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REVIEW

Diagnosis and treatment of hepatocellular carcinoma: An update

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies leading to high mortality rates in the general population; in cirrhotic patients, it is the primary cause of death. The diagnosis is usually delayed in spite of at-risk population screening recommendations, *i.e.,* patients infected with hepatitis B or C virus. Hepatocarcinogenesis hinges on a great number of genetic and molecular abnormalities that lead to tumor angiogenesis and foster their dissemination potential. The diagnosis is mainly based on imaging studies such as computed tomography and magnetic resonance, in which lesions present a characteristic classical pattern of early arterial enhancement followed by contrast medium "washout" in late venous phase. On occasion, when imaging studies are not conclusive, biopsy of the lesion must be performed to establish the diagnosis. The Barcelona Clinic Liver Cancer staging method is the most frequently used worldwide and recommended by the international guidelines of HCC management. Currently available treatments include tumor resection, liver transplant, sorafenib and loco-regional therapies (alcoholization, radiofrequency ablation, chemoembolization). The prognosis of hepatocarcinoma is determined according to the lesion's stage and in cirrhotic patients, on residual liver function. Curative treatments, such as liver transplant, are sought in patients diagnosed in early stages; patients in more advanced stages, were not greatly benefitted by chemotherapy in terms of survival until the advent of target molecules such as sorafenib.

Key words: Hepatocellular carcinoma; Surveillance;

Liver transplant; Sorafenib; Catheter ablation

Core tip: This paper reviews the most recent evidence on hepatocarcinoma including its molecular pathogenesis and prognosis, with special emphasis on its diagnosis, staging and treatment. The most recent Easter and Western international guidelines are also reviewed.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third cancer-related cause of death; it usually develops in patients with hepatic cirrhosis and is the primary cause of death in this patient group[1].

The prevalence of HCC varies worldwide, with a greater incidence in Asia (> 20 cases/100000) than in North America and Europe (< 5 cases/100000)[2]. Seventy to ninety percent (70%-90%) of patients with HCC also have cirrhosis although in Asia, there is a greater number of non-cirrhotic patients with HCC; their malignancy relates mostly to hepatitis B virus (HBV) and hepatitis C verus (HCV) infections[3].

There are several HCC staging systems but the most currently used is the Barcelona Clinic Liver Cancer (BCLC) staging system[4]. This system's advantage relies on its inclusion of early-stage patients in the therapeutic decision-making schema. BCLC is the system recommended by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL)[5,6]. The diagnostic methods of choice are magnetic resonance imaging and computed tomography in patients with the classical late washout pattern[6]. If not detected, a diagnostic biopsy must be obtained.

The mortality due to HCC is very high, particularly in patients diagnosed in late-stages and in correlation with the underlying liver disease; however, with the implementation of screening programs in high-risk populations[7], early-stage diagnoses have increased and opened the possibilities to curative therapy. These include surgical resection and the treatment of choice, orthotopic liver transplant. Patients outside the realm of curative therapy are managed loco-regionally (radiofrequency ablation, percutaneous ethanol injection and trans-catheter chemoembolization) or with systemic therapy (sorafenib, doxorubicin and bevacizumab) that have been proven to decrease mortality[8].

MOLECULAR PATHOGENESIS

The molecular pathogenesis of HCC is a complex process involving numerous events and genetic abnormalities that provide oncogenic capacities to preneoplastic cells.

There are molecular abnormalities common to the various etiologies of hepatocarcinoma, the most relevant being mutations of the beta-catenin gene (*CTNNB1* gene), the TP53 tumor suppressor gene and deletion of the Axin 1 and *Axin 2* genes, both negative regulators of beta-catenin[9]. There is also *VEGF* gene overexpression (vascular endothelial growth factor) that correlates with the tumor's angiogenic capacity[10] and has led to attempts to develop target therapies against VEGF[11]. Other oncogenic factors include the overexpression of extracellular matrix metalloprotease inducers (EMMPRIN or CD147) that have been associated to increased vascularization, invasion, metastases development and tumor recurrence[12]. Moreover, up-regulation of the JAK/STAT pathway that activates phosphorylation of the STAT3 transcription factor, found in 50%-100% of all HCC, is also related to angiogenesis and cellular differentiation; this has also recently become a therapeutic target[13,14]. Chromosomal instability is one of the most frequent abnormalities in hepatocarcinoma, whereby amplification of chromosome 1q is the most common followed by amplification of 8q and 5p[15]; HCC has also been associated to deletions of 4q, 8p, 13q, 16q, and 17p[16]. Micro RNA (miRNA) involvement has also been recently described in the development of malignancies since they can act like oncogenes or tumor suppressor genes; specifically in hepatocarcinoma, the relation between miRNA down-regulation (miR-122, miR-141), the up-regulation of others (mi-R21, miR-221), angiogenic capacity, metastases development and apoptosis has been well documented[17,18].

Furthermore, there are specific mechanisms involved in the different HCC etiologies such as hepatitis B infection (HBV), in which viral integration into the human genome leads to the production of truncated proteins such as HBx and pre S2/S that in turn, modulate signaling pathways and induce gene activation fostering oncogenesis[19,20]. Unlike HBV, in hepatitis C (HCV) infection there is no genomic integration and HCV-associated oncogenes have not been identified; hence, all pro-oncogenic abnormalities appear to be cytoplasmic and are conditioned by chronic inflammation, replicative senescence resulting from telomere shortening, oxidative stress, liver steatosis and miRNA overexpression, such as that of

miR-155[21,22].

RISK FACTORS AND PREVENTION

Most cases of HCC develop in patients with chronic liver disease (70%-90%)[23]. Risk factors depend on the region where the studies are conducted; for instance, HCV is a major factor in Europe, Japan and North America (50%-70%), HBV accounts for 10%-15%, alcohol 20% and others, 10%. In Asia and Africa, HBV is associated to 70% of cases and HCV to 20%[1,24] although the synergistic effect of non-alcoholic liver disease is becoming more relevant[25,26]. Diabetes mellitus is an independent risk factor in HCC[27]. Obesity is associated with an increased risk of HCC in both males and females[28]. Tobacco use also increases the risk while coffee intake decreases it[29,30].

The most frequent risk factor for HCC (50% of cases), is chronic HBV infection - including occult infection - secondary to exposure to aflatoxin B1[23,31]. Depending on the study, the relative risk of developing a tumor is close to 100-fold in HBV carriers *vs* non-carriers; in patients with associated cirrhosis, the risk is even greater[32] fostered by the viral load and the duration of infection[33]. HBV-related HCC may be prevented by vaccination and in patients with chronic infection and viral replication, treatment with antiviral agents may prevent progression of the liver disease and possibly, the long-term development of HCC, although recent evidence reveals that despite adequate viral suppression the risk remain high[34,35].

The incidence of HCC in individuals with cirrhosis due to HCV, is 3%-5% per year[36]. There is currently no available vaccine as in HBV, but preventing the progression of the acute infection to chronic hepatitis and finally cirrhosis with antiviral agents, prevents cancer development; however, the risk of HCC remain higher[37]. In randomized controlled trials, treatment has not been shown to modify disease progression rates or HCC development in patients with chronic HCV and advanced fibrosis[38,39]. There are recent studies showing that elimination of HCV in patients with compensated cirrhosis, decreases the risk of developing the tumor after 10 years[40]. Alcohol has an important influence on tumor development since it acts synergistically in individuals with chronic HBV and/or HCV infection[36]. HIV and HBV or HCV co-infection is an important risk factor, fostering faster liver disease progression than in individuals without HIV; if cirrhosis develops as a result, the risk for HCC is further increased[41].

SCREENING

At-risk population and benefit of early detection

Screening patients for HCC is recommended in high-risk populations in order to decrease associated mortality if detected in a curable stage[8]. Unfortunately, most detected cases are diagnosed in advanced stages since less than 20% of patients with cirrhosis are screened for HCC[42]; this is due, in great measure, to the first contact physicians' lack of knowledge of the recommended clinical guidelines although they care for 60% of these patients[43].

The decision to begin screening depends on the individual's risk and on whether they wish to be treated if diagnosed with HCC. Screening recommendations include: (1) patients with cirrhosis of any etiology, with conserved liver function (Child-Pugh A and B), lacking severe comorbidities; (2) decompensated cirrhosis (Child-Pugh C) on a transplant waiting list; (3) non-cirrhotic chronic HBV infection with active hepatitis or a family history of hepatocarcinoma; and (4) non-cirrhotic HCV infection and advanced liver fibrosis (F3)[5].

Screening methods

Liver ultrasound: Liver ultrasound twice a year is the screening procedure of choice since it is not an invasive method, it is easily available and its cost is moderate. Its sensitivity is 60%-80% and its specificity is above 90%[44]. A recent randomized prospective study revealed that its diagnostic yield was comparable to that of an annual triphasic computed tomography, and at a lower cost[45].

Serum alpha fetoprotein (AFP): Serologic tumor markers are of limited use: although more sensitive than other biomarkers with a cut-off point of 10.9 ng/mL[46], its diagnostic yield is inferior to ultrasound since its concentration depends on the tumor size and thus, preferentially detects tumors in advanced stages.

Ultrasound + alpha fetoprotein: If both strategies are combined, serum alpha fetoprotein levels only add 6%-8% to the number of cases undetected by hepatic ultrasound (HUS)[47]. The combination of these strategies increases the number of false positives as well as costs. There is currently insufficient evidence to support or refute the use of both methods in HCC screening/surveillance in the population with hepatitis B infection[44,48].

DIAGNOSIS

Pathology studies have revealed that most nodules < 1 cm detected in cirrhotic livers, are not HCC[49]. To date, HUS follow-up every 3-4 mo of lesions under 1 cm is recommended. If they grow, evaluation should be conducted according to the size of the lesion; if it remains stable, HUS is recommended every 4 mo[5,6]. In lesions greater than 1 cm, non-invasive diagnostic strategies should be followed with imaging methods; if a HCC diagnosis is not established, a liver biopsy is warranted. If this is inconclusive, the patient should be followed every 4 mo, but if the lesion grows or imaging patterns change, a second biopsy should be obtained[5].

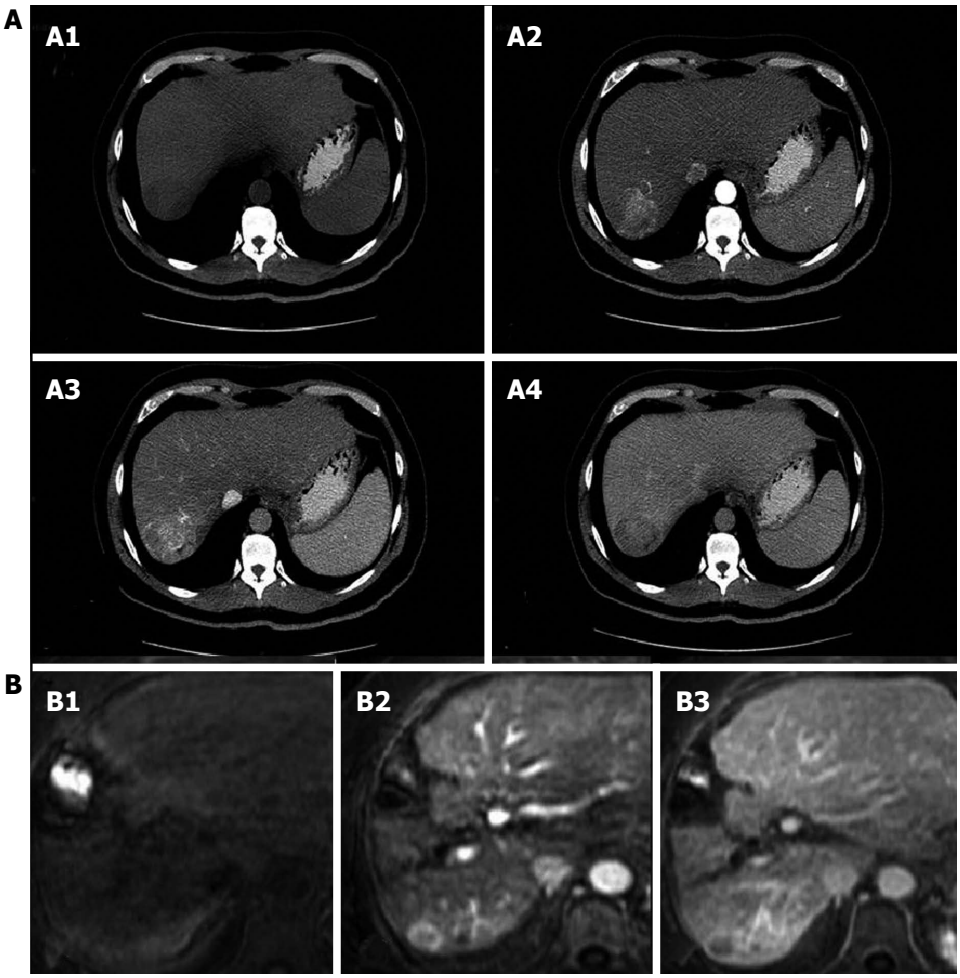

Figure 1 Contrast - enhanced computed tomography and Dynamic contrast-enhanced magnetic resonance imaging. A: Classical imaging pattern of hepatocellular carcinoma in contrast-enhanced computed tomography; A1: Simple phase, hypodense lesion in segment Ⅶ; A2: Arterial phase; A3: Enhanced portal; A4: 3 min late-phase washout; B: Diagnostic dynamic-contrast magnetic resonance imaging with classical pattern; B1: Simple phase; B2: Portal phase; B3: late-phase washout.

The clinical and economic impact of using guidelines in the diagnosis of HCC, such as those proposed by the AASLD and EASLD, has been recently prospectively evaluated. The sequential approach to hepatic lesions leads to a decreased need for liver biopsies when evaluating nodules between 1 and 2 cm, and also reduces costs when compared with lesions > 2 cm[50].

Non-invasive methods

There are some differences in terms of non-invasive diagnosis between Western and Eastern countries; these differences are reflected in different international guidelines pertaining to each geographical area: EASL[5], AASLD[6], Asian Pacific Association for the Study of the Liver (APASL)[51] and Japanese Society of Hepatology (JSH)[52].

Western guidelines (AASLD and EASL)

Imaging: Contrast - enhanced computed tomography and Dynamic contrast-enhanced magnetic resonance imaging: The diagnosis of HCC with non-invasive methods should be based on computed tomography (CT) and magnetic resonance imaging (MRI) results showing the characteristic pattern of early arterial enhancement followed by a contrast medium "washout" (Figure 1) phase in late venous phases; it is applicable to lesions > 1 cm[5,6].

Nodules between 1 and 2 cm have a malignancy rate of 14%-23%[53]. If this type of nodule has a characteristic contrast agent-mediated enhancement, the study's positive predictive value is close to 100% and its sensitivity is 71%, as long as it was performed in a center with sophisticated equipment[6]. If not characteristic, continued evaluation will require the use of two accepted imaging modalities: four-phase CT with contrast medium or dynamic contrast MRI. If these two methods do not reveal the characteristic HCC pattern, the lesion must be biopsied (Figure 2)[54].

Western liver societies do not consider contrast-enhanced ultrasound (CEUS) an appropriate study in the diagnostic approach to HCC due to the theoretical qualm in differentiating HCC from cholangiocarcinoma[55].

Eastern guidelines (APASL and JSH)

The guidelines proposed by the APASL and the JSH recommend following an algorithm that begins by

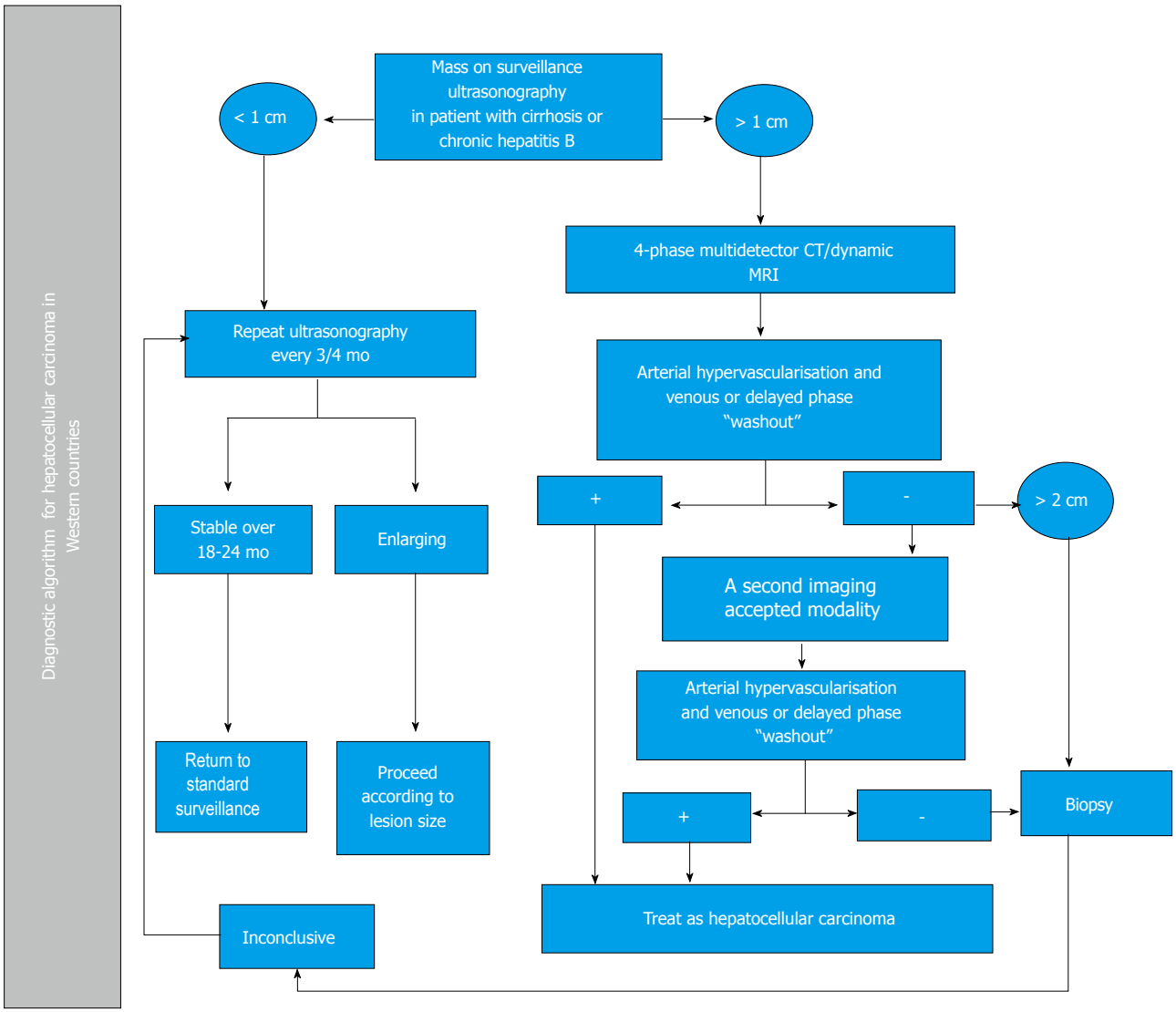

Figure 2 Diagnostic algorithm for hepatocellular carcinoma in Western countries. Modified from Bruix *et al*[6], with permission of the author and John Wiley and Sons. CT: Computed tomography; MRI: Magnetic resonance imaging.

evaluating the contrast medium pattern in the arterial phase of the imaging study and classifying it as hypervascular or hypovascular. Diagnostic tools include CT, dynamic contrast MRI and CEUS; hence, before the lesion can be classified as hypovascular, more than one study must be performed and should always include CEUS. Hypervascular lesions detected in the arterial phase as well as in the venous washout phase (classic pattern) or hypovascular lesions in the post-vascular phase of the CEUS with Sonazoid® as a contrast agent (in JHS guidelines), are diagnostic of HCC (Figure 3)[51,52]. None of the guidelines suggest that the use of positron-emission computed tomography (PET-CT) is pertinent in the diagnostic approach.

CEUS

This imaging method is accepted as part of the diagnostic approach of patients with HCC[56-58] in Eastern countries[51,52] but not in the West. Some of its advantages when compared with other imaging methods, include the fact that the microbubbles make it amenable to imaging patients in renal failure and also captures the arterial enhancement phase in real time. Moreover, the washout period has apparently been reported more consistently than with CT or MRI[57,58].

Histopathology

Liver biopsy should only be considered when evaluating nodules greater than 2 cm, if radiological findings are not compatible with HCC, or if findings in any nodule are inconclusive after a thorough work-up. But biopsies can yield false negative results even with immunohistochemical techniques[59]. Alpha fetoprotein is not a useful tissue marker due to its low sensitivity (25%-30%)[60]. Some strategies such as biopsying nodules showing arterial hypervascularity in at least one imaging study or the presence of typical synchronic lesions, have proven to increase sensitivity (62%) and specificity (79%) in the diagnosis of

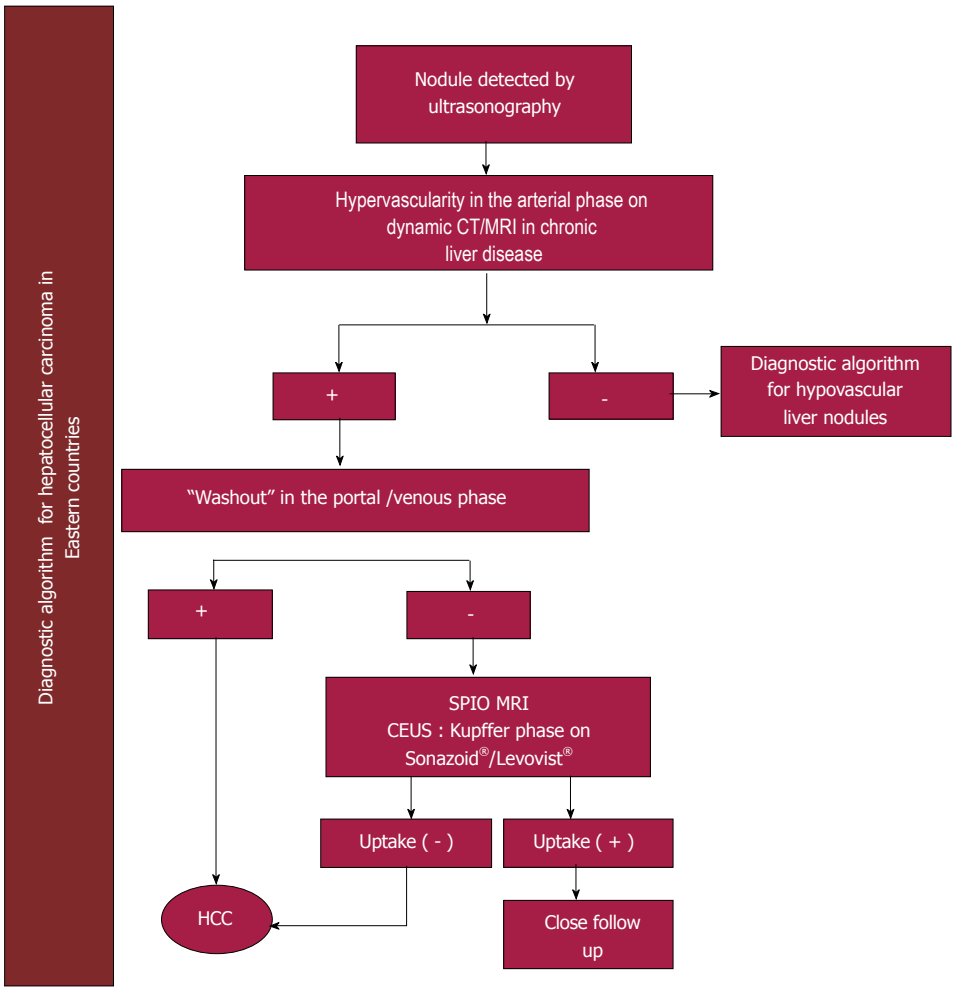

Figure 3 Diagnosis algorithm for hepatocellular carcinoma in Eastern countries. Modified from Omata *et al*[51], with permission of the author and Springer. HCC: Hepatocellular carcinoma; CT: Computed tomography; MRI: Magnetic resonance imaging; SPIO: Super paramagnetic iron oxide; CEUS: Contrast-Enhanced Ultrasonography.

malignancy in nodules between 1 and 2 cm and classified as indeterminate[53].

A histopathological diagnosis is established if the sample is positive for glypican 3, heat shock protein 70 (Hsp70) and glutamine synthetase. Positivity of at least two of these three markers has a diagnostic sensitivity of 72% and a specificity of 100%[60].

However, a negative biopsy does not preclude a HCC diagnosis since the rate of false negative results may reach 30%. This is due to sampling error or to the lack of specific histological findings[60].

Comparison of international guidelines

The main international societies studying the liver (AASLD, EASL, APASL and JSH) have similarities and differences in terms of HCC screening and diagnosis. The most relevant differences in the HCC diagnostic guidelines[5,6,51,52] in the West and the East hinge on the non-invasive diagnostic algorithm. All four guidelines accept the contrast medium enhanced classic pattern as definitively diagnostic of HCC. Western guidelines (AASLD and EASL) only consider acceptable the following imaging studies: four-phase computed tomography and dynamic-contrast magnetic resonance. Eastern groups propose algorithms that begin by evaluating the size of the lesion. The APASL and JSH recommend initiating the evaluation by analyzing the lesion's arterial vascularity (hyper or hypovascular). There are important differences between the Western and Eastern guidelines in terms of the non-invasive diagnosis of HCC.

STAGING

Determining the prognosis of patients with HCC is a crucial step in the management of these patients. An early diagnosis and effective treatment is associated with survival beyond 5 years[5,6].

Several classifications have been proposed in order to stratify patients according to their expected outcomes[4]. Obviously, although there are established guidelines and recommendations, therapy decisions should be individualized taking into account the available scientific evidence and the patient's personal profile.

Most cases of HCC develop in patients with cirrhosis

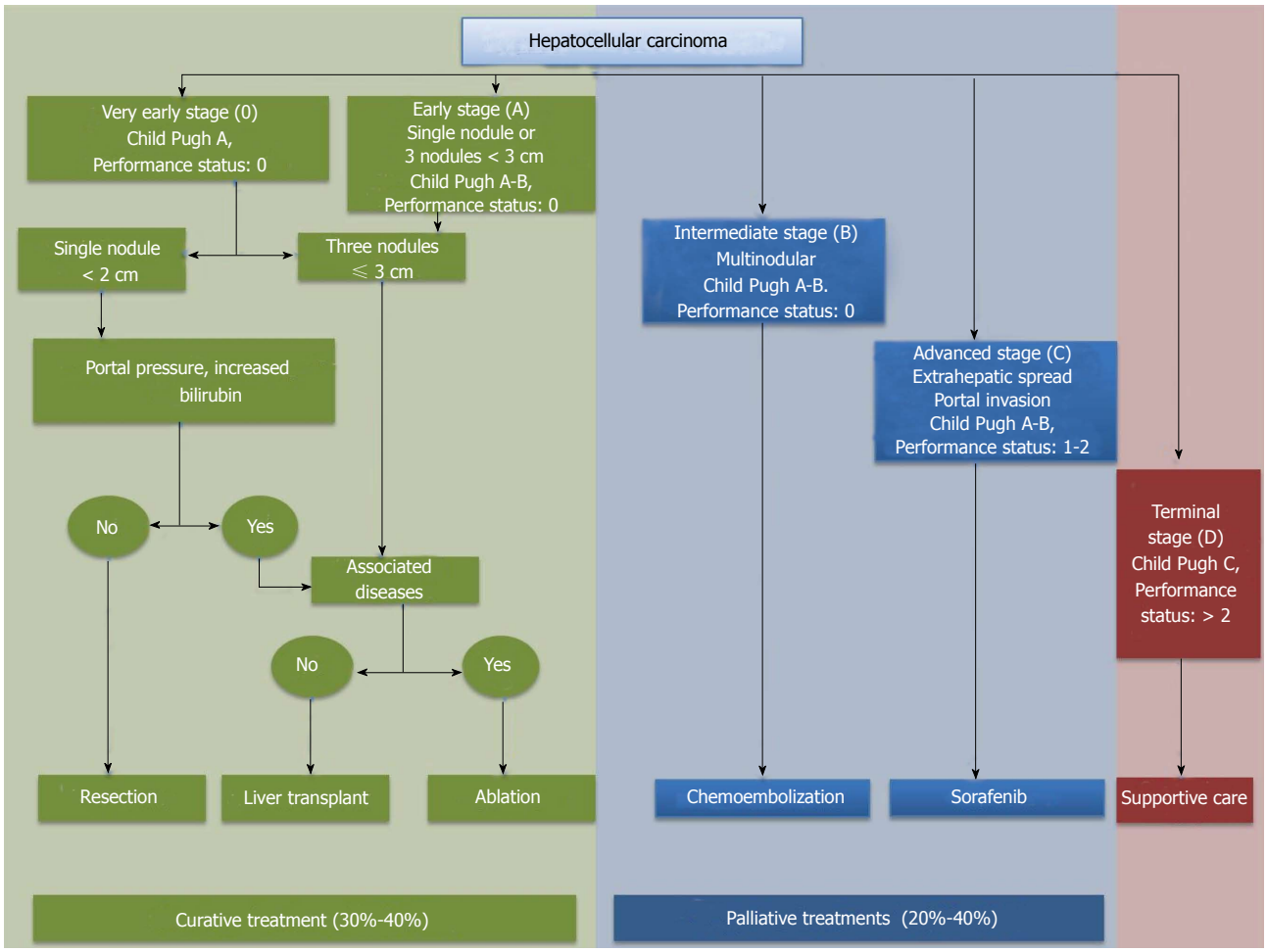

Figure 4 Barcelona Clinic Liver Cancer staging system and treatment strategy.

so for now, determining the patient's prognosis and therapy should consider the baseline degree of liver damage as well that due to HCC.

Several strategies have been proposed for prognostic staging and decision-making in patients with HCC: Child-Pugh[61], MELD[62], TNM classification[63], tumor volume estimation[64], evaluation of the patient's performance status (ECOG)[65], all characterized and limited by their one-dimensional assessment.

The most used classification is that developed by the Barcelona Clinic Liver Cancer group[66], a multidimensional strategy. This strategy has been validated in different scenarios and has established recommendations for each stage of the disease[67,68].

For now, the BCLC system is the recommended staging system by international guidelines (Figure 4)[5,6], since it stages the disease and proposes treatment according to the stage:

Very early stage (0)

Very early stage is patients with cirrhosis and compensated liver function (Child-Pugh A), with no signs of portal hypertension and with a single lesion ⩽ 2 cm (carcinoma "*in situ*"). The performance status according to ECOG must be 0. If treated by resection, these patients' 5-year survival is > 90%[69] and the tumor rarely recurs.

Early stage (BCLC A)

Early stage is patients with a single HCC lesion > 2 cm or three nodular lesions, each ⩽ 3 cm in diameter. Liver function should be evaluated according to the Child-Pugh classification and should be limited to groups A and B. The lack of significant portal hypertension and normal serum bilirubin levels are survival predictors in patients with a single lesion that undergo resection[70]. The determined size of the tumor is a criterion when considering liver transplantation as established in the Milan criteria[71]. If these criteria are not fulfilled other therapies are less effective[72]. The risk of vascular invasion is directly proportional to the size of the tumor. Five-year survival in these patients is over 50% after curative transplant[73,74].

Intermediate stage (BCLC B)

Intermediate stage includes patients with one, large HCC lesion as well as asymptomatic patients with multifocal disease and no vascular invasion or extrahepatic lesions. Their reported survival has been approximately 16 mo. Liver function must be

preserved (Child-Pugh A and B). These patients may undergo trans-catheter arterial chemoembolization (TACE) which is associated with an increased survival[75]. A recent meta-analysis of randomized clinical trials, suggests that ascites (a contraindication to TACE), is the most important adverse prognostic factor in this sub-group of patients[76].

Advanced stage (BCLC C)

This stage includes patients who do not fulfill BCLC B criteria. They are symptomatic (pain, general malaise or ECOG 1-2), they have vascular invasion or extrahepatic HCC involvement. Their survival has recently increased (10.7 mo) with sorafenib, a tyrosine kinase inhibitor[67,77].

Terminal stage (BCLC D)

This stage includes patients with severe hepatic dysfunction (Child-Pugh C) that are not liver transplant candidates and those patients with an ECOG score greater than 2. They have a dire prognosis and a survival under 6 mo while benefitting from conservative therapy (no intervention)[6].

Molecular classification

Evaluating a tumor's molecular classification provides a biological sub-classification that can optimize molecular therapies. These biomarkers allow improved staging. Increased alpha fetoprotein levels are associated to a poor or dire prognosis. Although an optimal cutoff point has not been established, it appears that high alpha fetoprotein levels predict an increased risk of HCC progression while the patient is on the liver transplant waiting list[78].

TREATMENT

HCC can be cured by surgical resection or liver transplant if it is diagnosed at an early stage; however, only 15% of cases are selected for management with these treatment modalities[79].

Liver resection

Deciding to perform a liver resection depends on three conditions: tumor size, tumor location and liver function. Resection is considered the treatment of choice in patients with solitary tumors limited to the liver, with no radiological evidence of vascular invasion and with normal liver function (normal total bilirubin, hepatic venous pressure gradient $\leqslant$ 10 mmHg, platelets > 100000 and no esophageal varices on endoscopy)[80]. The 5-year survival rate after tumor resection varies between 41% and 77%. Resection is also an option in multifocal HCC, fulfilling or not the Milan criteria or if the patient has mild portal hypertension and is not a liver transplant candidate[81,82]. Loco-regional therapy should be preferably considered in this group of patients, avoiding subsequent liver decompensation. The perioperative mortality after HCC resection in cirrhotic patients is approximately 2%-3%, greater than in patients with no cirrhosis. As a general rule, patients with some manifestation of decompensation (bleeding, ascites or portal hypertension), hepatic reserves are insufficient to consider surgical resection. Ideally, resection should only be considered in patients with tumors $\leqslant$ 5 cm in diameter[80,83], although there is consistently more evidence that size may not be a strict criterion in candidate selection; regardless, one must not ignore the fact that the greater the tumor mass, the greater the risk of vascular invasion or dissemination and the recurrence rate increases up to 70% at 5 years[79,84,85]. *De novo* tumor development may arise after primary resection, although most recurrences appear after 1 or 2 years as a result of dissemination of the primary tumor. The approach to post-resection has not been well studied yet, but repeating the resection is known to be of no value. Rescue liver transplantation or loco-regional therapies with or without multikinase inhibitors may be a viable alternative[86].

Liver transplant

In patients with unresectable tumors, the most feasible surgical option is orthotopic liver transplant (OLT) in conjunction with adjuvant therapies such as TACE or percutaneous ablation[80,86]. However, OLT is not an optimal choice in all patients and in spite of a necessary and prudent evaluation, patients should be well selected when dealing with a scarce resource such as organ donation[80]. In 1996, Mazzaferro *et al*[87] published a prospective cohort study including 48 patients transplanted because of HCC and in accordance with the Milan criteria (a single lesion $\leqslant$ 5 cm or 3 lesions $\leqslant$ 3 cm each); their survival rate at 4 years was 75%. Therefore, deceased donor liver transplant is a real option in these patients. Over time, experience with this treatment modality has increased and current 5-year survival is above 70% with a 15% recurrence rate, a similar survival to OLT without HCC[5,6,88].

There are several studies investigating the expansion of the Milan criteria, so as to not restrict the tumor size. The University of California proposed the San Francisco criteria that include patients with a single nodule $\leqslant$ 6.5 cm or 3 nodules $\leqslant$ 4.5 cm and with a total volume no greater than 8 cm; there are also other retrospective and prospective studies with very similar results to the Milan criteria[89]. In spite of these results, international guidelines insist on adhering to the Milan criteria while awaiting more solid data[5,6,51,52].

Interest in down-staging has recently increased targeting patients with HCC exceeding the OLT criteria and that are treated with loco-regional therapy (TACE and/or ARF) in order to decrease the tumor's size and then fulfill the OLT criteria[90,91]. Current data has led to conflicts, with some experts

recommending OLT only in patients that are down-staged effectively while others favor liver transplant as rescue therapy in spite of not having achieved the desired response[92,93]. Yao *et al*[91] published a study on a down-staging protocol using TACE and/or radiofrequency ablation, and reported a 1-year survival of 96.2% and 92.1% at 4 years, in patients who underwent OLT; they were also recurrence-free after an average follow-up of 25 mo.

The down-staging approach is controversial: some experts believe that large or multifocal tumors have the same recurrence risk in spite of successful down-staging[92]. One of the main poor response and recurrence biomarkers after transplantation is AFP. With a cut-off limit above 1000 ng/mL it could indicate microvascular invasion although further studies are required for confirmation[94].

Upon HCC diagnosis, this group of patients usually has stable liver disease, a disadvantage when awaiting an OLT. In this context, the United Network for Organ Sharing determined that patients fulfilling the Milan criteria should have a MELD score of 22 when added to the transplant waiting list, and the score should increase every 3 mo (the equivalent to a 10% increase in mortality); this is established after computed tomography or magnetic resonance confirmation of Milan criteria fulfillment[95]. This is turn, depends on the study region and on the number of patients on the waiting list, since some remain with stable liver disease and on the list for up to two years. Hence, the Living Donor Living Transplant program is a viable alternative; the risk of donor death and developing complications is 0.3% and 2% respectively. This option is limited to centers of excellence. Whether this group of patients has the same long-term survival as recipients of deceased donor livers remains to be established with certainty.

Loco-regional treatments

Loco-regional treatments in patients with HCC are chosen based on their oncological stage, performance status and underlying liver disease(s).

Early stage (BCLC A): Currently, the most commonly used ablation methods are percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA). PEI consists of the direct injection of ethanol into the HCC. This was the first treatment modality used before the development of RFA[96,97]. The curative capacity of PEI in tumors > 2 cm is limited and requires multiple injections over several sessions[98]. PEI can lead to complete tumor necrosis in 70% of nodules < 3 cm and in approximately 100% of nodules < 2 cm.

RFA is currently considered the safest ablation method and yields better results in BCLC A patients[97]. Complete response rates can reach 80% in patients with tumors < 3 cm, 50% in those with tumors between 3 and 5 cm and 25% in tumors > 5 cm. RFA is associated with a 5-year survival of 76%[98].

The available data is sufficient to conclude that RFA significantly improves survival and decreases local recurrence when compared to PEI. PEI use should be limited to circumstances when RFA is unavailable or technically not possible[99,100].

Intermediate stage (BCLC B)

Intra-arterial chemoembolization is the main treatment modality in unresectable HCC. This procedure requires the endovascular placement of a catheter until it reaches the hepatic artery and a microcatheter is guided to the segmental and sub-segmental branches. The chemotherapeutic agents most commonly used are cis-platinum and doxorubicin mixed as an emulsion with lipiodol, an oily radio-opaque contrast agent concentrated in the tumor and that promotes the exposure of neoplastic cells to the drugs. This emulsion is distributed in the affected segments or lobes and selectively infused in the tumor[99]. Survival rates are 82%, 47% and 26% at 1, 3 and 5 years, respectively. Therapy leads to tumor necrosis in 30%-50% of patients but rarely leads to a complete response especially after only one session[98]. Embolizing agents are administered after the chemotherapy emulsion following the same procedure. The most commonly used are: Gelfoam®, polyvinyl alcohol microparticles and trisacryl gelatin microspheres. Vascular obstruction thus decreases the chemotherapeutic agents' washout[98].

The soft embolization technique is very similar to TACE but without the administration of the chemotherapy emulsion with lipiodol. After diagnostic angiography, embolizing particles are injected directly into the tumor's afferent artery in order to produce tumor ischemia and necrosis. This technique is useful in patients with a significant tumor load and in whom future progression may lead to no viable treatment options. It has also been associated with less adverse effects[101].

Most advantages of soft embolization are shared with TACE and the debate continues on which technique offers the greatest benefits. Among the few controlled trials comparing TACE/soft embolization *vs* conservative treatment, survival was the greatest at 1 and 2 years with chemoembolization, 82% and 63% *vs* 75% and 50% with soft embolization and 63% and 27% with conservative management. Currently, the most commonly used standard technique is TACE. There is recent evidence that TACE in combination with sorafenib may decrease by 35% the risk of death in patients with intermediate and advanced HCC[102].

Terminal stage (BCLC D): This stage includes patients with Child-Pugh C and some with high score B liver disease associated to other comorbidities and terminal stage oncological symptoms. They must be very carefully evaluated and in most cases, loco-regional therapies are not an option since they can lead to the development of severe and even fatal

adverse effects[99].

Another application of intra-arterial embolization is in patients in an early HCC stage and in whom ablation therapy is precluded due to the tumor's location (close to the gallbladder, main bile ducts or main portal vein branches) or other contraindications.

Combined treatment

The combination of chemoembolization and radiofrequency ablation has proven to better control tumor growth in lesions between 3 and 5 cm.

The advantages of combined therapy include the fact that hypoxic aggression from embolization and the effects of the chemotherapy agents are synergistic in decreasing the tumor's blood flow and impedance. Moreover, a disruption of the intra-tumoral septa after chemoembolization, may foster the distribution of heat within the tumor and decrease perfusion-mediated tissue cooling, resulting in a greater ablated area. The suggested protocol is to first perform the selective chemoembolization followed by radiofrequency ablation within the subsequent 14 d[103].

An increase in survival has been demonstrated with combined treatment *vs* RFA with rates of 92%, 66% and 61% *vs* 85%, 59% and 45% at 1, 3 and 4 years, respectively. Recurrence-free survival rates have been reported as 79%, 60% and 54% *vs* 66%, 44% and 38% throughout the same follow-up periods[104].

Targeted system therapy

The molecular pathways involved in the pathogenesis of HCC are manifold but there are few therapeutic modalities specifically directed to these molecular targets that have yielded relevant results; the most studied and validated is the use of sorafenib. This molecule acts by inhibiting multiple kinases, including the Raf-1 and B-Raf serine-threonine kinases, VEGFR 1, 2 and 3 and PDGFR-β[105]. In the initial phase Ⅰ studies, sorafenib led to partial responses in various solid tumors and among them, one hepatocarcinoma case[106].

The SHARP study focused on the Western population. They assigned 602 patients with Child A cirrhosis and good performance status (ECOG 0 - 1 in over 90%), that had never received systemic therapy; they were randomized into a group treated with sorafenib 400 mg *bid* and a placebo group. Their main outcome was overall survival (OS) and symptomatic progression-free survival. Overall survival was significantly greater in the sorafenib arm, with a survival rate of 10.7 mo *vs* 7.9 mo (HR = 0.69, 95%CI: 0.55-0.87; $P < 0.001$) and there was no difference in terms of symptomatic progression (4.9 mo *vs* 4.1 mo; $P = 0.77$) although radiological progression did decrease when evaluated by RECIST (5.5 mo *vs* 2.8 mo, HR = 0.58, 95%CI: 0.45-0.74, $P < 0.001$). No patient had a complete response, only 2% of the patients had partial response in the sorafenib group and 1%in the placebo group. Up to 80% developed an adverse event, almost all grade 1 or 2. Grade 3 events not found in the placebo group included diarrhea and hand-foot syndrome, each in 8% of cases; there were no grade 4 events[67]. In an Asian phase Ⅲ study of 226 patients fulfilling similar selection criteria, results were very similar. The increase in OS was a little less marked, 6.5 mo *vs* 4.2 mo (HR = 0.68, 95%CI: 0.50-0.93; $P = 0.014$) and in terms of disease progression, 4.2 *vs* 2.8 mo (HR = 0.57, 95%CI: 0.42-0.79; $P = 0.0005$). Although survival in this study was not as good as in SHARP, this difference was attributed to the fact that they included patients with worse performance status and more advanced disease; HR were very similar[107]. A SHARP sub-analysis revealed that patients with HCV benefitted more from sorafenib (14 mo *vs* 7.4 mo, difference of 6.6 mo) when compared with patients with HBV (10.3 mo *vs* 8 mo, difference of 2.3 mo); one must emphasize that almost 75% of patients in the Asian study were infected with HBV while only 20% were so in the Western study, another possible explanation for the observed difference between studies.

In the United States, the Food and Drug Administration approved sorafenib without specifying the severity of liver disease, but in patients with Child B cirrhosis its benefits are much less evident. A retrospective analysis of 59 patients (26 Child A, 23 Child B, 10 Child C) revealed an OS of 8.3, 4.3 and 1.5 mo, respectively; grade 3-4 adverse events were present in 15% of Child A patients *vs* 30% in Child B[108].

In the GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafenib), there were also more reported G3-4 adverse events in Child B patients (67% *vs* 42%) and a greater possibility of abandoning treatment due to these adverse effects (40% *vs* 25%)[109].

Other strategies such as combining sorafenib with chemotherapy have been attempted. In a phase Ⅱ study of 96 Child A patients, two groups were defined: sorafenib 400 mg bid and doxorubicin 60 mg/m^2 *vs* doxorubicin and placebo, OS was 13.7 mo *vs* 6.5 mo ($P = 0.006$) and progression-free survival was 6.0 mo *vs* 2.7 mo[110]. A phase Ⅱ study is currently being conducted (CALGB 80802). Other studies of targeted therapy plus chemotherapy have yielded controversial results.

Other treatments such as sunitinib have been attempted but a phase Ⅲ study revealed worse survival (7.9 mo *vs* 10.2 mo when compared with sorafenib) and more frequent and severe toxicity[111]. Other molecules such as cetuximab, erlotinib and everolimus have also not proven to be superior to sorafenib or have not been studied comparatively.

Sorafenib is currently considered first-line systemic therapy due its effectiveness and toxicity profile. Some clinical markers (rash, hypertension) as well as molecular markers (VEGF genotypes, VEGF

polymorphisms, Mcl-1 expression, pERK) may reflect its efficacy, but none have been validated[109].

PROGNOSIS

In spite of advances in treatment, mortality in HCC remains high. In untreated patients, 1-year survival is 17.5% and 7.3% at 2 years[76]. Due to patient heterogeneity, their clinical status, the available therapeutic options and particularly the presence or lack of liver disease, prognosis is difficult to establish unlike in other neoplasias in which prognostic factors are solely determined by the tumor.

There are currently numerous staging systems[4] and although there is no consensus, the AASLD and EASL guidelines recommend the use of the BCLC system; according to this classification, 5-year survival of stage A patients is 50%-70% after curative treatment, 16-20 mo in stage B, 6-10 mo in stage C and 3-4 mo in stage D[66,73,74,76]. However, several factors of great impact on mortality are not considered in this classification.

HCV and HBV infection also compromise survival in non-cirrhotic patients undergoing curative surgery by conferring an increased and earlier risk of recurrence. Persistent HBV viremia also fosters an increased recurrence risk[4,35,112-115].

In patients without liver disease, HCC tends to be diagnosed at a more advanced age than in patients with cirrhosis and it is usually detected in latter stages (BCLC D in 51.6% *vs* 42% in patients with cirrhosis) due to the lack of screening; however, mortality in patients in intermediate stages is lower than that in patients with cirrhosis. In this group of patients, the BCLC classification correlates best with survival than other staging systems and their survival rates are better due to the possibility of providing curative treatment of larger lesions in turn, leading to decreased recurrences (27% *vs* 73%) and greater survival (81% *vs* 23%)[116,117].

Upon recent inclusion of molecular markers such as wtER, IGF and VEGF-1 in prognostic scoring systems such as CLIP, their precision has been favorable although they are not currently routinely used[118-120].

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