liver tumors through biopsy. In some cases, the poorly differentiated morphology can hinder the diagnosis, making it necessary to utilize hepatocellular differentiation markers. Those currently used are HepPar1, arginase-1, CD10, pCEA, GPC3, and BSEP. There has been a progressively greater use of biopsy, to include patients in clinical trials. In addition to confirming diagnosis, information is obtained with respect to histologic type, grade, microscopic vascular invasion, fibrosis stage, morpho-molecular type, and the phenotypic expression of markers with prognostic impact, such as CK19 and VETC.

Liquid biopsy involves the analysis of the tumor components that are released into the bloodstream. It is a minimally invasive procedure that reduces the costs and potential complications of tissue biopsy. In addition, it is easy to repeat during follow-up and enables treatment response and tumor burden to be monitored. It also makes the identification of emerging clones that are resistant to systemic therapies possible.

The following markers have been proposed: circulating tumor cells (CTCs), circulating free DNA, somatic mutations, circulating RNA, and DNA methylation. All of them can be tools for overcoming tumor heterogeneity, at both the genomic and transcriptional levels. Advances in the field of liquid biopsy have a promising future, regarding the early detection of HCC, with the consequent improvement in patient outcome and patient survival rates.[10,166,167]

24. Staging for prognostic and therapeutic purposes includes tumor characteristics, liver function, and the functional status of the individual.

In complete agreement: 100%.

Classifying HCC has been a subject of debate, given that the tumor exists in a context of liver injury. The Barcelona Clinic Liver Classification (BCLC) has been supported by American and European associations in their clinical practice guidelines. The BCLC defines 5 prognostic subclasses and enables specific treatments to be assigned to each stage of the disease. Five treatments can extend the life expectancy of patients with HCC: surgical resection, liver transplantation, locoregional therapies (ablation), chemoembolization, and systemic therapy. Around 40% of patients with early-stage HCC can be eligible for potentially curative therapy (resection, transplantation, or ablation) that can offer a mean survival of 60 months, compared with the historic 36-month survival. For patients with advanced disease, locoregional therapy and systemic therapy have shown improvement in survival, within the framework of controlled clinical trials. Patients with an intermediate tumor stage and conserved liver function can benefit from chemoembolization, with a mean survival of 26 months. Patients with advanced tumor disease (stage C) can benefit from systemic therapy.

The BCLC was designed precisely for use in clinical trials, in which the majority of participating patients had Child-Pugh class A disease, and includes aspects, such as the status of the underlying liver disease, the functional status of the patient (performance score), and tumor characteristics. It has an easy-to-use algorithm that connects tumor stages with treatment possibilities and was developed utilizing evidence from controlled clinical trials. Treatment assignment follows the levels of evidence based on the strengths of study design and aims, defined by the National Cancer Institute. Other classification systems have been designed, such as the Hong Kong Liver Cancer staging system, The Cancer of the Liver Italian Program (CLIP), the TNM, and the Japan Integrated Staging (JIS) score, but none have reached an international consensus, given that some do not include treatment assignment and others are used only in Asian countries.[9,10,168–172]

Financial disclosure

No financial support has been received in relation to this article.

Conflict of interest

LECG has collaborated with BMS, Exelixis, Viking, Madrigal, Novonordisk, Avant Santé, Cellpharma, and Gilead.

LLGC has collaborated with BMS, Exelixis, Galmed, Novartis, Cymabay, Genfit, Lilly, Madrigal, Novonordisk, Merk, and Galectin.

ERG has collaborated with MSD, Sanofi/Aventis, Roche/Genentech, AMGEN, and Bay.

The rest of the authors declare they have no conflict of interest.

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