ISSN 2377-1518

CANCER STUDIES AND MOLECULAR MEDICINE

OpenJournal

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Systematic Review

National Consensus for Screening, Diagnosis and Management of Hepatocellular Carcinoma in Panama, 2022

Moises Cukier, MD[1*]; José M. Cabada-Lee, MD[2]; Jorge D. Méndez-Ríos, MD, PhD[3,4]; Rafaél Arauz, MD[5]; Erik Arauz, MD[6]; Norberto Carreño, MD[7]; Ivette Clavel, MD[8]; Jan A. Cubilla-Rodríguez, MD[7]; Dafnia De Gracia, MD[9]; Iván Díaz, MD[10]; Olivia El Achtar, MD[10]; Kenia Franco, MD[11]; Julissa Lobardo-Quezada, MD[12];Yong Loo, MD[13,6]; Melisa I. Menéndez, MD[2]; Gaspar Pérez-Jiménez, MD[5]; José Pinto-Llerena, MD[13]; Lizka Richards-Cantoral, MD[2]; Mauricio Rodríguez-Bravo, MD[2]; Maylin Ruiz, MD[14]; Karen E. Suñé, MD[11]; Ignacio Veliz, MD[13]; Ruth Vergara-Vásquez, MD[15]

[1]*Department of Surgery, Pacifica Salud Hospital, Panama, Republic of Panama*
[2]*Department of Surgery, Caja del Seguro Social, Panama, Republic of Panama*
[3]*Department of Genetics, Caja de Seguro Social, Panama, Republic of Panama*
[4]*Universidad Interamericana de Panama, School of Medicine, Panama, Republic of Panama*
[5]*Department of Radiation Oncology, Instituto Oncologico Nacional, Panama, Republic of Panama*
[6]*Division of Oncology, Pacifica Salud Hospital, Panama, Republic of Panama*
[7]*Gastroenterology Section, Hospital Santo Tomás, Panama, Republic of Panama*
[8]*Department of Radiology, Instituto Oncologico Nacional, Panama, Republic of Panama*
[9]*Palliative Care Unit, Pacifica Salud Hospital, Panama, Republic of Panama*
[10]*Department of Surgical Oncology, Instituto Oncologico Nacional, Panama, Republic of Panama*
[11]*Palliative Care Unit, Instituto Oncologico Nacional, Panama, Republic of Panama*
[12]*Hepatology Unit, Gastrointestinal and Liver Institute, Panama, Republic of Panama*
[13]*Department of Medical Oncology, Instituto Oncologico Nacional, Panama, Republic of Panama*
[14]*Department of Radiology, Pacifica Salud Hospital, Panama, Republic of Panama*
[15]*Department of Anatomical Pathology, Instituto Oncologico Nacional, Panama, Republic of Panama*

[*]***Corresponding author***
Moises Cukier, MD
Chief, Division of General Surgery, Pacifica Salud Hospital, Pacific Boulevard, Panama City, Panama, Republic of Panama; E-mail: moisescukier@gmail.com

Article information

Received: October 31st, 2022; **Revised:** November 15th, 2022; **Accepted:** November 16th, 2022; **Published:** November 24th, 2022

Cite this article

Cukier M, Cabada-Lee JM, Méndez-Ríos JD, et al. National consensus for screening, diagnosis and management of hepatocellular carcinoma in Panama, 2022. *Cancer Stud Mol Med Open J*. 2022; 7(1): 3-14. doi: 10.17140/CSMMOJ-7-133

ABSTRACT

Introduction

Hepatocellular carcinoma (HCC) is considered the main primary neoplasm of the liver and its incidence is expected to increase in the next years. HCC is frequently associated with chronic liver disease secondary to hepatitis B or C infections, as well to alcohol abuse, fatty liver and metabolic syndrome. Multidisciplinary and individualized management has been shown to improve clinical outcome; nevertheless, in Panama and others Latin-American countries, there is no clear consensus for the management of this disease.

Methodology

Using Appraisal of Guidelines for REsearch and Evaluation II (AGREE II) methodology and the Institute of Medicine (IOM) criteria, we developed a multidisciplinary consensus for the management of hepatocarcinoma patients in Panama.

Results

This document synthesizes the current evidence on risk factors in conjunction with recommendations on the management of early, advanced and terminal disease. All healthcare personnel involved in the approach and treatment of hepatocarcinoma in Panama can find utility and applicability in their daily practice.

Conclusion

Here, we present the first National Consensus for the Screening, Diagnosis and Treatment of Hepatocellular Carcinoma in Panama.

Keywords

Hepatocellular carcinoma; Guidelines; Consensus; Panama.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver neoplasm, the sixth most common solid neoplasm and the third leading cause of cancer-related death worldwide.[1]

Its worldwide distribution is very heterogeneous and is closely related to the prevalence of risk factors associated with the development of the disease; it has a highly variable incidence, the highest in Southeast Asia and sub-Saharan Africa exceeding 15 cases per 100,000 inhabitants each year, while in North America 6.6 cases per 100,000 inhabitants each year, most of which are related to hepatitis B virus (HBV), hepatitis C (HCV) and alcohol abuse.[2]

In recent decades, there have been significant changes in the exposure to the risk factors associated to HCC. The introduction of universal vaccination against HBV and the implementation of modern antiviral agents for HCV have reduce the incidence of viral-related HCC. Additionally, the increase in prevalence of non-alcoholic fatty liver disease, obesity and metabolic syndrome in Western countries are becoming more prevalent in HCC patients.[3]

Chronic liver inflammation secondary to viral hepatitis is responsible for the chronic inflammatory process that involves necrosis and regeneration of the tissue, leading to cirrhosis. Once the molecular and structural damage are established, the risk of developing HCC does not disappear despite eradication and control of the virus.[4-6] This is also true for any disease that could lead to liver cirrhosis (hereditary hemochromatosis, primary biliary cirrhosis, autoimmune hepatitis), which are considered a risk factor for the development of HCC.[7,8]

The microenvironment of HCC is complex and includes non-tumoral and immune-related cells. It is known that these cellular components may vary in different stages. For example, it has been shown that 30% of tumors demonstrate immune activation in early stages, while 25% does not show any immune infiltrate. This variability affects our capacity to identify new biomarkers and new therapies against HCC.[9]

Due to the worldwide changes in risk factors prevalence and for the heterogeneity of international guidelines regarding diagnostic and treatment of HCC, we consider it is paramount to establish a multidisciplinary management consensus for our country taking into consideration our resources and the realities of our healthcare system.

METHODOLOGY

A multidisciplinary group of 27 national experts was formed within the framework of The Panama Cancer-2022 Meeting. The activity was open for the whole community to participate. Four (4) workgroups were established to address each stage of HCC management:

1. Diagnosis and Screening.
2. Management of Early Disease.
3. Management of Advanced Disease.
4. Management of Terminal Disease and Palliative Care.

The medical specialties of the experts included: Oncologic Surgery, Hepatobiliary Surgery and Liver Transplantation, Interventional Radiology, Medical Oncology, Gastroenterology, Palliative Care, Pathology and Radiation Oncology. The coordinating group consisted of a general coordinator and 3 table coordinators. Each working table was composed of 5 to 7 experts. Subsequent communications and consensus-reaching occurred from November 2021 to March 2022. The Appraisal of Guidelines for REsearch and Evaluation-II (AGREE II) methodology and the Institute of Medicine (IOM) criteria (IOM-Committee on Standards for Developing Trustworthy Clinical Practice Guidelines) were used.[10]

Questions to addressed required an approval of at least 75% of participants on the working groups. Before the final approval of all statements and of the consensus, a period for requesting modifications of the document allowed. It was finally followed by a period that allowed participants to request modifications of the document.

RESULTS

Diagnosis and Screening

The most important risk factor for HCC is liver cirrhosis regardless of its underlying cause. Ninety percent of HCC cases occur in the setting of chronic liver disease. The annual incidence of HCC in the cirrhotic patient associated with a viral infection range from 1 to 6%. Its incidence peaks at 70-years of age and it is presented more commonly in males on a 2-3:1 ratio.[11]

It is known that chronic hepatitis B and C virus infection together comprise 30-40% of HCC cases in the U.S. In Asia and Africa, where HBV is endemic, aflatoxin exposure is also an important risk factor.[12]

With the increasing obesity pandemic, nonalcoholic fatty liver disease and nonalcoholic steatohepatitis associated with metabolic syndrome or diabetes mellitus, have become important factors in the context of chronic liver damage. It has been estimated that 25% of the global population suffers from at least one of these chronic conditions.[13]

Alcohol-related cirrhosis is associated with an HCC incidence that ranged from 1 to 3% of cases, and it could increase from 15 to 30% in some geographical areas. Moreover, it has been well-documented the synergistic effect of alcohol-related cirrhosis with the presence of viral liver infections.[14] There have been also rare conditions associated with the development of HCC such as: Wilson's disease, porphyria cutanea tarda, alpha 1-antitrypsin deficiency, primary biliary cholangitis and hereditary hemochromatosis.[15]

The risk of progression from cirrhosis to HCC is variable and additional factors such as age, ability to adhere to screen-

ing, degree of hepatic fibrosis, and functional status of the patient should be considered when entering a screening program. There are multiple risk scales that have not been universally implemented due to geographical and etiological differences.[16]

In Panama, we screen for HCC in patients with liver cirrhosis of any etiology, patients infected with chronic hepatitis B (without liver cirrhosis), chronic hepatitis C, and also in patients with advanced fibrosis (without liver cirrhosis).

A good prognosis is related to the possibility of curative treatment at an early stage, and a favorable 5-year survival. This is why surveillance for high-risk patients is recommended for the reduction of HCC-related mortality rate.[17]

The ideal surveillance method is still in debate[17]; There are several methods available, but the ideal one must prove to be reliable, that generates reproducible results, operator-independent, and with a highly sensitivity and specificity. It should also be easy to implement in a clinical setting. Some research groups have proposed that an abdominal ultrasound surveillance with or without serum alpha-fetoprotein measurement might fulfill these requirements.[18]

The abdominal ultrasound is the most widely used surveillance method. The benefit of its use has been shown to impact overall survival. Some important limitations to this method exist such as: it is operator-dependent, identification of lesions is technical challenging, and it might be less sensitive in particular scenarios (non-alcoholic steatohepatitis, obesity, and on chronic alcohol-related liver damage).[19]

Cohort studies have demonstrated that the use of abdominal ultrasound at a 3-month interval does not increase survival time, but increase the number of additional diagnostic procedures. Nevertheless, screening for HCC has been shown to be a cost-effective in patients with all-cause cirrhosis, and in patients with chronic hepatitis B without cirrhosis.[20]

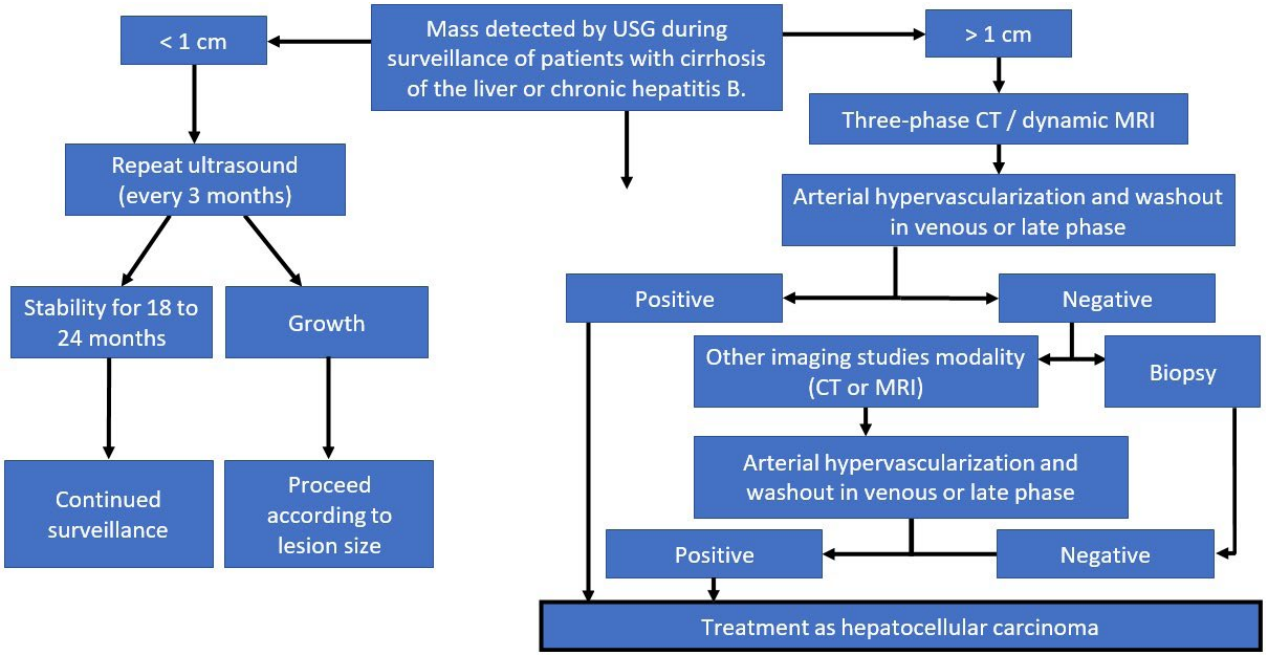
Dynamic liver tomography or magnetic resonance imaging (MRI) have been shown to provide greater sensitivity, but with a substantial increase in cost. They are currently considered alternative tools to ultrasound in the event of failure to visualize or detect nodules, which may occur in 20% of cases. Neither should be recommended since there is substantial evidence that the use of alpha fetal protein significantly impacts survival.[21]

Diagnosis: Imaging and biopsy: The benefits of semiannual ultrasound surveillances lie in the early identification of HCC and the use of effective therapist that increases life expectancy.[22]

The diagnosis of HCC may be done by imaging criteria. The American Association for the Study of Liver Disease (AASLD) has proposed the liver imaging reporting and data system (LI-RADS) classification system, which is divided into 7 categories to facilitate the characterization of indeterminate lesions and detection of HCC. This categorization serves as the basis for the detection of benign and malignant lesions, and for the standardization of diagnostic imaging using multiple accepted international recommendations.[23]

The diagnostic sensitivity by imaging is limited by the 10-millimeter cutoff for the tumor size on a liver ultrasound on high-risk HCC patients.

Figure 1. *Diagnostic Algorithm for HCC at Barcelona Liver Cancer Clinic*



Summarizes de Barcelona Liver Cancer Clinic Guideline algorithm for diagnostics. The algorithm suggests initial assessment using ultrasound and determination of the size of the lesion. It continues with the possibility of follow ups and re-evaluation using other image techniques such as CT scan, MRI and/or biopsy. Abbreviations: USG: ultrasonogram; cm: centimeters; CT computerized tomography; MRI: magnetic resonance imaging.

The pathophysiology of HCC progress in a multi-step fashion. The progression to neovascularization of the lesion up to a size of 10 to 20 millimeters facilitate visualization for its high vascularization. This allows the lesion to be contrasted against the liver parenchyma in triphasic studies. This is followed by a progressive decrease in portal irrigation that leads to a decrease irrigation of the lesion compared and can be contrasted to that of the hepatic parenchyma at the venous phase (Figure 1).

Careful evaluation of the patient provides the possibility of assessing the high pre-test probability of HCC in cirrhotic patients or those with a hepatitis B infection. This leads to a more precise diagnosis through arterial enhancement phase and "wash-out" phenomenon in the venous or late phase.[24]

There is a group of patients whose risk of HCC is lower. This occurs when the images are dubious, with no categorical or typical of HCC imagine. In these cases, directed biopsy and histopathological studies are necessary. The criteria for no concordant imaging pattern and/or suggestive of a non-HCC tumor should be based on biopsy.[25]

Non-invasive procedures for HCC based on the risk of typical vascular profile has demonstrated a sensitivity of 60% and specificity between 96 to 100% in lesions between 10 to 20 millimeters, but biopsy may be required in up to 40% of cases.[26]

Despite the frequent diagnosis using imaging criteria based on international guidelines, mandatory biopsy for all HCC cases continues to be controversial.

For this, we have reached a consensus for biopsy in HCC cases:

1. For lesions equal to or larger than 2 cm in liver with cirrhosis with atypical behavior in three-phase or dynamic studies.
2. For lesions equal to or larger than 2 cm in liver without cirrhosis.
3. For research purposes and/or to include samples in the tumor bank.
4. On patient with a known malignancy in another site, which allows ruling out metastatic disease.

It is important to note that early HCC tumors may differ from tumors detectable by imaging due to the absence of vascularity and immature angiogenesis. These changes and the content of fatty tissue may also affect histopathology diagnosis and its differentiation to dysplastic nodules during biopsy.

The cornerstone of early management at management centers includes the need for a multidisciplinary assessment for the determination of the etiology, ruling out chronic infection, assessment of comorbidities, imaging studies with determination of tumor burden and liver function, as well as staging by a team of experts for the determination of the best treatment options. The role of a Institutional Committee is paramount for confirming the diagnosis, staging and determining the treatment scheme to be used. The treatment plan may include the possibility of liver transplantation, assessment of the timing of therapy and even the modality of bridging therapy. Management Centers at the tertiary level of care allow for individual assessment and application of the best clinical practice protocol in HCC (Table 1).

Management of Early Disease

When a liver lesion is indeterminate and smaller than 1 cm, the possibility of HCC is quite low, but follow-up with hepatic ultrasonography (USG) is recommended for 3 to 6-months.[27]

The early approach with a correct staging strategy will allow a more accurate prognosis to be established prior to medical-surgical intervention. It will also facilitate the established of the right treatment algorithms. If available, the patient may be included in a clinical trial that recruits candidates that meet the standardized staging system.[28]

Table 1. *Recommendations on Diagnosis and Screening for HCC Patients*

	Surveillance and Screening
1.1	**Which patients are considered high risk for HCC?**
	Patients considered as high risk for hepatocarcinoma (HCC) are those with liver cirrhosis of any etiology, patients with chronic hepatitis B (without liver cirrhosis) and patients with chronic hepatitis C and advanced fibrosis (without liver cirrhosis).
1.2	**What is the recommended surveillance/screening method?**
	The recommended method of surveillance and screening is hepatic ultrasound.
1.3	**How often should surveillance be performed?**
	Hepatic ultrasound surveillance is recommended every 6-months in cirrhotic patients (estimated time of doubling in HCC size).
1.4	**What is the recommended diagnostic approach for solid liver lesions suggestive of HCC?**
	We recommend the diagnostic approach established by the Radiology Department of the Hospital Clinic de Barcelona.[24]
1.5	**When is a histopathological confirmation of liver lesions of HCC recommended?**
	Histological confirmation is recommended in the following conditions: • Lesions equal to or greater than 2 cm in liver with cirrhosis with atypical behavior in three-phase or dynamic studies. • Lesions equal to or larger than 2 cm in liver without cirrhosis. • Research objectives and/or tumor bank. • Patient with known diagnosis of malignancy in another site, benefit to rule out metastatic disease.
1.6	**If a diagnosis of a lesion suggestive or confirmed to be HCC is made, where should the patient be referred?**
	In Panama, all patients with suspected HCC should be referred to a specialized third level medical care center for diagnosis and management.

It is important to direct the staging approach depending on concomitant liver disease, and we recommend referral in the first instance to the liver clinic for registration, assessment and management of the underlying disease. It is a priority to establish with certainty whether we are treating a patient with cirrhotic or non-cirrhotic liver. If it is determined that the patient has a non-cirrhotic liver, it is required biopsy. Nevertheless, if the patient has a cirrhotic live, biopsy is recommended if diagnosis by imaging does not comply with the previously mention criteria.[29]

The Barcelona Liver Cancer Clinic Guidelines for staging and management in HCC establish a stratification into 4 categories based on laboratory and imaging studies:

- Potentially resectable or transplantable based on overall status and comorbidities.
- Unresectable disease.
- Confined but inoperable liver disease and/or cases of minimal or borderline extrahepatic disease.
- Metastatic disease.

Staging systems: The Barcelona Liver Cancer Clinic staging algorithm was introduced in 1999 and is the most widely used staging system in the world. It has enabled clinical trials to be developed and successfully integrated into clinical practice guidelines, staging patients into 5 groups and distributing potential treatment options by stage (Figure 2).[30]

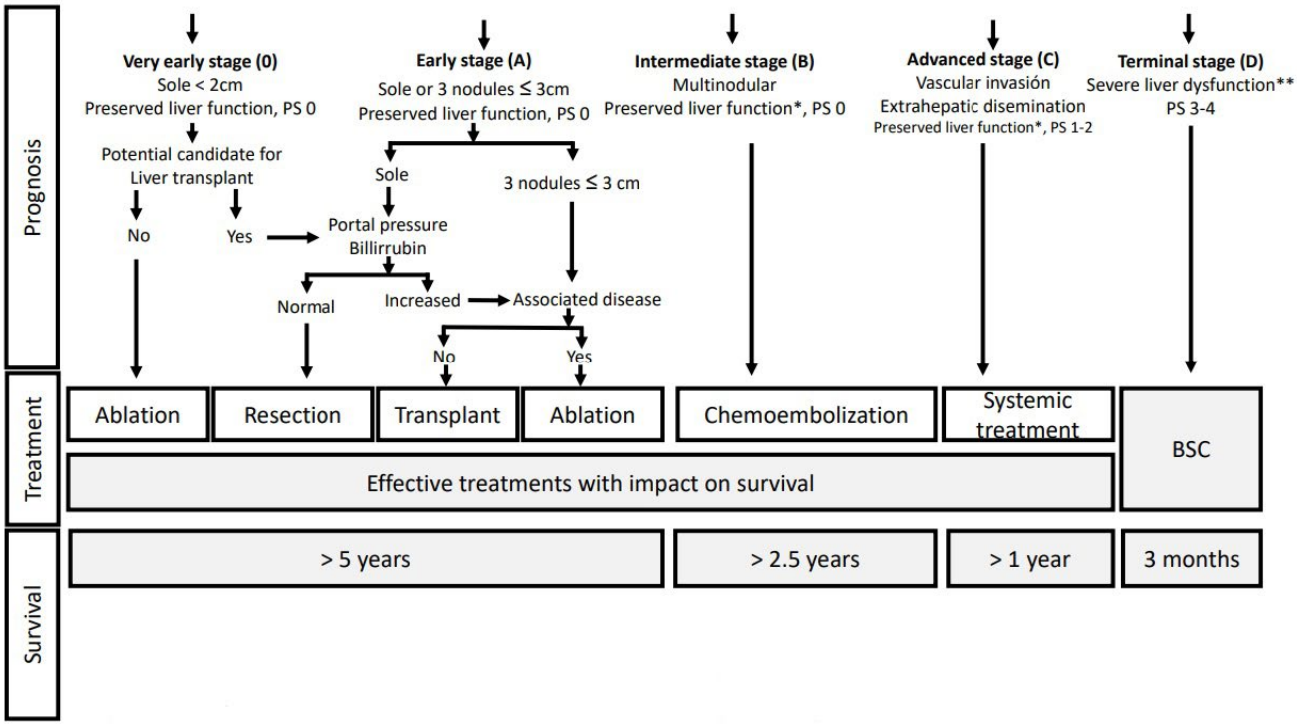
There is no ideal staging system in HCC due to limitations in staging methodology, as well for subjective liver function assessment systems when attempting to calculate actual liver functional reserve. It is important to differentiate limited liver disease from advanced or decompensated cases; this variability may represent a difference in long-term survival in an individual comparatively between stages.[31]

The main variables for the classification of HCC are associated with factors that directly affect prognosis such as: the clinical stage, treatment used, liver function, tumor growth rate, vascular invasion, extrahepatic burden, and overall patient status.[32]

Based on this, we consider that the classification system of the Barcelona Liver Cancer Clinic fits best the epidemiological and etiological characteristics of the disease in our country. It is also the classification our healthcare personal has the most experience with, providing satisfactory results upon the implementation of its therapeutical recommendations.

Treatment: At this stage, the objective for HCC treatment is curative, and it is essential to use an individualized plan through a multidisciplinary expert session. In early cases, without liver cirrhosis, resection is considered the first treatment option, since it has immediate applicability and does not contraindicate the possibility of future transplantation. In patients with hepatocarcinoma and cirrhosis, there are three types of management with curative intent that are capable of changing the natural history of the disease and prolong survival.[33]

Figure 2. *HCC Staging System Based on the Barcelona Liver Cancer Clinic*



Above Figure presents the process of staging HCC based on the Barcelona Liver Cancer Clinic Guidelines. Each stage suggests a series of evaluation to determine the best treatment plan, and present and approximation to the media survival.
**Note that the Child-Pugh classification is not sensitive in accurately identifying those patients with advanced liver failure who would merit consideration for liver transplantation.*
***Patients with end-stage cirrhosis due to severe liver dysfunction (Child-Pugh C or earlier stages with predictor events of poor prognosis, elevated MELD score) should be considered for liver transplantation. In these patients, the presence of HCC may be a contraindication for liver transplantation if it exceeds the inclusion criteria.*

Resection and image-guided ablative therapies are one of the valid treatment options in CHILD A/B patients with similar oncologic outcomes. Resection is recommended when dealing with patients with disease confined to the liver and for those tumors that can be resected in its entirety. This is important since it is known that post-resection mortality is intimately related to subsequent liver failure and non-hepatic related complications of surgery. Ablation, in the other hand, is recommended in cases of single tumors of less than 2 cm and in patients who cannot undergo surgery.[34]

Despite a complete resection of the tumor, the recurrence rate in HCC is 70% at 5-years, and transplantation is indeed the definitive treatment in early HCC disease. Complete resection eliminates the tumor and the underlying liver damage, reaching survival rates that exceed 70% in most series.[34]

The recommendation of liver transplant in patients with HCC and cirrhotic liver who meet defined criteria (Milan or San Francisco criteria) for selection requires a multidisciplinary evaluation according to the protocol of the National Liver Transplant Program. In some cases, highly selective embolization or locoregional ablation therapies may be considered with the objective of preserving non-tumor parenchyma, maximize treatment, and reduce likelihood of complications.

Management of intermediate disease: We define intermediate disease as Stage B according to the Barcelona Liver Cancer Clinic classification, in patients with multinodular disease and a good liver function.

The strategy of ablative treatment should be considered in patients who are not candidates for curative surgical treatment or as a bridging strategy for other curative options. Up to 75% of patients, even at Barcelona A stage, will not be candidates for surgical resection or transplantation due to underlying liver disease or comorbidities. Modalities include ablative treatments, targeted arterial therapies and radiotherapy aimed at local tissue destruction.[35]

With respect to ablative therapies, surrounding viable healthy tissue is important and the tumor must be accessible to a percutaneous, laparoscopic or open approach. This therapy can be curative in lesions less than or equal to 3 cm. Unresectable or inoperable lesions larger than 5 cm should be considered for targeted arterial treatment, systemic treatment or palliative radiotherapy.

Regardless of their location, tumors may be candidates for targeted arterial treatment with satisfactory control of non-target tissue involvement. In Panama, we have several options for ablative and arterial management: transarterial embolization (TAE), conventional transarterial chemoembolization (TACE), chemoembolization with doxorubicin-coated microspheres (DEB-TACE) and transarterial radioembolization (TARE).

Transarterial chemoembolization is the placement of chemotherapy and embolic material in the hepatic branches that irrigate the tumor and is considered a non-curative first-line treatment. This treatment modality has demonstrated response rates of 50% and disease control rates of 75%, impacting overall survival when compared to best medical support.[35]

In transarterial radioembolization, Ytrium-90 microspheres are injected into the branches of the hepatic artery supplying the tumor. At present, the evidence has failed to demonstrate superiority over the use of Sorafenib. The role in the HCC management algorithm in this context becomes uncertain, allowing its use to be considered in individual cases of intermediate stage HCC.[36]

Follow-up: Follow-up in HCC is fundamental, and in Panama it is done at specialized units such as at liver units, Liver Clinics or at Institutional Interdisciplinary Groups, thus avoiding management by a single specialist. The 5-year recurrence rates are 70% and 50% for patient with and without cirrhosis, respectively (Table 2).

Management of Advanced Disease

Requirements on follow-up and treatment may vary for each case. Each advanced stage case should be discussed in a multidisciplinary team which beholds the ultimate responsibility on decision-making. The multidisciplinary approach has shown to decrease the time for diagnosis and treatment and increases adherence to management guidelines.[36]

The patient with advanced-stage HCC requires a comprehensive management focus on goals such as increasing life expectancy and maintaining a balance between adverse effects and symptomatology. Symptomatic management and systemic treatment are important parts of supportive care, assuring the highest possible quality of life, and allowing referral to palliative care.[37]

Radiotherapy in HCC: The benefit of radiotherapy targeting the primary site in patients with hepatocellular carcinoma is controversial. The major limitation is given by the poor radiation tolerance of the organs at risk. New techniques of image-guided radiotherapy exist such as intensity-modulated radiotherapy, respiratory control and extracranial stereotactic radiotherapy. These techniques allow us to perform more precise treatments with less toxicity, but they have not shown an overall survival for patients. Nevertheless, similarly to treatment in other pathologies such as metastatic disease with brain or bone lesions, palliative radiotherapy is recommended for symptom reduction.[38]

Most bone metastases affect the axial skeleton (skull, spine, sacrum, pelvis). It is advisable that patients with unstable metastases be evaluated in conjunction with a neurosurgeon for preventive reasons or for the evaluation of defined fracture. Palliative radiotherapy schedules include 37.5 Gy in 15 sessions, 30 Gy in 10 sessions, 20 Gy in 5 sessions or a single dose of 8 Gy. The effectiveness for pain control among the treatment schemes has been shown to be equivalent. Patient expectation should be taken into account, but shorter treatment schemes should be reserved for patients with poor short-term prognosis.[39]

Table 2. *Recommendations on Diagnosis and Screening for HCC Patients*

	Diagnosis and Staging
2.1	**What is the recommended staging strategy?**
	2.1.1 The patient in whom HCC is detected with some degree of hepatic functional alteration should be referred in the first instance to the liver clinic for registration, evaluation and management of the underlying disease. It is a priority to establish with certainty whether the patient has a cirrhotic or non-cirrhotic liver.
	2.1.2 Biopsy is recommended in non-cirrhotic patients; and in cirrhotic patients in whom imaging does not meet radiological diagnostic criteria. (see recommendations 1.5)
	2.1.3 The recommended laboratory tests are: (to establish Child-Pugh Classification and MELD score): hemogram, creatinine, albumin, sodium, PT/TPT/INR, bilirubin, transaminases, alpha-fetoprotein and serology for Hepatitis B and C.
	2.1.4 CT with triphasic hepatic protocol and/or dynamic hepatic MRI is recommended to assess tumor burden and resectability. Chest/abdomen/pelvis CT is recommended to assess the extent of the disease.
	2.1.5 Do not repeat imaging studies in patients with recent conclusive studies (<3-months), unless alterations such as portal thrombosis or vascular invasion are suspected, which may alter the initial treatment strategy.
2.2	**What classification system is recommended for use in Panama?**
	The BCLC (Barcelona Clinic Liver Cancer) system.[31]
2.3	**What is the management recommendations for an early disease?**
	2.3.1 In patients with hepatocarcinoma without liver cirrhosis, resection is considered the first treatment option, since it could be performed immediately and does not contraindicate transplantation if it is later required.
	2.3.2 In patients with hepatocarcinoma and cirrhosis there are three types of management with curative intent, as they are able to modify the natural history of the disease and prolong survival according to BCLC system, therefore, we recommend:
	2.3.2.1 Resection as a treatment option applicable in patients with very early stages according to the BCLC system and who are not yet candidates for transplantation.
	2.3.2.2 Local ablation as an option with results similar to resection in patients with Child A/B and tumors≤3 cm,[6,7] or in patients who cannot undergo surgery.
	2.3.2.3 Liver Transplantation will be offered by a multidisciplinary group for HCC patients with cirrhotic liver disease that meet Milan criteria, or if they meet the San Francisco criteria according to the protocol of the National Liver Transplantation Program.
2.4	**What approach is recommended on intermediate disease cases according to the BCLC?**
	In these cases, the management will be decided and individualized in a Multidisciplinary Session.
2.5	**What is the recommended follow-up after initial treatment in patients with early disease?**
	We recommend follow-up in a Liver Unit, Liver Clinic or Institutional Interdisciplinary Group: 2.5.1 Postoperative antiviral treatment is recommended in HBV+ cases, with the purpose of reducing recurrences.
	2.5.2 So far, there is no proven benefit of adjuvant systemic therapy in these cases.
	2.5.3 All cases should be included in the National Cancer Registry.
	2.5.4 Treatment results shall be documented in institutional databases.

Patients with metastatic cancer progressing with brain lesions benefit from holocranial radiotherapy. There are no randomized studies demonstrating an increase in survival, but there is evidence for symptom control.

Radiotherapy modalities include whole brain irradiation, stereotactic radiosurgery (SRS) or both. Whole brain radiotherapy is used in multiple metastatic brain lesions, uncontrolled primary or poor functional status. Stereotactic radiosurgery is recommended for patients with fewer than 3 lesions and less than 3 cm. Radiosurgery improves survival in patients younger than 50-years old. The addition of radiotherapy to the whole brain after radiosurgery decreases the risk of new brain lesions, with no impact on overall survival and an unfavorable impact on the patient's neurocognitive ability.[40]

Systemic therapy in HCC: The combination of an immune checkpoint inhibitor antibody agent (atezolizumab) and an endothelial growth factor inhibitor (bevacizumab) is the most recent therapy approved for the management of Child-Pugh A patients. It's effectiveness has been demonstrated in phase III multicenter trials (IMbrave150) showing a significant impact on median progression-free survival (median 6.8-months 95% confidence interval (CI), 5.7-8.3) compared to sorafenib (4.8-months 95% CI, 4.0-5.6) with a hazard ratio (HR) of progression or death (0.59; 95% CI, 0.47-0.76; $p<0.001$).[41] Prior to initiation of combination therapy, an endoscopic evaluation and management of esophageal varices should be performed based on the risk of bleeding; in addition, a history of autoimmune disease and the presence of HBV and HCV coinfection should also be investigated. The maximum benefit of this therapy is obtained in patients with preserved liver function and absence of high-risk bleeding stigma or history of visceral bleeding.[42]

Prior to the approval of the atezolizumab-bevacizumab combination, systemic therapy with Sorafenib was the only option available in patients with advanced disease. Sorafenib and Lenvatinib are currently recommended regimens as therapeutic alternatives.[43] Atezolizumab-bevacizumab activity has benefit over sorafenib and even sustained complete response but not all patients will be appropriate candidates for this therapy.[44]

Sorafenib is an oral multi kinase inhibitor that suppresses cell proliferation and angiogenesis. It was the first drug approved by the Food and Drug Administration (FDA) for the treatment of HCC. It demonstrated an increase in median overall

survival from 7.9 to 10.7-months (HR 0.69; 95% CI 0.55-0.87) *vs.* placebo. The majority of patients in the relevant studies of sorafenib maintained preserved liver function. The need of having an adequate liver function for sorafenib treatment excludes most patients with impaired liver function, it affect dosing, and increase toxicity.[45]

Sorafenib remained as the only available first-line therapy because other agents such as erlotinib, brivanib, sunitinib, linifanib or everolimus, demonstrated insufficient antitumor activity, showed important toxicity in cirrhotic patients, and some of these other drugs did not provided adequate patient selection in their trials.

Lenvatinib is a kinase signaling inhibitor affecting the fibroblast, platelet-derived and vascular endothelial growth receptor with activity in HCC. Patients from a phase III, multicenter study, with unresectable HCC and no prior advanced disease treatment, presented a median survival with Lenvatinib of 13.6-months (95% CI, 12.1-14.9), and with sorafenib of 12.3-months (95% CI, 10.4-13.9 with HR of 0.92 (95% CI, 0.79-1.06). The safety and tolerability profile were adequate.[46]

The selection of an appropriate treatment option depends on the clinical, radiological analysis and biochemical profile of the patient trying to strike a balance between safety and maximum benefit.

Treatment options upon disease progression and its toxicity has become more complex. Previously there was no options available after failure of systemic treatment. Nowadays, transition to a second-line drug have expanded our possibilities for treatment. It is nevertheless important to clarify that the benefit of atezolizumab and bevacizumab as first-line therapy is not clear upon patient progression.

Regorafenib is another oral multi kinase inhibitor that have showed its efficacy in increasing median survival. In a double-blinded placebo-controlled randomized study in patients whose liver function was preserved and who had tolerated previous treatment with sorafenib, regorafenib impacted median overall survival by 10.6 *vs.* 7.8-months (HR 0.63; 95% CI 0.50-0.79; $p<0.001$). It was later approved in 2017 for its efficacy in cases where cancer progress despite sorafenib treatment.[47]

Ramucirumab is a monoclonal antibody against vascular type 2 endothelial receptor that was assessed in the REACH trial. Benefit of its use was observed in median progression-free survival (HR 0.63; 95% CI 0.52-0.75; $p<0.001$) and in time to progression (HR 0.59; 95% CI 0.49-0.72; $p<0.001$) relative to a placebo group in its phase III trial. Furthermore, worsening of symptoms were not significantly different than on the placebo group.48 The clinical trial REACH 2 assessed its efficacy and disease progression in patients with alpha fetoprotein levels greater than 400 ng/mL. Its benefits were demonstrated in overall survival and progression-free survival. Importantly, alpha-fetoprotein response is a relevant prognostic factor and was significantly modified in patients treated with ramucirumab *vs.* placebo, with survival of 13.6-months *vs.* 5.6-months (HR of 0.45; $p<0.001$).[48]

Stratification of HCC patients according to the pattern of progression on systemic therapy (e.g. local disease growth or de novo extrahepatic involvement and/or previously non-existent vascular invasion), will eventually modify the landscape in first or second line of treatment (Tables 3 and 4).

Management of Terminal Disease and Palliative Care

Stage D of the Barcelona clinic cancer staging guidelines provides clear classification of any HCC with Child-Pugh C decompensated cirrhosis and altered functional status. The spectrum of symptoms is related to cirrhotic decompensation and includes: ascites, variceal bleeding, peripheral edema and hepatic encephalopathy. These mass-like effects on the abdomen produces dull pain in more than 65% of patients and its association with fatigue, weakness, cachexia, anorexia and vomiting is not uncommon.[49]

There is emotional, physical, and psychological compromise that requires comprehensive multidisciplinary management. HCC is a generally poor prognostic condition associated with tu-

Table 3. *Recommendations on Advanced Disease Management of HCC Patients*

	Advanced Disease Management
3.1	**Who makes up the multidisciplinary team in the approach to the management of the patient with advanced HCC?**
	The multidisciplinary team, preferably multi-institutional, should be composed of Hepatologist, Medical Oncologist, Radiation Oncologist, Palliative Care, Interventional Radiologist, Nutritionist, Social Worker and Mental Health (but not restricted to other disciplines).
3.2	**What is the first line of treatment in patients diagnosed with advanced HCC?**
	The treatment of choice in patients with Child-Pugh A is Atezolizumab+Bevacizumab. The main contraindications for the use of Atezolizumab + Bevacizumab are: history of autoimmune disease, presence of esophageal and gastric varices with risk of untreated bleeding and Hepatitis B or C virus coinfection.
3.3	**What other therapeutic options do patients have in first line?**
	Consider treatment options such as Sorafenib (Child-Pugh A and B) or Lenvatinib (with a Child-Pugh A, no portal invasion, liver involvement<50%).
3.4	**What therapeutic options do we have after progression to first line?**
	3.4.1 In patients who have progressed to Sorafenib we have Regorafenib or Ramucirumab (AFP≥400 ng/mL) as therapeutic options.
	3.4.2 In the absence of Phase III studies, and with a patient who is already receiving Atezolizumab+Bevacizumab, the use of other first-line treatment options may be considered.

Table 4. *Recommendation on Terminal Disease (Patient with poor hepatic reserve (Child-Pugh C) or ECOG functional status 3-4*

	Advanced Disease Management
4.1	**Why refer a patient with hepatocarcinoma to palliative care?**
	The patient with hepatocarcinoma is often asymptomatic in the early stages, but experiences great discomfort due to advanced disease, adverse effects of treatment, or fast deterioration of underlining cirrhosis.
4.2	**When should patients with hepatocarcinoma be referred to palliative care?**
	4.2.1 Refer patients with HCC presenting with oncologic disease leading to poor performance status (ECOG 3-4) or corresponding to BCLC class C or D.
	4.2.2 Patients with limited treatment options due to limited access to cancer treatment or more than 2 chronic diseases concomitant to the main disease (preventing usual treatment).
	4.2.3 Patient with symptoms secondary to the oncologic disease that require evaluation and monitoring (liver failure as the cause of symptoms must be ruled out).
	4.2.4 When the patient does not wish to pursue treatment options.
4.3	**How management objectives are defined during for palliative care of patients with hepatocarcinoma?**
	Identify and set the objectives of care tailored to the patient and their relatives' preferences of QoL; continuously adjusting care to meet them over time.
4.4	**What are the recommended approaches by the palliative care team to the patient with hepatocarcinoma?**
	Patients, family members and caregivers should be aware of palliative care options, which constitutes a tool in the comprehensive management of biopsychosocial and spiritual needs.

mor burden and underlying cirrhosis. With a median survival of 3-months, 15-20% of patients with HCC debut at this stage.[50]

End-stage liver disease affects individuals of active working age and represents 90% of patients below the age of 70 years with a significant social and economic burden.[50]

Palliative care can be initiated at all stages of the disease. However, clinical guidelines are established for patients with stage C or D whom present 2 or more chronic diseases concomitant with HCC or when the patient does not wish to continue with the treatment.

We have this treatment modality as the only option in those patients in which disease-modifying therapy is not available and/or the patient is not a candidate to receive it.[51]

Currently, there are no precise prognostic indicators to identify patients who are candidates for palliative therapy. Generally, the healthcare providers have limited experience in palliative care, even when this group of patients requires additional supportive management to impact their quality of life due to the substantial discomfort and suffering in terminal stage of the disease. Thus, in many cases, the patients must refer to a palliative care physician.[52]

Some limitations in the implementation of palliative care in HCC patients are represented by lack of resources, stigmatization and cultural barriers.

A tool called NECPAL CCOMS-ICO© has been used to identify the need for palliative care involving liver disease. Applied in a prospective observational study, it was shown that only 65.8% of cases were identified by the clinical team when in fact 84.2% of the study cohort required palliative intervention according to this tool.[53]

The main general objectives associated with the care of the terminally ill HCC patient are: symptom management, family support, home care services, end-of-life care (EoLC) and discussion of the evolution of the disease.[53]

Studies that have assessed the perception of the disease from the patient's point of view have demonstrated the challenges they face during disease progression, treatment hesitations, and the complex interaction that a patient with HCC lives with in terms of dynamic modifications over time.[54]

Palliative care has a role in impacting emotional and physical symptoms and reducing the economic costs associated with patient care. Patients with adequate symptom control experience less uncertainty and greater ability to cope with unpredictable scenarios.[55]

Standard management of HCC involves an attempt to prolong survival, but a critical gap in practice and research regarding end-of-life (EoL) palliative care has been shown to exist. The literature records a lack of an integrative palliative model with respect to clinical practice in hepatology.[55]

The palliative care team recommends focusing on areas that require priority attention such as physical symptoms, pain, psychological status, physical well-being, and advanced EoL planning in conjunction with a referral to the local expert group for comprehensive case management.[55]

Healthcare professionals should assess patients' perceptions and goals when initiating treatment; this position changes as the EoL approaches. Also offering a capacity to monitor and work on their quality of life during the progression of the disease will allow individualizing treatment based on adjustments over time. The approach must be multidisciplinary and in time to focus not only on the patient but also on his or her social and family environment.

CONCLUSIONS HCC CONSENSUS

Hepatocellular carcinoma is a complex disease in which patient

care requires experience and a depth understanding of the different stages and management options. A multidisciplinary intervention is needed to provide multiple point-of-view that positively impact patient care and outcomes. Due to this complexity, institutions that provide healthcare to HCC patients need guidelines adjusted to their reality and capability. To improve HCC management in our country and to serve as a point of reference in the region, we have developed the first HCC management guidelines in Panama.

We recognize the limitations and the non-mandatory nature of this consensus guideline in which the healthcare provider can conduct their practice not based on the recommendations given by this panel of experts. Still, we think it's imperative as an initial step to strengthen our multidisciplinary groups in HCC.

Implementing this guideline will promote public policies to strengthen early diagnosis, management, and treatment of the disease and highlight the importance of palliative care. Its adoption will also encourage funding for research on treatment efficacy, life expectancy, and quality of life for our patients.

AUTHOR'S CONTRIBUTIONS

Study Design

MC, JC, YL, IV.

Collected and Contributed Data

MC, JC, JM, RF, EA, NC, IC, JAC, DD, ID, OE, KF, JL, YL, MM, GP, JP, LR, MRB, MR, KS, IV, RV.

Wrote the Paper and Performed Analysis

MC, JC, JM, ID.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*. 2012; 142: 1264-1273.e1. doi: 10.1053/j.gastro.2011.12.061

2. Younossi Z, Stepanova M, Ong JP, et al. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. *Clin Gastroenterol Hepatol.* 2019; 17(4): 748-755.e3. doi: 10.1016/j.cgh.2018.05.057

3. Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: A systematic review. *J Hepatol.* 2010; 53: 348-356. doi: 10.1016/j.jhep.2010.02.035

4. Ioannou GN, Beste LA, Green PK, et al. Increased risk for hepatocellular carcinoma persists up to 10 years after HCV eradication in patients with baseline cirrhosis or high FIB-4 scores. *Gastroenterology*. 2019; 157: 1264-1278.e4. doi: 10.1053/j.gastro.2019.07.033

5. Kanwal F, Kramer JR, Asch SM, Cao Y, Li L, El-Serag HB. Long-term risk of hepatocellular carcinoma in HCV patients treated with direct acting antiviral agents. *Hepatology*. 2020; 71: 44-55. doi: 10.1002/hep.30823

6. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: A retrospective study. *Hepatology*. 2007; 45: 579-587. doi: 10.1002/hep.21492

7. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: A meta-analysis of observational studies. *Ann Intern Med.* 2013; 158: 329-337. doi: 10.7326/0003-4819-158-5-201303050-00005

8. Chen C-J, Yang H-I, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B. virus DNA level. *JAMA*. 2006; 295: 65-73. doi: 10.1001/jama.295.1.65

9. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: Advancing guideline development, reporting and evaluation in health care. *CMAJ*. 2010; 182(18): E839-E842. doi: 10.1503/cmaj.090449

10. Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. *Gastroenterology*. 2019; 156(2): 477-491.e1. doi: 10.1053/j.gastro.2018.08.065

11. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention, and management. *Nat Rev Gastroenterol Hepatol.* 2019; 16(10): 589-604. doi: 10.1038/s41575-019-0186-y

12. Fujiwara N, Friedman SL, Goossens N, Hoshida Y. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. *J Hepatol.* 2018; 68(3): 526-549. doi: 10.1016/j.jhep.2017.09.016

13. Konyn P, Ahmed A, Kim D. Current epidemiology in hepatocellular carcinoma. *Expert Rev Gastroenterol Hepatol.* 2021; 15(11): 1295-1307. doi: 10.1080/17474124.2021.1991792

14. McIntyre CA, Chou JF, Gonen M, et al. Hepatocellular carcinoma in patients with no identifiable risk factors. *HPB (Oxford).* 2021; 23(1): 118-126. doi: 10.1016/j.hpb.2020.05.005

15. Massarweh NN, El-Serag HB. Epidemiology of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *Cancer Control.* 2017; 24(3): 1073274817729245. doi: 10.1177/1073274817729245

16. Frager SZ, Schwartz JM. Hepatocellular carcinoma: Epidemiology, screening, and assessment of hepatic reserve. *Curr Oncol.*

2020; 27(Suppl 3): S138-S143. doi: 10.3747/co.27.7181

17. Liu XN, Cui DN, Li YF, Liu YH, Liu G, Liu L. Multiple "Omics" data-based biomarker screening for hepatocellular carcinoma diagnosis. *World J Gastroenterol*. 2019; 25(30): 4199-4212. doi: 10.3748/wjg.v25.i30.4199

18. Sachar Y, Brahmania M, Dhanasekaran R, Congly SE. Screening for hepatocellular carcinoma in patients with hepatitis B. *Viruses*. 2021; 13(7): 1318. doi: 10.3390/v13071318

19. Clark T, Maximin S, Meier J, Pokharel S, Bhargava P. Hepatocellular carcinoma: Review of epidemiology, screening, imaging diagnosis, response assessment, and treatment. *Curr Probl Diagn Radiol*. 2015; 44(6): 479-486. doi: 10.1067/j.cpradiol.2015.04.004

20. Yang JD, Heimbach JK. New advances in the diagnosis and management of hepatocellular carcinoma. *BMJ*. 2020; 371: m3544. doi: 10.1136/bmj.m3544

21. Ganne-Carrié N, Nahon P. Hepatocellular carcinoma in the setting of alcohol-related liver disease. *J Hepatol*. 2019; 70(2): 284-293. doi: 10.1016/j.jhep.2018.10.008

22. Yaprak O, Akyildiz M, Dayangac M, et al. AFP level and histologic differentiation predict the survival of patients with liver transplantation for hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int*. 2012; 11(3): 256-261. doi: 10.1016/s1499-3872(12)60157-x

23. Eilard MS, Holmberg E, Naredi P, Söderdahl G, Rizell M. Addition of alfa fetoprotein to traditional criteria for hepatocellular carcinoma improves selection accuracy in liver transplantation. *Scand J Gastroenterol*. 2018; 53(8): 976-983. doi: 10.1080/00365521.2018.1488180

24. Ayuso C, Rimola J, García-Criado Á. Imaging of HCC. *Abdom Imaging*. 2012; 37(2): 215-230. doi: 10.1007/s00261-011-9794-x

25. Hoffmann-Eßer W, Siering U, Neugebauer EAM, Brockhaus AC, Lampert U, Eikermann M. Guideline appraisal with AGREE II: Systematic review of the current evidence on how users handle the 2 overall assessments. *PLoS One*. 2017; 12(3): e0174831. doi: 10.1371/journal.pone.0174831

26. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021; 7(1): 6. doi: 10.1038/s41572-020-00240-3

27. Loomba R, Lim JK, Patton H, El-Serag HB. AGA clinical practice update on screening and surveillance for hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: Expert review. *Gastroenterology*. 2020; 158(6): 1822-1830. doi: 10.1053/j.gastro.2019.12.053

28. Ding H, Tu H, Qu C, et al. Guideline Open Access Hepatoma Research Guideline for stratified screening and surveillance in patients with high risk of primary liver cancer (2020). *Hepatoma Res*. 2021; 7: 17. doi: 10.20517/2394-5079.2021.13

29. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice Guidance by the American Association for the study of liver diseases. *Hepatology*. 2018; 68(2): 723-750. doi: 10.1002/hep.29913

30. Cheung TTT, Kwok PCH, Chan S, et al. Hong Kong consensus statements for the management of unresectable hepatocellular carcinoma. *Liver Cancer*. 2018; 7(1): 40-54. doi: 10.1159/000485984

31. Lubel JS, Roberts SK, Strasser SI, et al. Australian recommendations for the management of hepatocellular carcinoma: A consensus statement. *Med J Aust*. 2021; 214(10): 475-483. doi: 10.5694/mja2.50885

32. Ozkan H, Kamran M, Raees A, Jafri W. Updates on the diagnosis and management of hepatocellular carcinoma. *Euroasian J Hepatogastroenterol*. 2021; 11(1): 32-40. doi: 10.5005/jp-journals-10018-1335

33. Ayuso C, Rimola J, Vilana R, et al. Diagnosis and staging of hepatocellular carcinoma (HCC): Current guidelines. *Eur J Radiol*. 2018; 101: 72-81. doi: 10.1016/j.ejrad.2018.01.025

34. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017; 389(10064): 56-66. doi: 10.1016/S0140-6736(16)32453-9

35. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. *Lancet*. 2018; 391(10126): 1163-1173. doi: 10.1016/S0140-6736(18)30207-1

36. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol*. 2022; 76(3): 681-693. doi: 10.1016/j.jhep.2021.11.018

37. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008; 359(4): 378-390. doi: 10.1056/NEJMoa0708857

38. Hawkins MA, Dawson LA. Radiation therapy for hepatocellular carcinoma: From palliation to cure. *Cancer*. 2006; 106: 1653-1663. doi: 10.1002/cncr.21811

39. Sze WM, Shelley M, Held I, Mason M. Palliation of metastatic bone pain: Single fraction versus multifraction radiotherapy (Review). *Cochrane Database Syst Rev*. 2004; 2002(2): CD004721. doi: 10.1002/14651858.CD004721

40. Muller-Riemenschneider F, Bockelbrink A, Ernst I, et al. Stereotactic radiosurgery for the treatment of brain metastases. *Radiother Oncol*. 2009; 91: 67-74. doi: 10.1016/j.radonc.2008.12.001

41. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizum-

ab in unresectable hepatocellular Carcinoma. *N Eng J Med*. 2020; 382(20): 1894-1905. doi: 10.1056/NEJMoa1915745

42. Bruix J, Chan SL, Galle PR, Rimassa L, Sangro B. Systemic treatment of hepatocellular carcinoma: An EASL position paper. *J Hepatol*. 2021; 75(4): 960-974. doi: 10.1016/j.jhep.2021.07.004

43. Jindal A, Thadi A, Shailubhai K. Hepatocellular carcinoma: Etiology and current and future drugs. *J Clin Exp Hepatol*. 2019; 9(2): 221-232. doi: 10.1016/j.jceh.2019.01.004

44. Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2018; 15(10): 599-616. doi: 10.1038/s41571-018-0073-4

45. Gordan JD, Kennedy EB, Abou-Alfa GK, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO Guideline. *J Clin Oncol*. 2020; 38(36): 4317-4345. doi: 10.1200/JCO.20.02672

46. Syed YY. Ramucirumab: A review in hepatocellular carcinoma. *Drugs*. 2020; 80(3): 315-322. doi: 10.1007/s40265-020-01263-6

47. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019; 20(2): 282-296. doi: 10.1016/S1470-2045(18)30937-9

48. Carvalho JR, Vasconcelos M, Marques da Costa P, et al. Identifying palliative care needs in a Portuguese liver unit. *Liver Int*. 2018; 38(11): 1982-1987. doi: 10.1111/liv.13865

49. Patel AA, Woodrell C, Ufere NN, et al. Developing priorities for palliative care research in advanced liver disease: A multidisciplinary approach. *Hepatol Commun*. 2021; 5(9): 1469-1480. doi: 10.1002/hep4.1743

50. Atiq O, Tiro J, Yopp AC, et al. An assessment of benefits and harms of hepatocellular carcinoma surveillance in patients with cirrhosis HHS public access. *Hepatology*. 2017; 65(4): 1196-1205. doi: 10.1002/hep.28895

51. Kumar M, Panda D. Role of supportive care for terminal stage hepatocellular carcinoma. *J Clin Exp Hepatol*. 2014; 4: S130-S139. doi: 10.1016/j.jceh.2014.03.049

52. Firkins JL, Tarter R, Driessnack M, Hansen L. A closer look at quality of life in the hepatocellular carcinoma literature. *Qual Life Res*. 2021; 30(6): 1525-1535. doi: 10.1007/s11136-021-02789-2

53. Laube R, Sabih AH, Strasser SI, Lim L, Cigolini M, Liu K. Palliative care in hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2021; 36(3): 618-628. doi: 10.1111/jgh.15169

54. Hansen L, Rosenkranz SJ, Vaccaro GM, Chang MF. Patients with hepatocellular carcinoma near the end of life: A longitudinal qualitative study of their illness experiences. *Cancer Nurs*. 2015; 38(4): E19-E27. doi: 10.1097/NCC.0000000000000188

55. Bai M, Reynolds NR, McCorkle R. The promise of clinical interventions for hepatocellular carcinoma from the west to mainland China. *Palliat Support Care*. 2013; 11(6): 503-522. doi: 10.1017/S1478951512001137