Review Article

Narrative review of hepatocellular carcinoma: from molecular bases to therapeutic approach

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Abstract: Hepatocellular carcinoma (HCC) is considered a serious health problem worldwide as it is one of the most prevalent malignancies in the world and with devastating outcomes. According to the 2020 estimation of global burden cancer by the International Agency for Research on Cancer (IARC), HCC ranks third in mortality among cancer deaths despite the incidence rate ranks sixth. In most cases, a history of pre-existing chronic liver disease (CLD) is mandatory, usually established in the stage of cirrhosis. Globally, hepatitis B virus (HBV) continues to be the main cause of cirrhosis and HCC, especially in countries of East Asia and Sub-Saharan Africa where there are no universal vaccination programs against this virus. Other CLD include alcoholic liver disease (ALD), hepatitis C virus, nonalcoholic fatty liver disease, and in more infrequent cases, chronic aflatoxins exposure. Due to this large clinical spectrum that encompasses HCC, it is necessary to systematically review each CLD associated with the development of this cancer by studying its prevalence, molecular pathogenesis, risk factors associated with the progression of HCC, and specially prevention strategies. Finally, regarding the treatment of HCC, great advances have been made in the last decade. Surgical resection, transplantation, and in some cases ablation, are the only curative treatment for HCC, although tumor recurrence is commonly seeing in the follow-up process. Locoregional therapies are still controversial, whether they really provide an overall survival benefit or not, as well as in what type of patients would benefit most from this therapy. Regarding systemic therapies, a recently published phase 3 clinical trial demonstrated greater superiority in the overall survival of atezolizumab plus bevacizumab compared to Sorafenib as a first-line treatment in unresectable HCC patients. This finding will definitely bring a new perspective in the management of these kind of patients.

Keywords: Hepatocellular carcinoma (HCC); review; liver cancer

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Introduction

To date, hepatocellular carcinoma (HCC) is considered a serious public health threat in most parts of the world comprising a broad spectrum of liver diseases with important clinical and histological differences within them, and therefore, variable prognosis depending on the characteristics of each patient. Although great technological and scientific advances have been done in recent decades, HCC still represents the 17th most prevalent cause of cancer in the world, and the third-leading cause of cancer mortality (1).

Understanding and educating our population about the most important causes that have been associated with the development of HCC, as well as discussing and implementing a series of specific strategies that have been shown to be effective in the places where they have been carried out successfully, could represent a window of opportunity for low-cost primary prevention that associates substantial benefits in all national and international health systems that are willing to fulfill these objectives. In the long run, this could reduce the exposure to environmental and occupational risk factors associated with the development of chronic liver disease (CLD) representing a decrease in the surveillance costs of HCC.

Similarly, the medical field is getting each time even closer towards an ideal, more precise, and personalized medicine through the discovery and understanding of several genetic and epigenetic mechanisms involved in different diseases. In the area of oncological hepatology, great advances have also been seen in this regard. So, it would be essential to review what have been the most important advances, and the clinical relevance of these findings in the medical practice.

For this purpose, the objective of this review is to discuss the main scientific advances in the molecular biology of HCC, concisely discussing its clinical significance, the new horizons to consider, the risk factors associated with HCC development, the new advances in the therapeutic approach of this cancer, and the primary prevention measurements that have most demonstrated effectiveness in reducing the clinical spectrum of CLDs and their consequent evolution to HCC.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/dmr-20-116).

Epidemiology aspects

According to data from the International Agency for Research on Cancer (IARC), only in 2018 there was an incidence of 841,080 new cases of liver cancer in the world and a mortality of 781,631 deaths predominantly in male gender (1). Moreover, HCC is twice as common in men as in women (male-to-female ratio exceeding 2.5 for incidence and mortality) (2,3).

In the past, HCC was seen almost as an exclusive condition of East Asian and Sub-Saharan African population (4). However, despite the fact that these groups continue to have high incidences of liver cancer (17.7 cases per 100,000 inhabitants in Eastern Asia) (1), the global epidemic of overweight and obesity, as well as the high consumption of alcoholic beverages have conditioned a noticeable increase in the prevalence of CLD, and a transition in the main etiologies of liver cirrhosis and HCC worldwide (5). Globally, hepatitis B virus (HBV) remains as the leading cause of cirrhosis and HCC due to the lack of universal vaccination in most low-income and lower-middle income countries (6). Interestingly, recent evidence points to the fact that alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) and its severe form, nonalcoholic steatohepatitis (NASH) are becoming important causes of cirrhosis in Asia, potentially exceeding HBV in years to come (7,8). In upper-middle income and high-income Western countries where they have rigorous vaccination programs against HBV, things change a little. In the United States, hepatis C virus (HCV) is the leading cause of liver cirrhosis and liver transplantation (9,10), while NAFLD has become the most rapidly growing cause of liver morbidity and mortality in North America (9,11) and together with ALD representing the two main CLDs in age-standardized death rate and age-standardized years of life lost in the last decade (12). This reveals the need for more aggressive and effective preventive strategies against these health problems that are becoming more frequent in the daily life of our society.

In addition, there is genetic susceptibility among population groups with certain diseases that put them at risk to develop HCC. For instance, a study reported a significant increase in the prevalence of cirrhosis among first-degree relatives of patients with cirrhosis. Meanwhile, another study found familial clustering and potential maternal linkage for insulin resistance for NAFLD and cirrhosis (13). Moreover, mutations in the genes for hemochromatosis (HFE), alpha 1-antitrypsin deficiency (SERPINA1), glycogen storage diseases (G6PC, SLC37A4), porphyria (HMBS, UROD), tyrosinemia (FAH) and Wilson's disease (ATP7B) increase susceptibility to HCC while genome-wide association studies

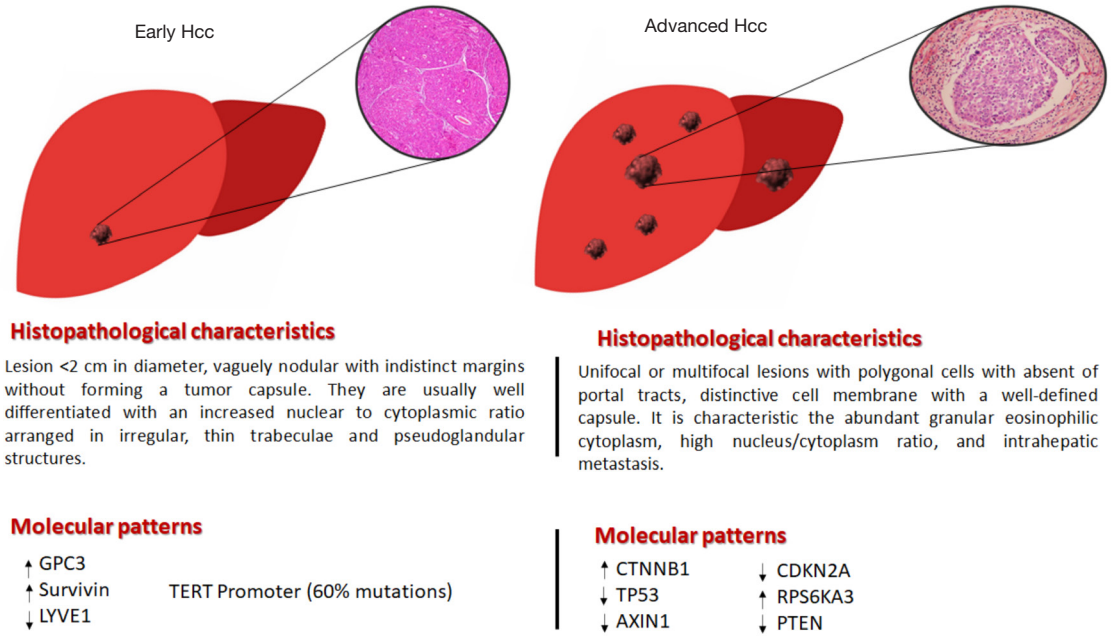

Figure 1 Histopathological and molecular characteristics of hepatocellular carcinoma. GPC3, glypican 3; LYVE1, lymphatic vessel endothelial hyaluronan receptor-1; TERT, telomerase reverse transcriptase; CTNNB1, catenin beta-1; TP53, tumoral protein-53; CDKN2A, cyclin dependent kinase inhibitor-2A; RPS6KA3, ribosomal protein S6 kinase-A3; PTEN, phosphatase and tensin homolog.

(GWAS) in Asians with HBV and HCV support the evidence of polymorphism related with HCC, in this case was several loci located in HLA region (14)

Regarding the incidence rate of HCC, it is impressive to observe how from 1992 to 2017 the incidence rate has practically doubled (4.5 to 8.7 new cases per 100,000 inhabitants) (15). If we add to the equation, the lack of current criteria for the surveillance of patients at risk for the development of HCC, as well as the poor pharmacological response of current treatments in advanced clinical stages, the discouraging prognosis of HCC in the near future are widely exposed.

On the other hand, the economic burden that HCC demands is not a small thing to consider. The diagnosis and treatment of this disease imply an enormous expense in both medical and economic resources, with variable costs between the different studies reported. In Canada, the 5-year net cost of care of a patient with HCC was reported at $77,509 ($60,410–$94,607) representing a higher expense of this condition compared to other cancers (12,16). In the United Stated, the direct costs per patient per year (PPPY) ranged from $29,354 to $58,529 with median overall costs of up to $176,456 per patient (17), while in Taiwan, the direct costs of HCC were a little lower with an estimated cost PPPY of $ 25,716 (18).

Molecular pathogenesis

HCC is the result of a series of disturbances at the cellular and molecular level, derived from a chronic liver insult that produces significant damage to liver cells, and completely deregulates cells proliferation mechanisms (19). This in turn begins to trigger the formation of a vaguely nodular lesion with increasingly known histological and molecular patterns, which as the liver insult progresses, begins to spread throughout all segments of the liver architecture until the development of a clinically-advanced cancer (*Figure 1*) (19,20). HCC is a very heterogeneous tumor. Recent basic research findings have suggested an important role for liver progenitor cells in the development of HCC (21,22). On one side, progenitor cells per se could give a rise to the development of neoplastic cells, and in a similar way, mature hepatocytes could undergo dedifferentiation into progenitor cells and also give a rise to neoplastic cells (23). Although these pathways are still unclear, it has been suggested that liver cancers with stem cell patterns are more aggressive and have a worse prognosis than those without these characteristics (24,25). Irrespective of the involvement or not of progenitor cells,

it is clear that dysregulations between liver cells and their microenvironment is a crucial step for the development of neoplastic lesions (26). Approximately, 90% of liver tumors develop under chronic inflammation conditions (23). In this sense, this could explain why immune-related therapies are each time more used as a therapeutic strategy for HCC.

Within this complex relationship between liver cells and their microenvironment, extracellular vesicles (EVs) are worth mentioning their increasingly evident role in cancer immunoregulation. EVs are vital communication pathways that possess cells with the rest of their environment in physiological and pathological situations (27). In HCC, EVs have been associated with local spread through the release of oncogenic micro-RNAs like -584, -517c and -378 (28). Furthermore, EVs could decrease the pharmacological response to immunological therapies with immune checkpoint inhibitors by promoting chemoresistance of neoplastic cells (29). Unfortunately, the great findings made in the basic sciences of HCC have not yet been successfully transferred to clinical practice. The molecular alterations most frequently associated with the development and progression of HCC continue to represent a challenge for its implementation as prognostic biomarkers, and as effective therapeutic targets.

Genomic events

TERT promoter

The most frequent and important mutation identified in patients since early stages of HCC is in the TERT promoter, seen in almost 60% of patients with this condition (30-32). Some studies have also identified this mutation in dysplastic nodules (31). On the other hand, in patients with overt HCC, other gene mutations have been discovered as important biologic modulators of this tumor. HCV infection (and absence of HBV) is associated with mutations in this gene (33-35).

Wnt/β-catenin pathway

The Wnt/β-catenin pathway regulates stem cells pluripotency and cell fate decision during development. In HCC, *CTNNB1*-gene mutation has been found on over 40% of liver tumors (36,37). Its upregulation is believed to favor the proliferation of tumor cells in advanced HCC stages (38). Mutations in this gene are associated with young age and moderately/poorly differentiated HCV-related HCC (34,35,39). Otherwise, AXIN1 serves as a negative regulator of the Wnt/β-catenin pathway and its downregulation in HCC specimens has been found in almost 20% of cases (36,38).

TP53 pathway

Mutations in TP53 signaling are more associated with HBV infection and absence of HCV (35). On the other hand, TP53 mutation is also related to diet since certain toxins present in a variety of food, such as aflatoxins are involvement in the development of HCC due to epoxidation and DNA adduction (40). These mycotoxins are produced by *Aspergillus* fungi and contaminate grains and cereals, especially in endemic areas of HBV like Southeast Asia. In fact, there is a kind of synergism between HBV infection and aflatoxins exposure (41,42). Moreover, chronic dietary exposure to aflatoxin B1 is capable to induce TP53 mutation at codon 249 of that gene by adduction of AGG to AGT, Arginine to Serine (R249S mutation) (43).

TP53 signaling downregulation is a characteristic commonly found in most cancers and in HCC is not the exception. In liver tumors, TP53 mutation is associated with worse prognosis and poor clinical outcomes due to a downregulation of immune response (44). Also, the TP53 signaling is an essential modulator of angiogenesis thought the regulation of the vascular endothelial growth factor (VEGF-A) (38). Mutations in TP53 signaling are more associated with HBV infection and absence of HCV (35).

Other pathways

The CDKN2A, also called P16, is another key tumor suppressor gene that suppresses the activity of the oncogenes CDK4 and CDK6, and its mutation is seen in a variable proportion of patients with overt HCC of both HBV and HCV etiologies (45). Likewise, the ribosomal protein S6 kinase (RPS6KA3) plays a crucial regulation in the MAPK/ERK and mTOR signaling. Mutations in this gene are associated with an altered cell growth and differentiation (38). Finally, the PTEN is a tumor suppressor gene involved in antagonizing the PI3K-AKT-mTOR pathway. Its downregulation is found in half of patients with HCC (46).

Metabolic pathways

Metabolic dysfunction plays an important role in the

development of HCC, this is important due to the higher prevalence of metabolic syndrome or just metabolic diseases alone, such as diabetes. The case of patients with NAFLD/NASH is particularly interesting because they present patatin-like phospholipase-3 (PNPLA3) I148M sequence variant that is an independent risk factor for HCC. The proinflammatory state of NAFLD/NASH that derived from adipose tissue generate the perfect conditions to develop a primary lesion and DNA, hence, mutations in cell lines (47).

On the other hand, the effects of adipose tissue even in the absence of NAFLD is still important; it seems trough different models of liver metabolic inflammation that intrahepatic CD4 T cells population may be depleted by lipid-mediated mitochondrial dysfunction (48). Regarding to this matter, patient with obesity exhibit a leaky gut that combined with dysbiosis, the translocation of microbiota-associated molecular patterns (MAMPs) and metabolites from gut to the liver induce activation of hepatic stellate cells (HSCs) to form fibrosis and therefore HCC development by inducing a senescence-associated secretory phenotype (SASP) in HSCs (48,49). Another important mechanism related to obesity is lipotoxicity, where lipotoxic free acids and cytokines like chemokine C-C motif ligand (CCL) from adipose tissue activate Kupfer cells (KCs) and consequently HSCs leading to an abnormal production of extracellular matrix (50).

Finally, patients with T2DM suffer from severe forms of metabolic dysfunction because insulin resistance and hyperinsulinemia increase the formation of free fatty acid which leads to activation of adipose tissue and accumulation of reactive oxygen species (ROS) within it. This causes impairment of signaling cascade such as PI-3 kinase, adiponectin, IL, TNF-α, and even more generation of ROS. Finally, those process activate NF-kB and, STATs signaling pathway and HSCs leading to hepatocarcinogenesis (51).

Epigenetic events

Epigenetics is currently an expansive field of study. Micro-RNAs are small non-coding RNA molecules that are involved in RNA silencing and post-transcriptional regulation of gene expression. Their study in cancer has clarified our knowledge in this field and has helped us to develop novel biomarkers and selective drugs specific for each microRNAs profile (26,52). However, we are barely touching the surface of this amazing field of epigenetics, so there is still much work to be done. In HCC, micro-RNA-122 is probably the most studied molecule in this regard. Micro-RNA-122 is a liver-specific micro-RNA that has a key function in the Wnt/β-catenin pathway and its deregulation is believed to confers resistance to pharmacological treatment in patients with HCC (53). Moreover, there are new types of endogenous functional non-coding RNAs (ncRNAs) that have been demonstrated to play important roles in the development of HC. Thus, long non-coding RNAs (lncRNAs) induce liver carcinogenesis by regulating crucial molecular pathways such as the Wnt-Beta Catenin and the STAT3 (51). In addition, circular RNAs (circRNAs) such as circRHOT1 in HCC patients predicted a poor prognosis (54). Pathway analysis suggested that putative target genes of these essential circRNA are involved in HCC-associated signaling pathways, such as Wnt, transforming growth factor beta (TGFβ), and Ras (55).

The studies of both molecules have shown promising results as tools in HCC prognosis. Due to their secretion into body fluids, lncRNAs were proposed also as non-invasive biomarkers in patients with HCC (51).

Unfortunately, the heterogenicity of the few studies carried out, and the inability to differentiate between chronic liver injury and HCC make that it is still not possible to take advantage of the full potential of this biomarker (56,57). Other micro-RNAs studied in HCC are micro-RNA-200a (58), micro-RNA-214 (59), micro-RNA-155 (60), micro-RNA-221 (61), and micro-RNA-21 (62).

Immunological events

During the last decade, a concept known as tumor microenvironment (TME) has become one of the most important models in explaining the progression of cancer. The complex ecosystem of HCC incorporates not only tumor cells, but also nonmalignant cells, vessels, lymphoid organs or lymph nodes, nerves, intercellular components, and metabolites located within the tumor. In fact, about of 30% of HCCs have immune activation. The interplay between all those cells allows to active pathways involved in tumor growth, survival and even metastasis (3,63).

TME in all cancers are mainly composed by immune cells besides cancer cells. In HCC, TME is mainly infiltrated by lymphocytes; each type of t cells, such as regulatory T cell (Treg) and cytotoxic T cells, play a role in tumor invasion and metastasis; even recurrence after resection (48,64).

Moreover, Treg who accumulate mainly in tumoral liver tissues, suppress immune activity against the tumor by

inhibition of CD8 T cells perforins and granzymes activity. In addition, CD8 T cells can be inhibited by other immune cells such KCs by phagocytic and cytokine secretion activities, especially by releasing IL-10 and TGFβ (20). In addition to the latter mechanism, KCs suppress CD8 T cells activity by producing programmed death-ligand 1 (PDL-1), which at the same time inhibit cytotoxic T lymphocyte antigen 4 (CTL-4) favoring HCC malignant progression (48,65,66) Finally, when KCs are activate by IL-1 and TNF-α, the produce osteoponin, a protein involved in angiogenesis, fibrogenesis and carcinogenesis (66,67).

Other macrophages populations besides KCs also play a major role in HCC. Tumor cells can attract and activate macrophages through a variety of growth factor and interleukins; thus, they suffer a transformation into activated M2 macrophages. Increased content of these macrophages associates with angiogenesis and metastasis. Further, it is known that tumor growing means a lack of architecture in its structure, this also apply to TME. An abnormal structure and disorganized growth promote hypoxia leading to activation of M2 macrophages with a phenotype for immunosuppression (48,66).

Therefore, an imbalance among immune cells in HCC TME not only induce to tumoral growing but also survival due to inhibition of immune response and by increasing levels in TGF-β and angiogenic factors, providing subtracts for cancer cells.

Risk factors

As it was stated before, HCC is almost two times more frequent in males than females. The latter, among other factors, may be related with sex hormones imbalance. As an example, in 2001 a case control study in Greece reported that men with HCC had higher levels of estradiol and lower levels of testosterone when compared with controls (68). In addition to the previous study, in 2016 another research found that total testosterone levels were significantly decreased in subjects with HCC but there was no relation between HCC and other sex hormones such as progesterone. In fact, they conclude that there was no strong relation between sex hormones and HCC (69). Furthermore, there is controversial evidence in those kind of studies since there is wide contrasting evidence between them. Yet, it is important to notice that sex hormones play a role in HCC carcinogenesis despite the lack of clear relation with a specific hormone. Besides, *in vitro* studies have shown that dihydrotestosterone (DHT) and testosterone enhance the growth and proliferation of hepatic tumor cell line by the increasing DHT receptors on tumoral cells and surrounding liver tissue (70). On other hand, estrogen receptor, progesterone receptor and androgen receptor which are also involved in cell growth and proliferation are detected in a variable proportion of HCC. Moreover, estrogen induction of microsomally activated catechols by aryl hydrocarbon hydroxylase and estrogen 2-/4-hydroxylase causes excess of free radicals and unrepaired DNA adducts and strand breaks, that produce a mutagenic and irreversible DNA damage (71).

In contrast, there are modifiable risk factors also related with gender. In this matter, metabolic factors like NAFLD/NASH, are the most important because they are becoming an increasingly common cause of HCC worldwide (3). Fox example, type II diabetes mellitus (T2DM) is more common in males than females, obesity is more prevalent in females than males while males are overall more likely than females to have NAFLD/NASH (72).

Regarding to ethnicity, Hispanic and Asian race are the two most important ethnic groups associated with HCC development due to higher prevalence viral hepatitis and susceptibility to aggressive metabolic diseases, especially for Hispanics (73-75). The latter explains that undoubtedly, the most important risk factor for HCC development is to count with a preexisting CLD since either metabolic diseases, viral infection or gender may confer a liver lesion that can be progress from steatosis or chronic inflammation to fibrosis and cirrhosis (*Figure 2*) (19). Cirrhotic patients evolve faster to HCC at a rate of 1% to 4% per year after cirrhosis is established (74,76). The most frequent CLD etiologies that evolve to HCC at a 5-year period are hemochromatosis (21%), HCV cirrhosis (17%), and HBV cirrhosis (10–15%) (74).

HBV

HBV is the leading cause of cirrhosis and HCC worldwide representing at least 50% of all cases of HCC (77). According to the WHO, 257 million people were living with chronic HBV infection in 2015 (78). The main risk factors for the development of HCC in HBV-infected livers are family history of HCC, demographic factors (male gender, advanced age, Asian or African ethnicity), hypertension (79), environmental factors (heavy alcohol consumption, tobacco smoking, exposure to aflatoxins) (80), and viral factors [higher levels of HBV DNA, positivity of HB surface antigen and HB e antigen, chronicity of infection, co-infection with HCV, hepatitis D virus (HDV)

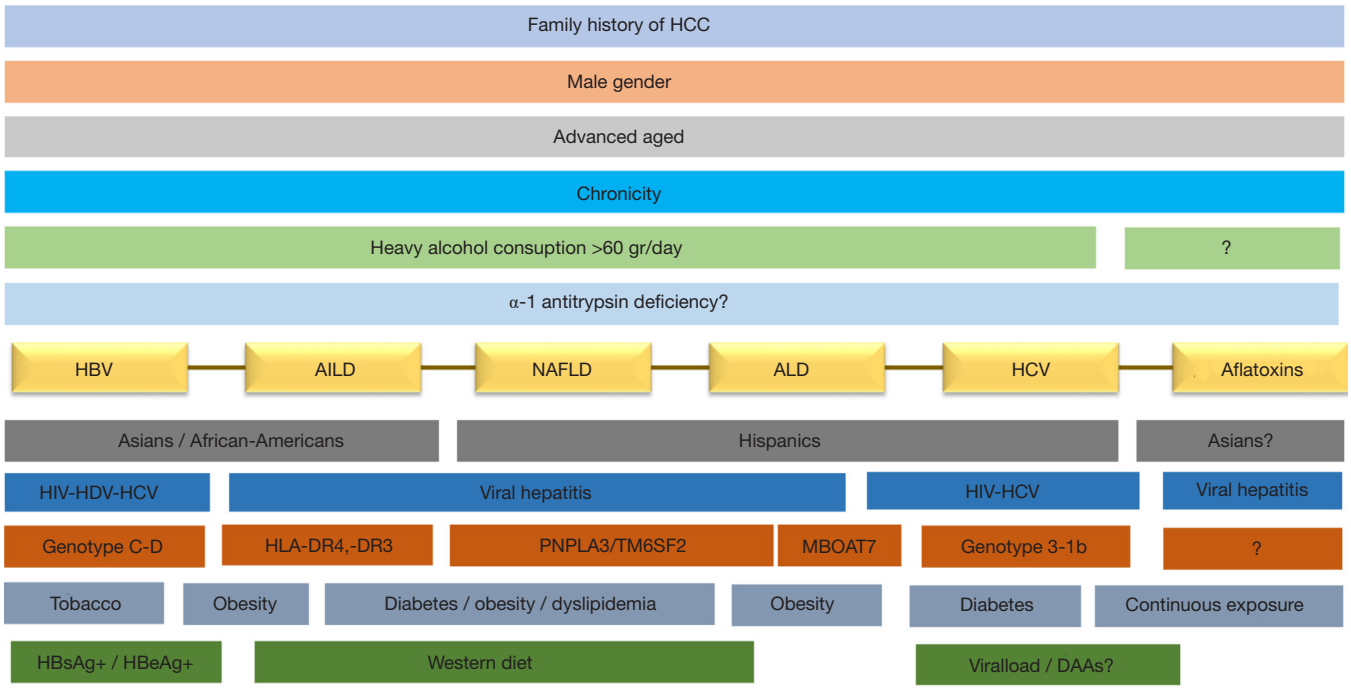

Figure 2 Risk factors associated with progression to hepatocellular carcinoma based on each chronic liver disease. HCC, hepatocellular carcinoma; HBV, hepatitis B virus; AILD, autoimmune liver diseases; NAFLD, nonalcoholic fatty liver disease; ALD, alcoholic liver disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HDV, hepatitis D virus; PNPLA3, patatin-like phospholipase domain-containing protein-3; TM6SF2, transmembrane 6 superfamily-2; MBOAT7, membrane bound O-acyltransferase domain containing-7; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; DAAs, direct-acting antivirals.

and/or human immunodeficiency virus (HIV)] (80). In Asian population, genotype C is more associated with cirrhosis and HCC development, while in East Europe and North America, genotype D is the most frequent in this regard (81). Also, genotype D is associated with HCC in young HBV-infected people without cirrhosis (82).

Hepatitis C virus

HCV is the most frequent etiology of cirrhosis in the Unites States (9). WHO estimates that globally there are 71 million people with chronic HCV infection (78). Active HCV infection has an estimated increased risk for HCC development of 15–20 folds (74). Risk factors for progression to HCC include family history of HCC, demographic factors (male gender, advanced age, Hispanic ethnicity), hypertension, diabetes, obesity, heavy alcohol consumption, and viral factors (genotypes 3 and 1b, chronicity of infection, co-infection with HBV and/or HIV) (83-85). There is still some uncertainty as to whether or not new direct-acting antiviral (DAAs) agents against HCV may be associated with the development of *de novo* HCC, and with the risk of tumor recurrence. The studies conducted in this regard have shown conflicting results (86-89). A recent meta-analysis supports the position of no association between DAAs and HCC development and recurrence (90).

NAFLD

NAFLD is the hepatic manifestation of metabolic syndrome (91). With the increasing epidemic of overweight/obesity as well as other metabolic diseases like T2DM and hypertension, it is believed that NAFLD will represent the most frequent CLD, and therefore will be the leading cause of cirrhosis and HCC in the near future (92,93). Risk factors for HCC development are family history of HCC, demographic factors (male gender, advanced age, Hispanic ethnicity), obesity, T2DM, hypertension, dyslipidemia, gut dysbiosis, high-fat, high-cholesterol, high-fructose diet (Western diet) and genetic modifiers (PNPLA3 and

TM6SF2) (94,95).

Alcohol

Heavy alcohol drinking is an important risk factor for HCC, either by causing direct liver damage by the toxic metabolites derived from ethanol, or by synergizing with viral infections or another CLD, especially when the consumption is above 60 g/day (20,96,97). Compared with non-drinking persons, the pooled relative risk for HCC development in heavy drinking persons (>3 drinks per day) was 1.16 (95% CI, 1.01–1.34) (98).

Autoimmune liver diseases (AILD)

AILD are uncommon causes of HCC. A recent systematic review and meta-analysis found that the pooled incidence rate for HCC in patients with autoimmune hepatitis (AIH) was 3.06 per 1,000 patient-years (P=0.002) and 10.07 per 1,000 patient-years (P=0.015) in AIH cirrhosis (99). The overall recurrence of HCC in AIH is estimated in 5.1% to 6.2% (100). Asian ethnicity, advanced age, male gender, and high alcohol consumption were found to be associated with HCC development, while concomitant primary biliary cholangitis (PBC) was associated with lower HCC risk (83).

In PBC, the incidence of HCC in a Chinese cohort was 4.13% and was considerably higher in men. The significant risk factors found were body mass index ≥25 (P=0.045) and history of alcohol intake (P=0.040) (101).

Aflatoxins

Aflatoxins are metabolites derived from the fungi Aspergillus flavus and *Aspergillus parasiticus*. They are poisonous carcinogens and mutagens found in soil, decaying vegetation, hay, and grains in tropical and subtropical climates in sub-Saharan Africa, Eastern Asia, and South America. Aflatoxin B1 exposure has been related with an increased risk of HCC acting synergistically with HBV (102). A meta-analysis comprising 5 studies found an increased in the risk of cirrhosis associated with aflatoxins exposure with an adjusted pooled odds ratio of 2.5 (P=0.429) (103). Interestingly, specific mutations in TP53 and in *ADGRB1* gene in HCC associated with aflatoxin exposure (104).

Surveillance

HCC surveillance continues to represent a challenge for many health professionals due to the lack of evidence in the adequate selection of patients for their study, the high cost of some imaging studies, and the lack of adequate biomarkers with high diagnostic sensitivity and specificity that are cost-effective for its standardization. To address that problem there are important efforts to identify some of the populations that would benefit from HCC screening to improve surveillance. According to current guidelines of the AASLD, the patient at the highest risk for HCC are Asian male and female with VBH infection, all carriers with VHB or VHC with cirrhosis and/or family history with HCC, genetic hemochromatosis with cirrhosis and patients with alpha-1 antitrypsin deficiency and cirrhosis (105). There is also a recommendation to perform abdominal ultrasound (US) with or without serum alpha-fetoprotein (AFP) every 6 months in cirrhotic Child-Pugh stage A and B patients, and non-cirrhotic HBV patients with moderate to severe risk for HCC. All patients on the waiting list for liver transplantation (including cirrhotic Child-Pugh C) should be screened for HCC (106-108).

Although abdominal US is a cost/effective tool for HCC detection, it has suboptimal performance in men, overweight subjects, Child-Pugh B cirrhosis and ALD cirrhosis, while it was inadequate in Child-Pugh C cirrhosis and NASH cirrhosis (109). In this regard, contrast-enhanced US (CEUS) could be a more reliable study to perform in these patients as it has shown in a recent meta-analysis of 53 studies a pooled sensitivity and specificity to detect HCC of 0.85 (95% CI: 0.84–0.86) and 0.91 (95% CI: 0.90–0.92), respectively. A pooled positive and negative likelihood ratio of 6.28 (95% CI: 4.49–8.77) and 0.16 (95% CI: 0.12–0.22), respectively, a pooled diagnostic odds ratio of 55.01 (95% CI: 35.25–83.47), and an area under the curve of 0.9432 (110). However, reliably studies to assess its utility in patients with suboptimal characteristics for US screening are still lacking. Serological marker AFP has only demonstrated to be reliable when it was combined with US (111). Other biomarkers like des-gamma-carboxyprothrombin, lens culinaris agglutinin-reactive fraction of AFP, glypican-3, etc. still need further evidence to be considered (112). Circulating-free DNA of HCC in plasma is a novel tool for diagnosis and probably for surveillance that could be used in the near future (113).

Diagnosis

All patients under US surveillance in whom a lesion suggestive of malignancy ≥1 cm is found, should be

immediately submitted to multiphasic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) for diagnostic confirmation (106–108). If the lesion is <1 cm it should be monitored closely every 3–6 months for 1–2 years (114). If the lesion remains or disappears, routine surveillance should be done. If the lesion grows or a new lesion develops, CT or MRI must be performed.

The Liver Imaging Reporting and Data System (LI-RADS) emerged as an easy-to-interpret classification system for reporting standardization of images obtained by CT and MRI of patients with suspected HCC diagnosis (114). A systematic review supports LI-RADS as an excellent tool for HCC diagnosis presenting a high discriminatory degree against other liver malignancies (115). In cirrhotic patients with an US liver lesion ≥1 cm submitted to CT or MRI where a solid ≥2 cm lesion with arterial phase non-rim hyperenhancement with late wash-out is found, HCC is confirmed, and no liver biopsy should be done. However, when the lesion does not satisfactorily achieve this criteria, individualized decisions should be done, and liver biopsy could be performed. CEUS could be performed as a second-line option when CT or MRI was inconclusive, and as a prior step before liver biopsy (106-108).

Staging

Since almost all patients with HCC have a pre-existing CLD that determines the clinical condition of the patient depending on the years of evolution and the associated complications, the TNM scale did not adequately satisfy the staging and prognosis of patients with HCC. As a result of this need, different scales began to emerge that not only evaluated the size and tumor invasion, but also evaluated the patient's liver function and quality of life.

Since the Okuda score proposed in 1985, different staging systems have emerged such as Cancer of the Liver Italian Program (CLIP), Tokyo score, bilirubin-albumin-AFPL3-AFP-DCP (BALAD), Advanced Liver Cancer Prognostic System (ALPCS), Hong Kong Liver Cancer (HKLC), Italian Liver Cancer Study (ITA-LI.CA), etc. (116) Most of these classifications have the disadvantage of having only been validated in their own regions of origin, and only for certain etiologies of HCC. Although there is not an universally fully accepted classification, the Barcelona Clinic Liver Cancer (BCLC) established in 1999 was the first system to recommend evidence-based clinical and surgical treatment for each stage (117). Currently, the BCLC classification is the recommended staging system by the European Association For the Study of The Liver and the American Association for the Study of Liver Diseases for its external validation in multiple clinical trials, and for being a dynamic classification in constant evolution that offers evidence-based first-line and second-line treatment strategies for each class of HCC (106,107).

Treatment

Therapeutic management of HCC is a complex subject to discuss. Ideally, each case should be individualized and evaluated by a multidisciplinary group that includes hepatologists, oncologists, surgeons, and radiologists with experience in this type of tumor. However, the resources available to each institution, the experience of the hospital center, and the patient's decision must be considered in all cases. Staging systems can help us evaluate which options are the most viable for each patient. In this context there are two important scales, the BCLC staging criteria and Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status have become an important tool in the decision of treatment modality. The second one is a five-point scale on which higher numbers reflect greater disability where stage 0 (BCLC stages 0-B) may be treated with ablation, resection, transplantation, or chemoembolization while patients in stages 1–2 (BCLC stage C) require systemic therapies with sorafenib among other. Finally, those in stages beyond 2 (BCLC stage D) are non-transplantable and benefit from supportive care (3,118,119).

Resection

Resection is considered the therapeutic management of choice in those patients with a solitary tumor ≤3 cm with preserved liver function, and normal portal pressure ≤10 mmHg (BCLC stage 0 or A). Resection even showed greater overall survival in BCLC stage B patients ideal for resection compared to any locoregional treatment, whereas in BCLC stage B not ideal for resection, it was superior to embolization but not to ablation (120). Regarding the type of approach, laparoscopic liver resection has shown a superiority over open liver resection as it is significantly associated with fewer transoperative complications, better successful achievement of R0 resection, wider resection margin, minor days of hospitalization, and lower morbidity and 30-day mortality rates with no differences in tumor recurrence and overall survival (121). Unfortunately, tumor recurrence with

resection is high with an estimated 70% recurrence rate at a 5-year period (122).

Ablation

Image-guided percutaneous radiofrequency ablation is considered a good option in the management of early-stage HCC that are not candidate for surgery. Ethanol injection is considered another modality of ablation but has no shown worst results *vs.* radiofrequency (123). A meta-analysis showed that radiofrequency ablation has the maximum benefit in terms of overall survival and recurrence-free survival (compared with resection) in Child-Pugh A stage, single-nodule tumor <2 cm and AFP <20 ng/mL (124). Other ablation techniques in current study are new-generation microwave ablation and irreversible electroporation. Prospective confident studies that evaluate these techniques are still lacking.

Transarterial embolization therapies

Transarterial chemoembolization (TACE) is the first-line treatment for HCC patients BCLC stage B or as down staging therapy in potential patients for LT. TACE consists on the joint administration of chemotherapeutic agents (doxorubicin or cisplatin and lipiodol), and the subsequent embolization of the arteries that supply blood to the tumor causing an entrapment of cytotoxic agents confined to the neoplastic cells, ischemia and reduction in tumor burden. Transarterial embolization is a similar modality in which the introduction of chemotherapeutic agents is avoided. Both were demonstrated to be superior in overall survival compared with tamoxifen (125) and symptomatic treatment (126) in unresectable HCC patients, however, there is still a lack of consensus about which transarterial modality is the most effective and secure for patients. Although there is still no clear evidence suggesting superiority of TACE *vs.* TAE (127,128), most authors preferer TACE as the best option for intermediate stage HCC, and it has also been suggested in advanced stage HCC (BCLC stage C) by achieving a longer median overall survival compared with sorafenib (9.2 *vs.* 7.4 months respectively) (129), but it was found to be less cost effective (130).

In recent years, the introduction of TACE with drug eluting beads (DEB-TACE) was presented as a better modality that would deliver chemotherapeutic agents (mainly doxorubicin) with lower adverse effects. A meta-analysis found that DEB-TACE had higher overall survival and was safer than conventional TACE suggesting that DEB-TACE could be the most adequate option to consider in intermediate stage HCC (131).

Systemic therapies

Nowadays, BCLC staging criteria is one of the most useful system to determinate therapeutic strategies of HCC. Patients in stage C, which means an advance stage with extrahepatic spread o portal invasion but preserved liver functions, are the ones who received systemic therapy. In this case, there are 5 main drugs: sorafenib and lenvatinib in the first line and regorafenib, cabozantinib and ramucirumab in the second line (3,119).

Before the development of sorafenib in 2008, there were no effective systemic treatments that prolonged overall survival in patients with advanced stage HCC. Sorafenib is a multiple kinase inhibitor that acts on different signaling pathways especially on the Raf/MEK/ERK pathway and also acts as an anti-angiogenic agent by inhibiting VEGF-2, platelet-derived growth factor, and c-KIT receptor. Sorafenib achieved a longer median overall survival *vs.* placebo (10.7 *vs.* 7.9 months) in the European-American trial (SHARP) (132) and a median overall survival of 6.5 *vs.* 4.2 months in the placebo arm in the Asian Pacific trial (133). Therefore, sorafenib is considered the first-line treatment in advanced stage HCC or intermediate stage HCC that failed locoregional therapies.

Other treatments, such as linifanib (134), brivanib (135), erlotinib (136), and sunitinib (137), subsequently emerged with the intention of emulating or surpassing the results obtained by sorafenib as first-line treatments, however, none of them showed significant results until the arrival of lenvatinib, another multiple kinase inhibitor, which demonstrated a median overall survival not significantly different *vs.* sorafenib (13.6 *vs.* 12.3 months respectively) with similar adverse effects reported in both groups in a non-inferiority clinical trial (138). Therefore, in 2018, lenvatinib obtained by FDA approval as first-line treatment in conjunction with sorafenib for HCC.

For the second-line treatment, regorafenib was tested in HCC patients at Child-Pugh stage A that tolerated sorafenib but still progressed despite treatment. Regorafenib demonstrated an overall survival time of 10.6 *vs.* 7.8 months in the placebo arm (139) and was approved by the FDA as second-line treatment in 2014. Cabozantinib is another second-line approved treatment that showed a median

overall survival time of 10.2 *vs.* 8.0 months in placebo group in previously treated HCC patients who presented progression (140).

Immune-based therapy is an increasingly notorious reality in the treatment of patients with cancer. Ramucirumab is a VEGF-2 immune checkpoint inhibitor that in a randomized double-blind multicenter phase 3 clinical trial failed to improve overall survival *vs.* placebo in patients with advanced HCC who failed first-line treatment, however, later it was shown to improve overall survival in patients with advanced HCC and serum AFP levels ≥400 ng/mL (141), being approved as a second-line treatment in HCC patients with AFP ≥400 ng/mL. The programmed cell death-1 (PD-1) immune checkpoint inhibitor nivolumab showed an objective response rate of 15% in the dose-escalation phase and 20% in the dose-expansion phase leading to its approval by the FDA as a second-line treatment (142). The use of nivolumab as first-line treatment compared to sorafenib is currently being evaluated in a randomized multi-center phase III study (NCT02576509) (143). Pembrolizumab is another PD-1 inhibitor that recently failed in its phase III clinical trial by no achieving significant outcomes in median overall survival time *vs.* placebo [13.9 *vs.* 10.6 months respectively (P=0.0238)] (144). Recently, the results of the phase 3 clinical trial of atezolizumab plus bevacizumab *vs.* sorafenib in unresectable HCC patients who had not previously received systemic treatment were recently published. Remarkably, overall survival at one year was 67.2% with atezolizumab-bevacizumab and 54.6% with sorafenib, with a median progression-free survival time of 6.8 and 4.3 months, respectively (145). These findings suggest that atezolizumab-bevacizumab could be considered in coming years as the first-line treatment in unresectable HCC patients.

Prevention strategies and future directions

As we have seen, despite the great advances in diagnosis and in the different therapeutic modalities that exist for the management of HCC, future projections indicate a growing wave of new cases of HCC, which translates into an increase in mortality from this type of cancer. For this reason, reinforcing the strategies that have been shown to be effective in reducing the number of factors associated with this disease is of vital importance.

Reducing the incidence of viral hepatitis by 90% and mortality by 65% by 2030 is an astonishing goal that the WHO has set as part of the Global Health Sector Strategy on Viral Hepatitis 2016–2021 (146). Within this strategy, it is proposed to make a universal coverage of the HBV vaccine, continuing medical education in the populations at greatest risk though a sustainable and financeable program specific for each region where it is applied. Regarding ALD, although alcohol abstinence is the main goal to be achieved in patients with harmful alcohol consumption, in clinical practice it is difficult to achieve this goal, as it represents a radical change in the lifestyle of patients leading to a poor rate of success in many cases. Recent studies have demonstrated that by achieving a reduction of one or two levels in the WHO drinking risk levels is enough to improve physical health and quality of life of patients, and predict a lower likelihood of liver disease (147-150). Therefore, if we motivate patients to achieve a slight and gradual reduction in their alcohol consumption until they reach to an acceptable point of consumption, could represent a more effective strategy that allows reducing the burden of harmful alcohol consumption and all their direct and indirect consequences. Finally, since NAFLD is becoming the all-leading CLD worldwide, better strategies to combat metabolic diseases should be done. Recently, we discuss the political, economic and social strategies they were carrying out in Europe against NAFLD and how they could be extrapolated to a global context (151). Basically, limitation of fast food and sweetened beverages advertising, nutrition labelling, implementation of lifestyle changes and nutritional education programs in schools are the most important things to implement, and hopefully this could reduce the metabolic diseases burden that we are currently experiencing today.

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