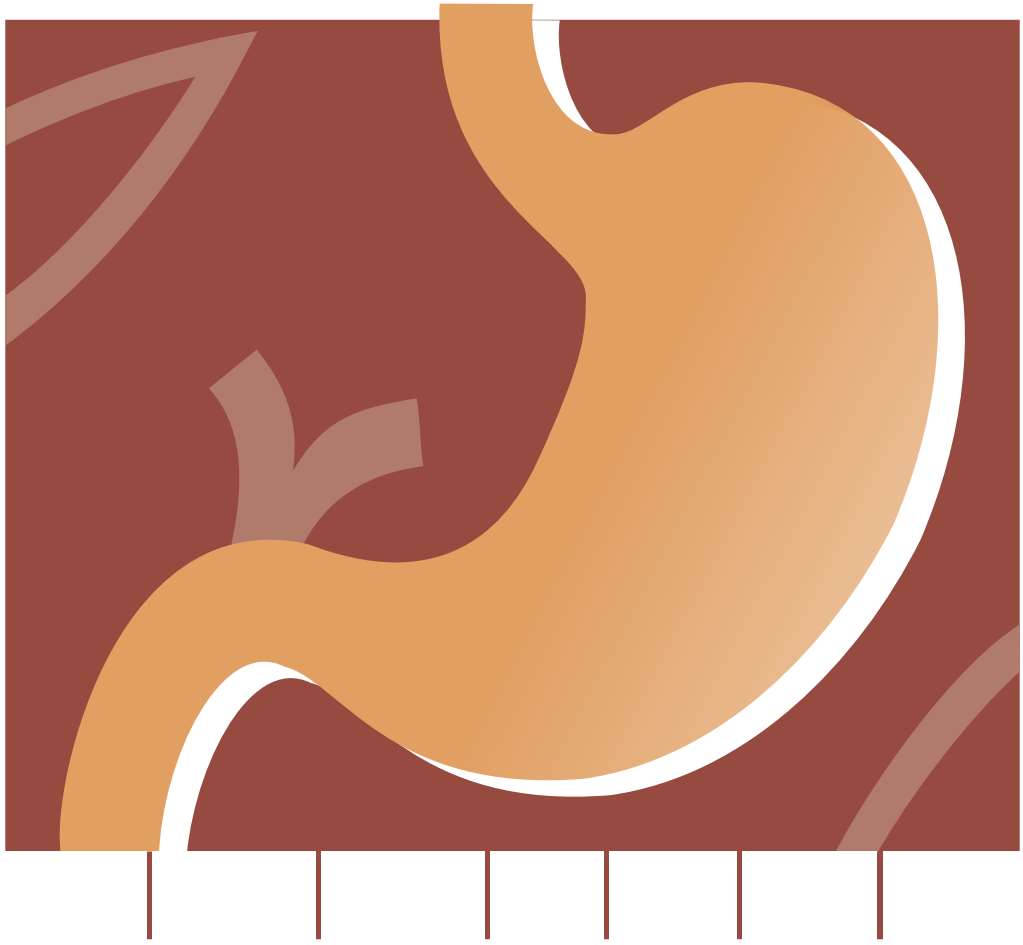
ISSN - 1319-3767

Volume no. 26, Supplement 1, October 2020

The Saudi Journal of Gastroenterology

Official publication of the Saudi Gastroenterology Association



Clinical Practice Guidelines

Online full text at www.saudijgastro.com

PubMed Indexed

Wolters Kluwer

Medknow

Clinical Practice Guidelines

Saudi Association for the Study of Liver diseases and Transplantation practice guidelines on the diagnosis and management of hepatocellular carcinoma

Saleh A. Alqahtani[1,2], Faisal M. Sanai[3,4], Ashwaq Alolayan[5], Faisal Abaalkhail[6,7], Hamad Alsuhaibani[8], Mazen Hassanain[9,10], Waleed Alhazzani[11], Abdullah Alsuhaibani[8], Abdullah Algarni[12,13], Alejandro Forner[14], Richard S Finn[15], Waleed K. Al-hamoudi[1,3]

[1]Liver Transplant Centre, King Faisal Specialist Hospital and Research Centre, [3]Liver Disease Research Center, College of Medicine, King Saud University, [5]Adult Medical Oncology, King Abdulaziz Medical City, [6]Department of Medicine, Gastroenterology Section, King Faisal Specialist Hospital and Research Centre, [7]College of Medicine, Al Faisal University, [8]Department of Radiology, King Faisal Specialist Hospital and Research Centre, [9]Department of Surgery, College of Medicine, King Saud University, [12]Department of Oncology, King Abdulaziz Medical City, [13]College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, [4]Department of Medicine, Gastroenterology Unit, King Abdulaziz Medical City, Jeddah, Saudi Arabia, [2]Division of Gastroenterology and Hepatology, Johns Hopkins University, Baltimore, Maryland, [10]Department of Pediatrics, Baylor College of Medicine, Houston, Texas, [15]Division of Hematology and Oncology, David Geffen School of Medicine at UCLA, Los Angeles, California,United States, [11]Department of Medicine, McMaster University, Hamilton, ON, Canada, [14]Barcelona Clinic Liver Cancer Group, Liver Unit, Hospital Clinic Barcelona, IDIBAPS, CIBEREHD, University of Barcelona, Barcelona, Spain

Address for correspondence: Dr. Saleh A. Alqahtani, Liver Transplant Unit, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.
E-mail: salalqahtani@kfshrc.edu.sa
Submitted: 27-Aug-2020 **Accepted:** 10-Sep-2020 **Published:** 06-Oct-2020

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer and forms a major global health problem. In fact, HCC currently ranks as the fourth most common cause of cancer-related mortality worldwide, with an anticipated increase in incidence in the future.[1] Given the high prevalence of liver disease in the Kingdom of Saudi Arabia (KSA), it is unsurprising that HCC represents a huge medical burden in this part of the world. Together with the increasing recognition of its clinical relevance, major progress has been made in the prevention, detection, diagnosis, and treatment of patients with HCC. More pertinently, the management of HCC has evolved dramatically since the publication of the previous Saudi guidelines in 2012.[2] To provide an update of these guidelines, a thorough review of the available HCC literature was performed, with a specific interest in the situation in KSA. We hope that these guidelines will help further improve the care of HCC patients in KSA.

METHODOLOGY

The committee assigned to revise the 2012 Saudi HCC guidelines comprises hepatologists, hepatobiliary surgeons, oncologists, radiologists, and an expert in evidence-based medicine. Firstly, an in-depth literature review was performed of all recent publications related to the epidemiology, risk factors, prevention, surveillance, and treatment of patients with HCC. A particular emphasis

Access this article online

Quick Response Code:

Website: www.saudijgastro.com

DOI: 10.4103/sjg.SJG_477_20

How to cite this article: Alqahtani SA, Sanai FM, Alolayan A, Abaalkhail F, Alsuhaibani H, Hassanain M, *et al.* Saudi Association for the Study of Liver diseases and Transplantation practice guidelines on the diagnosis and management of hepatocellular carcinoma. Saudi J Gastroenterol 2020;26:S1-40.

was given to publications from the Middle East, with a focus on studies from KSA. All available literature was critically examined, and the available evidence was subsequently classified according to its strength. All recommendations (strong or weak) in these updated guidelines were graded based on their respective level of evidence (low, moderate, high) [Table 1]. In a final step, all members of the guideline committee critically scrutinized the consensus document, after which two international experts in the field of hepatology and oncology reviewed the guidelines.

A summary of all recommendations is listed in the Supplementary Table.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

In 2018, HCC was the sixth most common cancer and the fourth most common cause of cancer death worldwide.[1] Annually, more than 841,000 people are diagnosed with HCC, and about 782,000 die with it per year.[3] Data from the 2020 global cancer report indicate a cumulative incidence of liver cancer from birth to 75 years of 1.6% in males and 0.6% for females.[3] In general, advancing age is associated with a progressive increase in the incidence of HCC, with a peak incidence at 70 years.[4] Interestingly, the HCC incidence shows a significant geographical imbalance [Figure 1]. For example, East and South-East Asia are characterized by particularly high HCC incidence rates [age-standardized incidence rate (ASR) of 17.7 and 13.3 per 100,000, respectively], whereas the incidence in Europe (ASR: 5.1 per 100,000) and North America (ASR: 6.6 per 100,000) is much lower.[3] On a global scale, the incidence of HCC has been increasing over the past decades. In fact, between 1990 and 2015, the incidence of newly diagnosed HCC cases increased by 75%.[5] In the United States of America (USA), HCC incidence increased from 1.4 per 100,000 per populationin the late 1970s to 6.7 per 100,000 in 2012.[6]

Table 1: Categories of evidence quality

Level of evidence	Explanation
High	Strong scientific basis. Further research is very unlikely to change our confidence in the statement.
Moderate	Convincing evidence is available. However, further research can potentially have an important impact on the confidence we have in this statement.
Low	Strong scientific evidence for the statement is lacking. Research is ongoing, and the outcome of this is very likely to have an important impact on this statement.

The burden of HCC is likely to increase further in the next decades, mainly as a result of the global rise of obesity and obesity-related fatty liver disease. Projections estimate that by 2030, HCC will become the third cause of cancer-related death in the Western world.[6]

According to the most recent cancer incidence report of the Saudi Cancer Registry (2015), liver cancer ranked as the sixth most common cancer among Saudi males and 12th among Saudi women.[7] In 2015, a total of 376 cases of liver cancer were reported among Saudi nationals, representing 3.1% of all diagnosed cancers. The vast majority of these liver cancers (75%) consisted of HCC cases, and the male preponderance of liver cancer is adequately reflected by the 2015 Saudi data with a male to female ratio of 2.7 to 1. The ASR for liver cancer among males was 4.0 per 100,000 as compared to 1.5 per 100,000 in females.[7] GLOBOCAN data from 2018 indicate a fairly similar liver cancer incidence in Saudi Arabia with an overall ASR of 4.5 per 100,000 (6.2 and 2.5 per 100,000 for males and females, respectively).[3] As such, the current liver cancer incidence in the KSA is in line with the incidence reported in Northern Europe (ASR 4.7 per 100,000).[3] Of note, the incidence data in KSA for 2018 are lower than the 5.3 per 100,000 ASR reported by the Saudi Cancer Registry in 2006 and the 6.42 per 100,000 ASR that was reported in 2017.[2,3] Data on HCC-related mortality in KSA for 2018 indicate an ASR of 4.2 per 100,000 (5.8 per 100,000 and 2.4 per 100,000 for males and females, respectively).

Within the country, substantial regional differences are observed with respect to HCC incidence. The five regions with the highest ASR for males were Riyadh (10.4 per 100,000), followed by the Najran (7.7 per 100,000), and the Tabuk region (7.0 per 100,000). Among females, the regions with the highest ASR were Riyadh (4.9 per 100,000), the Eastern region (2.8 per 100,000), and the Tabuk region (2.6 per 100,000).[8]

Risk factors and etiology

The most significant risk factor for the development of HCC is the presence of cirrhosis, regardless of its etiology.[9] However, various risk factors are pertinent in the development of HCC, such as hepatitis B virus (HBV), hepatitis C virus (HCV), non-alcoholic fatty liver disease (NAFLD), diabetes and obesity, alcohol and aflatoxin B1, which are discussed briefly below.

Cirrhosis

Cirrhosis is the most significant risk factor for the development of HCC regardless of the underlying etiology. Long-term follow-up studies have found that approximately

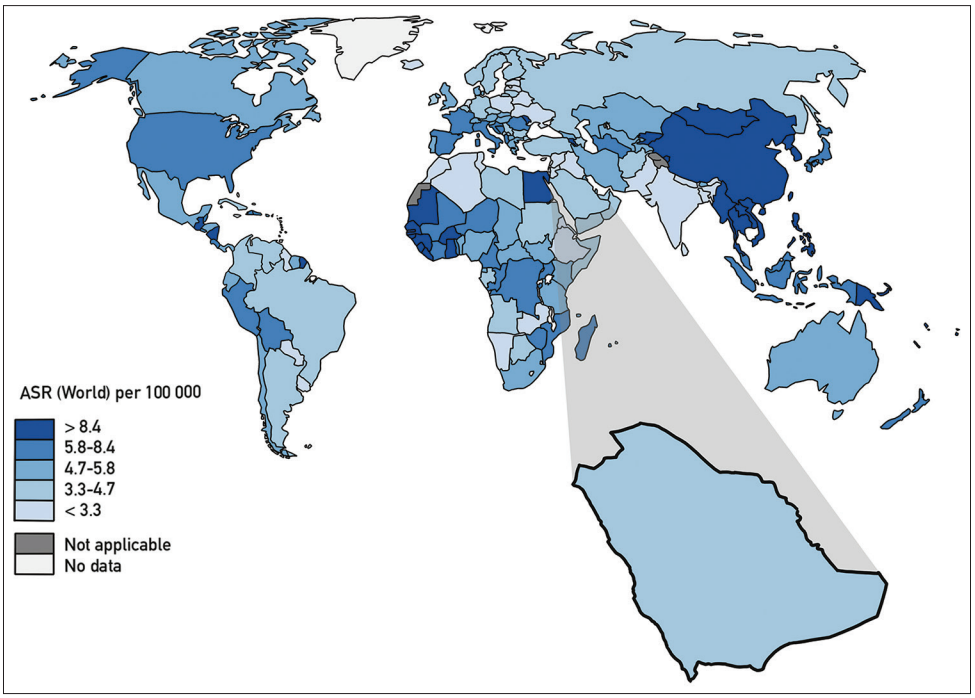


Figure 1: Estimated age-standardized incidence rates for liver cancer in 2018 (both sexes, all ages; per GLOBOCAN 2018 database)[3]

1–8% of patients with cirrhosis develop HCC per year (e.g., 2% in HBV-infected cirrhotic patients and 3–8% in HCV-infected cirrhotic patients).[10] In a population-based study in the UK, people with cirrhosis had an estimated cumulative 10-year incidence of HCC of approximately 4%.[11] Overall, it is estimated that 80–90% of patients with HCC have underlying cirrhosis.[12] Recent data indicate a threefold higher HCC risk in cirrhotic patients with HCV compared to patients with alcoholic-related liver disease or NAFLD-related cirrhosis.[13] In general, the severity of cirrhosis in addition to older age and male gender were found to correlate with a higher risk of developing HCC among patients with cirrhosis.

Hepatitis B

HBV is generally considered to be the strongest epidemiologic risk factor associated with HCC. Worldwide, chronic HBV accounts for almost 50% of all HCC cases, but the magnitude of this risk factor varies greatly demographically (e.g., very high in East Asia, lower in Europe).[14] Compared to uninfected individuals, the risk of developing HCC is increased 15- to 20-fold in patients with an HBV infection.[15] A higher risk of developing HCC with an aging HBV-infected population is apparent. A recent registry-based analysis from Saudi Arabia found a substantially higher proportion of HBV-related HCC in 2015 patients (11.9%), compared to those in 2010 (0.7%).[16] In multiple population-based studies, genotype C is associated with a higher risk of HCC than genotypes A2, Ba, Bj, and D. In Saudi Arabia, a majority of HBV-infected patients have genotype D; however, a specific analysis of the relationship between HBV genotype and clinical outcome in Saudi patients did not reveal a different risk of HCC for genotype D patients compared to other genotypes.[17] In other studies, a high hepatitis B viral load,[18] and hepatitis virus e antigen seropositivity[19] were shown to be independent predictors of HCC development, with the viral load being a risk factor of progression to cirrhosis.[20] In most instances, HBV-related HCC occurs in the context of cirrhosis, but in about 10% of HBV-positive HCC cases, no cirrhosis is seen.[21,22] In this respect, being of African-American (odds ratio [OR] [95%CI: 6.78[2.05–22.4]) or Asian (OR[95%CI]: 11.6[2.63–50.8]) origin with HBV was associated with a higher chance of developing HCC in the absence of cirrhosis.[23]

Hepatitis C

Although HBV is the most common underlying HCC etiology worldwide, HCV is responsible for most cases in Western countries,[5] as in KSA, accounting for 35–50% of HCC cases.[24-27] Relative to the uninfected population, HCV-infected patients have an approximately 17-fold increased risk of developing HCC. Following the development of cirrhosis, the annual incidence of HCC in chronic HCV patients is 1–4%.[28] With the efficacy of current direct antiviral agents (DAAs) in HCV-infected patients and the World Health Organization's (WHO) plan to eradicate HCV by 2030, one can foresee this risk

factor will become less important in the future. However, various studies show that DAA-cured HCV patients with stage 4 fibrosis, or even stage 3 fibrosis, remain at risk of developing HCC.[29]

NAFLD, diabetes, and obesity

With the increasing global prevalence of diabetes and obesity, NAFLD has become a major risk factor for HCC.[30] Although most patients with NAFLD-related HCC have underlying cirrhosis, there is a subset of patients with NAFLD-associated HCC without cirrhosis. In fact, 41.7% of patients with NAFLD-associated HCC had no cirrhosis.[31] This is an alarming finding, especially when considering the development of HCC screening strategies. In a large study from the USA, early age obesity has an impact on HCC development and prognosis. Interestingly, this is the first study that indicates that a temporal relationship exists between past obesity and the occurrence of future HCC.[32]

A study using modeling NAFLD burden predicted that NAFLD-related HCC cases in KSA would increase from 580 cases in 2017 to 1,790 cases in 2030. In total, the NAFLD prevalence was estimated at 8,451,000 (25.7%) in 2017 in Saudi Arabia and is predicted to increase to 48% (at 12,534,000) by 2030.[33] Among 235 HCC patients admitted to a center in KSA during 2009–2011, the majority were overweight/obese and had NAFLD risk factors, including 57.9% with diabetes, 52.3% with hypertension and 12.8% with dyslipidemia.[26] Because the levels of obesity and diabetes in the KSA are similar to the high levels observed in Western countries,[34] it will be essential to mitigate the growing burden of NAFLD in KSA and its impact on the increasing incidence and prevalence of HCC.

Alcohol

The association between heavy alcohol use and HCC risk has been consistently shown in several analyses. In 2016, a meta-analysis of 19 prospective studies estimated a 16% increased risk of liver cancer among consumers of three or more alcoholic drinks per day and a 22% increased risk among consumers of six or more alcoholic drinks per day.[35] Importantly, the association between alcohol intake and the risk for HCC is strongly related to the development of liver cirrhosis. In the KSA, alcohol consumption is low and not a significant contributor to the development of HCC.[25]

Aflatoxin B1

Aflatoxins are a class of carcinogenic mycotoxins produced by *Aspergillus fungi* and are frequent contaminants of a number of staple foods, particularly maize and groundnuts. Aflatoxin B1 (AFB1) is the most potent of these compounds and has been strongly associated with the development of HCC.[36] The correlation between the degree of exposure to AFB1 and the incidence of HCC is direct, with an OR of 6.37:1.0 (range 3.74:1.0 to 10.86:1.0) for developing a tumor.[37] AFB1 exposure particularly heightens the development of HCC in individuals with an HBV infection.[38]

Studies of AFB1 exposure in the KSA have revealed that chronic exposure leads to an increase in aspartate (AST) and alanine aminotransferase (ALT) levels in patients with liver dysfunction. Age, as an indicator of duration of exposure, also correlated with higher AFB1 levels. Thus, it is probable that in some HCC patients, long-term exposure to AFB1 could be a legitimate risk factor.[39] One study showed aflatoxin contamination in rice imported to Riyadh, KSA, which could contribute to the risk of HCC.[40] Thus, early detection of AFB1 exposure, along with hepatitis B and C reduction, can mitigate the synergistic effects of the two causative factors and decrease the risk of developing HCC.[39]

Other risk factors

The effect of cigarette smoking on HCC risk has been widely examined but yielded inconsistent findings. In 2009, a meta-analysis estimated a 1.5-fold increased risk of HCC among current smokers, a risk similar to that imposed by obesity.[41] However, these data need to be addressed with care given the fact that the impact of concomitant alcohol use on HCC risk in smokers is difficult to assess.

Several heritable disorders are associated with an increased risk of HCC, such as patients with hemochromatosis who are believed to have an approximately 20-fold increased risk of developing HCC.[42] Other inherited metabolic diseases of the liver, such as type 1 glycogen storage diseases and alpha 1 antitrypsin deficiency, were also associated with an increased risk of developing HCC.[12]

Finally, the incidence of HCC is higher in patients with an HIV infection compared to patients without HIV. HIV adds to the risk of HCC in patients with concomitant viral hepatitis infection.[43] The only study on HIV coinfection in the KSA found that the prevalence of viral hepatitis B (3%) and C (12%) was high in HIV patients.[44]

HCC etiology in the KSA

The incidence of HCC in KSA has decreased slightly in recent years,[3] which is somewhat surprising given the relatively high prevalence of the two major risk factors for HCC (hepatitis B and C) in the country. A large epidemiologic study in 1992 found that 7% of Saudi

children were positive for HBsAg.[45] In addition, the prevalence of hepatitis C is also substantial, at 1–3%.[46] There is also a relatively high prevalence of diabetes (20%) and obesity (30%), two factors closely associated with NAFLD.[33]

In 2013, *Alswat et al.* reported the clinicopathological features of 363 patients diagnosed with HCC between June 2003 and July 2008 from a Saudi registry.[24] The median age of this patient cohort was 66 years, and 73.6% of them were male. A majority of patients had a viral etiology, with HCV and HBV being responsible for 48.2% and 28.7% of cases, respectively. The majority of the patients were diagnosed with an advanced stage of the disease: 53% of patients had a Cancer of the Liver Italian Program (CLIP) score of 4–6 (advanced stage), 55% had large multinodular tumors, and 16% of patients had vascular invasion or extrahepatic spread at the time of diagnosis. Most of the patients in the cohort presented with decompensated cirrhosis (44% Child-Pugh-Turcotte [CPT] B, 26% CPT C). Overall, 84% of patients died during the study period, and the presence of portal hypertension, a bilirubin level >22 μmol/L, and severe encephalopathy were associated with poor survival.[24]

More insight into the etiology of HCC cases in KSA comes from retrospective analyses of HCC cases diagnosed in tertiary care centers. The first study looked at the records of 128 patients diagnosed with HCC between 2008 and 2014 in Jeddah.[25] HCV and HBV were responsible for 33.6% and 24.2% of HCC cases, respectively. In total, 62.5% of patients had liver cirrhosis at the time of diagnosis, meaning that surprisingly about a third of patients developed HCC in the absence of any clinical evidence of cirrhosis.[25] The second analysis included data from 235 patients with HCC between January 2009 and September 2011.[26] The mean age in this cohort was 65 years, and 71.5% of patients were male. Viral hepatitis was responsible for the underlying liver disease in 75% of patients (46.8% HCV, 26.4% HBV, 2.6% HCV + HBV). The development of HCC on underlying cirrhosis was noted in 81.3% of the patients.[26] A final study was performed in Gizan, which contrasts the other reports, as it found that HBV infections were more prevalent among HCC patients (66.9%) compared to infections with HCV (11.9%). HBV infection was the major risk factor for HCC in this analysis (OR[95%CI]: 34.3[14.8–79.1], $P < 0.001$). Also, among HCV-infected patients, the HCC risk was increased, but to a lesser extent (OR[95%CI]: 12.2[3.2–47.2]; $P < 0.001$).[47]

Data from the Institute for Health Metrics and Evaluation Global Burden of Disease Study published in 2017 show changes in the etiological distribution of HCC in KSA. From 1990 to 2017, the ASR for HBV-related HCC declined by 20%, while the ASR for HCV-related HCC increased by 9.1%.[2] This evolution probably reflects the effect of the elaborate HBV vaccination program that was set up within the country. However, the most important change over this period consists of the 47.4% increase in the ASR for non-alcoholic steatohepatitis (NASH)-associated HCC.[2] As mentioned previously, the increasing prevalence of diabetes and obesity in the KSA will likely further impact this evolution.

Summary: Epidemiology and Etiology

- The incidence of HCC is increasing worldwide and is one of the leading causes of cancer-related death.
- GLOBOCAN data from 2018 indicates an overall liver cancer age-adjusted incidence rate of 4.5 per 100,000 in the KSA.
- Over the last 30 years, the etiological distribution of HCC in KSA has changed considerably: chronic HBV and HCV are now the most common etiologies, while NAFLD is emerging as an important etiology because of a rising incidence of obesity and metabolic risk factors.

PREVENTION

Preventing HCC development is addressed by targeting specific risk factors discussed above. Vaccinations and current treatment strategies for HBV and HCV will inevitably reduce the global burden of HCC.

Vaccination

The most important preventive strategy for HCC consists of universal HBV vaccination. The WHO recommends vaccination against hepatitis B for all newborns and high-risk groups. A large study in Taiwan, which successfully implemented the hepatitis B immunization program, found a reduction in hepatitis B-related HCC incidence from 0.92 per 100,000 person-years in an unvaccinated cohort to 0.23 in a vaccinated cohort.[48] Incomplete immunization was the most important predictor of HCC after adjusting for maternal hepatitis B serostatus among Taiwanese,[49] stressing the importance of complete vaccination. In a study from rural China, the incidence of HCC and the mortality rates of severe end-stage liver diseases and infant fulminant hepatitis were significantly lower in a vaccinated group than the control group with efficacies of 84% (95%CI: 23–97%), 70% (95%CI: 15–89%), and 69% (95%CI: 34–85%), respectively.[50]

Similarly, hepatitis B vaccination has also significantly reduced the HBV infection rates in KSA.[51-54] In fact, a recent review of the hepatitis B care pathway in the country demonstrated that significant improvements had been made in the last decades. These efforts result in an estimated current HBV prevalence of approximately 1.5% in the KSA.[54] Although there are no formal studies on the outcomes of hepatitis B vaccination on HCC incidence, there are some suggestions that the HBV-related HCC incidence has reduced. Three newer studies done between 2011 and 2014 found higher HCV-related HCC rates compared to HBV,[24,55,56] as opposed to older studies between 1990 and 2004, where HBV was the predominant HCC etiology.[47,57]

Antiviral therapy

Several effective antiviral agents (e.g., pegylated interferon alfa, entecavir, tenofovir disoproxil fumarate [TDF], and tenofovir alafenamide) have been developed for the treatment of patients with HBV. Historical data indicates a reduction in the HCC incidence when interferon was used in HBV patients, and long-term therapy with nucleotide or nucleoside analogues also appears to favorably impact HCC incidence.[58] More recently, 5-year data reveals a further decrease in HCC incidence with entecavir or TDF treatments.[59] In the KSA, the care pathway for HBV treatment, such as existing mandated national screening structures, established protocols for those who test positive and subsequent linkage-to-care are inadequate. Thus, in the absence of a virologic cure, a concerted effort should be made to provide safe and effective lifelong treatment.[54]

In patients with HCV, all-cause mortality and the risk of HCC is reduced when patients achieve a sustained virological response (SVR).[60] A meta-analysis of a number of observational studies found that an SVR after interferon-based treatment resulted in more than a 70% reduction of HCC incidence and an absolute risk reduction of 4.6% at all stages of liver disease.[61] However, there is a residual risk in patients with cirrhosis who achieve SVR, warranting surveillance.[62] Introducing DAAs in the treatment of HCV has been a major breakthrough. Surprisingly, some earlier reports suggested that HCC risk might potentially increase, particularly early tumor recurrence after achieving SVR with DAA therapy.[63,64] However, more recently, a meta-analysis showed no evidence that the risk for HCC occurrence or recurrence is different between patients receiving DAA or interferon therapy.[29]

In 2017, the WHO announced an ambitious plan to eliminate HCV worldwide by 2030. Quickly thereafter, the Saudi Ministry of Health endorsed the same goal, as data from 2016 revealed that anti-HCV antibody prevalence in Saudi nationals was about 0.7%, with approximately 70% of these individuals having an active infection. An estimated 0.5% of Saudi nationals are actively infected with HCV, about 20% of these patients have been previously diagnosed, and 50% of them received subsequent treatment. Fifty percent of treated HCV patients have been cured using standard therapy with pegylated interferon and ribavirin, while the other half was treated with new DAA therapy in the past three years, resulting in >90% cure rates.[65] Eliminating HCV by 2030, through an integrated program of prevention, detection, and treatment would result in a 90% reduction in the number of new HCV cases in KSA, preventing about 3,000 deaths and potentially resulting in approximately 260 fewer cases of HCC by 2030.[66]

Other preventive measures

Most preventive strategies in the context of HCC have centered on the viral causes of HCC. Although vaccination and antiviral treatment remain the primary means of prevention, counseling patients on dietary modifications, weight loss, and tobacco/alcohol cessation are recommended. Numerous epidemiological studies show a consistently protective effect of coffee with respect to lowering the incidence of HCC. One of these studies consists of a nested case-control analysis of the European Prospective Investigation into Cancer and Nutrition, which confirmed an inverse relationship between coffee intake and HCC (risk ratio of four or more cups *vs*. less than two cups of coffee per day was 0.25; 95%CI: 0.11–0.62).[67] Based on these results, the updated HCC guidelines of the European Association for the Study of

Recommendations: Prevention

- For all newborns and in high-risk patients, we recommend administering the HBV vaccine to reduce HCC risk **(Strong recommendation, high-quality evidence)**.
- In patients with chronic viral hepatitis, we recommend antiviral treatments to maintain HBV suppression, or a sustained viral response for HCV to reduce the risks of cirrhosis and HCC **(Strong recommendation, high-quality evidence).**
- As coffee consumption can decrease the risk of HCC in patients with chronic liver disease, it is recommended to encourage patients to increase their coffee intake **(Weak recommendation, moderate-quality evidence)**.

the Liver (EASL) have endorsed a statement to encourage patients with chronic liver diseases to drink coffee to decrease liver-related mortality and HCC development.[68]

SURVEILLANCE

Identifying risk factors for HCC and installing the appropriate methods for HCC surveillance in high-risk population groups are crucial to enable an early diagnosis. Diagnosing HCC at an early stage has important clinical implications, as it confers a survival benefit compared to patients diagnosed at more advanced stages of the disease.[9] This is fueled by the fact that patients with early stage HCC still have curative treatment options (e.g., liver resection, liver transplantation) at their disposal.

Target population

Surveillance for HCC is complicated by the fact that more advanced liver disease (i.e., cirrhosis) is associated with a higher HCC incidence, but simultaneously, the feasibility of curative therapy reduces with advanced liver disease.[68] This situation complicates the identification of high-risk populations in which HCC screening is advised. Nevertheless, results of a meta-analysis including 15,158 patients demonstrate that HCC surveillance is associated with improved overall survival (OS) through the detection of HCC at a very early stage (i.e., when patients are still eligible to receive potentially curative treatment).[9]

Most international guidelines for HCC state that surveillance is indicated in patients with cirrhosis and patients with chronic HBV and high-risk features. However, some important nuances should be considered in this regard.[68] Cost-effectiveness studies suggest that surveillance of HCC in cirrhotic patients is warranted.[9] However, this is not the case for all patients with cirrhosis. In fact, in patients with advanced stage cirrhosis (CPT C), or some CPT B patients, curative HCC therapies can no longer be applied when transplantation is not an option. Therefore, EASL recommends to reserve surveillance for HCC in CPT class A cirrhotic patients (as they may be candidates for resection or local ablative therapies), and CPT B and C patients who are candidates for liver transplantation (as the presence of HCC impacts the priority on the list and the transplantability of the patient).[68] Nevertheless, while a curative treatment is no longer an option for these CPT B and C patients, locoregional or systemic therapies in selected cases can still provide some clinical benefit. However, whether the latter strategy is cost-effective is subject to debate.

Patients with chronic HBV are at an increased risk of HCC, even in the absence of cirrhosis, warranting general surveillance. In a Chinese study, of more than 18,800 patients with current or previous HBV infection, 6-monthly HCC screening with alpha-fetoprotein (AFP) and ultrasound (US) showed a reduced mortality rate of 37% in the screened arm (despite adherence to the surveillance of only 60%).[9] However, the exact degree of HCC risk for non-cirrhotic HBV patients seems to be influenced by numerous factors (e.g., gender, HBV replication rate, geographical region).[9,69,70] Several prognostic models have been proposed to assess the risk of developing HCC, but none of the studies has universal applicability. In conclusion, surveillance of all patients with chronic hepatitis B without evidence of cirrhosis cannot be recommended at this time. However, it may be offered in certain high risk groups (e.g., patients above 40 years of age, patients with a family history of HCC, patients with high viral load, patients with indications of advanced liver fibrosis determined by non-invasive fibrosis markers or biopsy).[2]

It is generally accepted that all cirrhotic HCV-infected patients must undergo surveillance. For HCV patients without cirrhosis, there is no evidence supporting routine surveillance. One exception to this rule consists of chronic hepatitis C patients with bridging fibrosis in the absence of cirrhosis (Metavir F3), who are at significant risk of developing HCC and therefore, surveillance can be considered in this setting.[71]

Insights into the incidence of HCC in patients with non-viral chronic liver disease (i.e., alcoholic steatohepatitis, NASH, genetic haemochromatosis, alpha-1-antitrypsin deficiency, etc.) is limited. Nevertheless, the available data suggests that these types of HCC usually occur in the context of cirrhosis. As indicated before, NASH-related HCC can also occur in non-cirrhotic patients.[30] However, the incidence of HCC in these non-advanced patients is expected to be insufficiently high to deserve universal surveillance, especially given the large prevalence of NAFLD in the general population. In the future, more research is needed to identify high-risk patients with NASH in whom HCC surveillance could be cost-effective.

Surveillance tests

Safe and effective screening tools are needed after identifying the target population for HCC surveillance. The available methods can broadly be divided into two categories: imaging and tumor marker tests. The most commonly used imaging test for HCC surveillance consists of US, which has a sensitivity of approximately 60% and a specificity of more than 90%.[72] The sensitivity of US is influenced by several factors, including operator variability

and lesion size. With respect to the latter, a meta-analysis of 19 studies demonstrated that US has an overall sensitivity to detect preclinical HCC of 94%, but that this drops to only 63% when considering the detection of early stage HCC.[73] The detection of HCC in a background of cirrhosis is often challenging and requires sufficient operator expertise. Notwithstanding these issues, the US remains popular, mainly because it is non-invasive, easy to use, and relatively inexpensive. Other imaging techniques, such as computed tomography (CT) or magnetic resonance imaging (MRI), are more sensitive than US, but they also come with an increased cost and the need for contrast agents to achieve adequate sensitivity.

Serum tumor markers are an attractive alternative for surveillance and early diagnosis of HCC since they allow a non-invasive, objective, and reproducible evaluation. The most widely evaluated blood test for early diagnosis of HCC consists of AFP. With respect to AFP, it is important to underline that this tumor marker test was mainly tested in the diagnostic setting, and its performance as a diagnostic test should not be translated to the surveillance setting. In fact, as a tool for HCC screening, AFP proved to be suboptimal, including in Saudi patients, with low sensitivity and unsatisfactory specificity.[22,74] When combined with US in patients with active liver inflammation, AFP levels only provided an additional detection rate of 6–8%, with a significant increase in the number of false positives.[75] As such, AFP is not the perfect marker, and its use as a surveillance tool for the early detection of HCC is controversial. Although the EASL guidelines state that AFP measurements are not recommended in this setting, the American Association for the Study of Liver Diseases (AASLD) guidelines stipulate that US, with or without AFP, is the preferred surveillance tool.[68,76] The explanation for the suboptimal performance of AFP in the surveillance setting is twofold. First of all, flares of HBV or HCV infection in chronic patients or exacerbations of the underlying liver disease can lead to fluctuations in AFP levels in patients.[77] In addition to this, an important proportion of early stage HCC cancers do not present with increased AFP levels. To address this issue, several other serum biomarkers have been evaluated (des-γ carboxyprothrombin, lectin-bound α-fetoprotein, glypican 3, Golgi protein 73, and Dickkopf 1), but study results are inconsistent.[78-81] In this respect, a recent study assessed the potential of Golgi protein 73 as a diagnostic biomarker for the early detection of HCC in Saudi patients.[82] HCC patients had significantly elevated levels of serum Golgi protein 73 compared to patients with cirrhosis, non-HCC hepatitis patients and normal controls. As such, these findings indicate that Golgi protein 73 is a promising serum biomarker for HCC (sensitivity and specificity 95% and 95% for serum Golgi protein 73 [ELISA] and 100% and 95% for Golgi protein 73 mRNA [RT-PCR] *vs*. 80% sensitivity and specificity for AFP). Interestingly, the study also reported a lack of correlation between Golgi protein 73 levels and HBV/HCV positivity. Therefore, measuring

Recommendations: Surveillance

We recommend surveillance every six months for the following populations:

- Cirrhotic patients with CPT stage A and B, regardless of etiology **(Strong recommendation, high-quality evidence)**.
- Patients awaiting liver transplantation, regardless of etiology **(Strong recommendation, high-quality evidence)**.
- Treated patients with HCV-induced advanced fibrosis (F3) or cirrhosis (F4), even after achieving SVR **(Strong recommendation, high-quality evidence)**.

We suggest HCC surveillance every six months for the following populations:

- Non-cirrhotic HBV patients with high risk for HCC (age >45 years, high viral load, advanced fibrosis) **(Weak recommendation, low-quality evidence)**.
- Treated HBV patients with baseline risk factors for HCC **(Weak recommendation, low-quality evidence)**.
- Early HCC detection confers survival benefit compared to delayed detection of HCC **(Strong recommendation, moderate-quality evidence)**.
- Patients at a high risk of developing HCC, particularly patients with cirrhosis regardless of the etiology, should be entered into surveillance programs **(Strong recommendation, moderate-quality evidence)**.
- For patients requiring HCC surveillance, we recommend performing abdominal US (with or without AFP) every 6 months **(Strong recommendation, moderate-quality evidence).**
- Patients on the waiting list for liver transplantation should be screened for HCC to detect and manage tumor occurrence or tumor response **(Strong recommendation, low-quality evidence)**.
- Tumor serum biomarkers for the accurate early detection of HCC are lacking. The available data indicate that AFP is not a suitable marker in this setting. As such, we suggest against the use of tumor serum biomarkers alone **(Weak recommendation, low-quality evidence)**.

Golgi protein 73 levels is not expected to give false-positive results in non-HCC HBV/HCV patients.[82] These results warrant further investigation to estimate and clarify the role of Golgi protein 73 in the early diagnosis of HCC.

Surveillance interval

Most specialists suggest a screening interval of 6 months, based on data suggesting that the time from an undetectable lesion to grow to a 2-cm lesion is about 4–12 months.[9] A shorter interval of 3 months did not translate into any clinical benefit, and while screening with a longer interval of 12 months appeared to be cost-effective, it was found to result in fewer early stage HCC diagnoses and shorter survival.[83-85] Therefore, with the available data, 6-monthly surveillance is the preferable choice.

DIAGNOSIS

Various imaging techniques and strategies are available to facilitate a correct diagnosis, staging, and treatment of patients with HCC. In fact, thorough screening and assessment of the patient will enable the treating specialists to give an accurate prognosis and offer the best outcome for the patient.

Imaging

Imaging forms the cornerstone of the diagnostic paradigm for HCC. In fact, in cirrhotic patients, HCC can be diagnosed based on imaging findings alone.[68] This imaging-based diagnosis of HCC is based on the vascular derangement that occurs during hepatic carcinogenesis and the high pre-test probability of HCC in the setting of cirrhosis. Importantly, an imaging-based diagnosis is only valid in patients with cirrhosis and not in the non-cirrhotic setting (where pathological confirmation is required).

To diagnose HCC, contrast-enhanced imaging methods are needed. The typical hallmark of HCC consists of a combination of hypervascularity in the arterial phase (non-rim, arterial phase hyperenhancement [APHE], according to LI-RADS [Liver Imaging Reporting and Data System]) and washout during the portal venous and/or delayed phases. With respect to the type of contrast-enhanced imaging technique, only multiphasic CT and MRI are recommended. Several meta-analyses have evaluated the diagnostic performance of these two imaging modalities.[86-88] In these analyses, MRI is associated with slightly higher sensitivity compared to CT, with a specificity of 85–100%.[87] This higher sensitivity for MRI *vs*. CT is most pronounced in the detection of smaller lesions (sensitivity with MRI *vs*. CT for lesions >2 cm: 48% and 62%, respectively).[88] In a prospective comparison of both imaging modalities (N = 544), MRI was associated with a sensitivity and specificity of 72.3% and 89.4% in lesions of 2-3 cm and 70.6% and 83.2% in lesions of 1–2 cm. With CT, the sensitivity and specificity was 71.6% and 93.6% in larger lesions and 67.9% and 76.8% in lesions 1–2 cm in size.[89] This analysis also showed that combining CT and MRI resulted in a 100% specificity in lesions from 1 to 2 cm. However, this came at the cost of a drop in sensitivity to 55.1%.[89] As such, these results do not support the use of combined CT and MRI imaging. Other studies show that MRI with hepatobiliary agents has a higher sensitivity than multiphasic CT with similar specificity. Importantly, this difference proved to be particularly pronounced (and statistically significant) in small lesions.[90,91] Several studies have compared hepatobiliary agent-based MRI and MRI using extracellular contrast agents. Two meta-analyses pooling the data of different retrospective studies suggest a higher sensitivity of MRI with hepatobiliary agents.[86,87] However, two recent prospective studies came to a different conclusion and indicated that gadoxetic acid was not superior to MRI with extracellular contrast.[88,92,93] Of note, the non-invasive diagnostic criteria for HCC differ slightly with these two types of contrast agents: when using extracellular contrast agents or gadobenate dimeglumine; this is defined as APHE with washout in the portal venous or delayed phases, while for MRI using gadoxetic acid this only consists of APHE with washout in the portal venous phase.

The use of contrast-enhanced ultrasound (CEUS) in the diagnosis of HCC is controversial, mainly because this technique can misdiagnose patients with intrahepatic cholangiocarcinoma (ICC) as having HCC. In fact, the pattern of APHE followed by washout at CEUS is not specific for HCC. This pattern also occurs in approximately half of all mass-forming ICC cases with cirrhosis, which could lead to a misdiagnosis of around 1% of nodules arising in the context of cirrhosis.[94,95] To address this issue, the definition of the typical HCC hallmarks for CEUS was refined to APHE followed by a late (>60 s) washout of mild degree (this pattern is also the basis for the current CEUS LI-RADS proposal).[96] In a large retrospective study, which included more than 1,000 lesions in a cirrhotic context, the new CEUS definition showed a positive predictive value of HCC of almost 100%, without a single case of misdiagnosed ICC.[97] When CEUS is compared with either CT or MRI, its sensitivity is significantly lower, especially in nodules of 1–2 cm (mainly due to a lower detection rate of washout compared with CT or MRI).[98] Based on these findings, CEUS is not recommended as a first-line imaging technique for non-invasive diagnosis of HCC. Moreover, the use of CEUS in this setting is also not cost-efficient, as

CT or MRI are still necessary to adequately stage tumors. Similarly, fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan is not recommended for early diagnosis of HCC because of the high false-negative rate.[99] More recently, choline–PET has been introduced for the diagnosis of HCC, and initial studies suggest higher diagnostic accuracy compared to FDG PET, particularly in well-differentiated HCC.[100]

The imaging features of HCC that develop in patients without liver cirrhosis do not differ from what is seen in cirrhotic patients. However, the specificity of the previously described hallmarks of HCC (i.e., APHE and the washout) is lower in non-cirrhotic livers than in a cirrhosis context, which is due to the fact that non-cirrhotic livers can also harbor other aberrations, such as hepatocellular adenoma and hyper-vascular metastases.

Pathology

The pathological diagnosis of HCC is based on the criteria formulated by the WHO. Published in 2010, the 4th edition classifies tumors of the digestive system into five morphological subtypes of HCC: fibrolamellar HCC (FL-HCC), scirrhous HCC (S-HCC), undifferentiated carcinoma, lymphoepithelioma-like carcinoma, and sarcomatoid HCC.[101] Pathologic differential diagnostic assessment of focal liver lesions in cirrhosis includes distinguishing HCC from other primary (ICC, combined HCC/CC) and secondary metastases. Both well- and poorly differentiated hepatocellular neoplastic lesions pose diagnostic challenges. To determine malignancy in a well-differentiated HCC that morphologically resembles benign hepatocytic lesions, immunohistochemical staining for CD34 (showing diffuse sinusoidal capillarization), and a panel of glutamine synthetase (GS), glypican-3 (GPC-3), and heat shock protein 70 (HSP-70) can be used.[102,103] Both, the International Consensus Group of Hepatocellular Neoplasia and the WHO have adopted this three-marker panel in their recommendations.[104] In addition to this, reticulin special stains can be useful, as the aforementioned benign and pre-neoplastic entities generally retain a reticulin network, while this is not the case for HCC. Importantly, these stains are neither 100% specific nor 100% sensitive.[105] Therefore, a careful review of histomorphology and clinical and imaging correlation is essential to establish a firm diagnosis of HCC.

The specificity of liver biopsy-based diagnosis of HCC has been reported to reach up to 100%, but in routine diagnostics, these numbers are difficult to reach because of the differential diagnostic challenges in highly differentiated hepatocellular tumors.[106] The sensitivity of liver biopsy-based diagnosis of HCC depends on location, differentiation, and size of the lesion, as well as the expertise of the person performing the biopsy and the pathologist. In clinical practice, it is reported to be in the range of 90% for all tumor sizes.

In addition to aiding the diagnosis of HCC, immunohistological markers can also help to identify HCCs with a poorer prognosis. Markers, such as keratin

Recommendations: diagnosis

- For cirrhotic patients suspected of having HCC, we recommend using non-invasive criteria or pathology assessment to confirm the diagnosis **(Strong recommendation, high-quality evidence)**.
- For patients suspected to have HCC, we recommend performing contrast-enhanced multiphasic CT or MRI to confirm the diagnosis **(Strong recommendation, high-quality evidence)**.
- The use of CEUS in the diagnosis of HCC is more controversial, as this technique can misdiagnose patients with ICC as having HCC. As such, we advise against the routine use of CEUS to diagnose HCC **(Weak recommendation, moderate-quality evidence)**.
- Imaging-based diagnosis relies on the identification of the typical hallmarks of HCC. These hallmarks differ according to the imaging technique that is being used: APHE with washout in the portal venous or delayed phases on CT and MRI using extracellular contrast agents or gadobenate dimeglumine, APHE with washout in the portal venous phase on MRI using gadoxetic acid **(Strong recommendation, high-quality evidence)**, APHE with late-onset (>60 s) washout of mild intensity on CEUS **(Ungraded statement)**.
- Non-invasive diagnostic criteria are only valid in patients with cirrhosis or patients with chronic HBV **(Strong recommendation, moderate-quality evidence)**.
- We recommend performing a diagnostic biopsy to confirm HCC diagnosis for non-cirrhotic patients, or when imaging fails to display a specific vascular profile **(Strong recommendation, moderate-quality evidence)**.
- For pathological diagnosis of HCC, we recommend using international consensus recommendations, including histological and immunobiological analyses **(Strong recommendation, high-quality evidence)**.

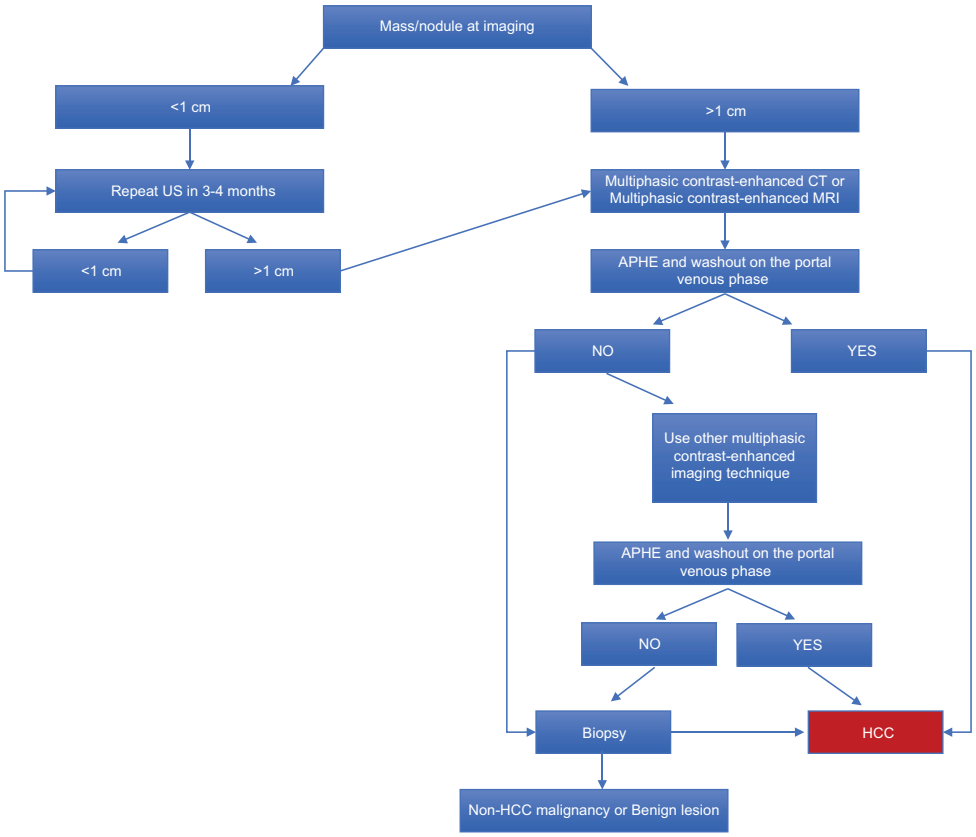


Figure 2: Algorithm for HCC diagnosis in cirrhotic patients

19 (K19), epithelial cell adhesion molecule (EpCAM), and CD133 were reported to be associated with a poor outcome in HCC.[107,108]

Taking a liver tumor biopsy does come with the potential risk of bleeding and needle track seeding. However, these complications are infrequent, usually manageable, do not affect the course of the disease, and do not have an impact on the OS of patients. In a meta-analysis looking at the bleeding risk of liver tumor biopsies, mild bleeding complications were reported in 3–4% of patients with only 0.5% requiring transfusions.[109]

Summary: HCC diagnosis

For patients with cirrhosis or chronic HBV, non-invasive diagnosis based on contrast-enhanced imaging has become a standard of care [Figure 2]. However, a biopsy of the lesion is still indicated in cases where the image-based diagnosis remains inconclusive, particularly in lesions smaller than 2 cm in diameter, in which the diagnostic performance of contrast-enhanced imaging is lower. In patients with a non-cirrhotic liver or without a history of chronic HBV, imaging alone is not sufficient for a diagnosis, and histopathological verification should be performed to confirm the diagnosis of HCC. For lesions less than 1 cm in diameter, it is recommended that follow-up imaging is obtained after 3–6 months using the same modality as the initial test. If the lesion grows in size, then the recommendations for lesions above 1 cm should be followed. If there is no growth, the lesion must be re-imaged in 3–6 months, and if no growth has been demonstrated over two years, the patient may revert to the routine surveillance program.

STAGING

Staging and prognosis

Accurate disease staging is a crucial step in the management of patients with HCC. First and foremost, adequate cancer classification allows physicians to establish a prognosis for their patients and enables the selection of the best treatment for the individual patient. In addition to this, cancer staging also helps to create a common language for researchers to exchange information and design clinical trials with comparable criteria. Since most patients with HCC also suffer from associated liver disease, their prognostic assessment should not only consider the tumor stage but also incorporate the degree of liver impairment. Additionally, the presence of cancer-related symptoms has consistently shown a negative effect on survival. Finally, to be clinically relevant, an ideal staging system should not only be able to separate patients into distinct prognostic

groups but should pair this with guidance on the optimal treatment for each subclass.[110] Several independent prognostic factors have been identified in studies evaluating the natural history of cancer and cirrhosis. Broadly, these factors can be grouped into three categories: tumor characteristics (i.e., number and size of the nodules, vascular invasion, extrahepatic spread), liver function (i.e., CPT class, bilirubin and albumin level, ascites, portal hypertension), and functional characteristics of the patient (e.g., Eastern Cooperative Oncology Group [ECOG] performance status [PS], presence of symptoms).[111]

The most commonly used staging system in oncology consists of TNM staging. However, this system has some important drawbacks in the context of HCC. Firstly, TNM staging does not incorporate information on liver function or functional status. In addition to this, pathological information is necessary for tumor staging in this system (to assess microvascular invasion), which is only available for a minority of patients with HCC.[112] To overcome these issues, several more comprehensive staging systems have been developed. Of these staging systems, only two scores include the three types of prognostic variables listed above and assign a specific treatment to the different patient subclasses: the Barcelona Clinic Liver Cancer (BCLC) staging system and the Hong Kong Liver Cancer (HKLC) staging system.[110]

The prognostic ability of the BCLC has been validated in European, American, and Asian populations,[113,114] and both EASL and AASLD have endorsed this staging system in their most recent guidelines.[68,115] Not only does this system include prognostic variables related to tumor status, liver function, and general functioning, but also considers treatment-dependent variables obtained from clinical studies.[116] BCLC is also a dynamic system that enables the incorporation of novel advances in the prognosis and treatment of HCC. In fact, since its original publication in 1999,[116] the system has been updated several times according to the results of clinical data that modified practice (e.g., incorporation of sorafenib as a first-line treatment for advanced tumors in 2008, the consideration of ablation as a first-line treatment in selected patients with solitary HCC smaller than 2 cm, etc.).[110,116]

Compared with BCLC, the HKLC system can distinguish differential prognosis between patients with mild tumor-related symptoms and those with more severe symptoms. Furthermore, the HKLC can identify patients with intermediate or advanced HCC who still may be eligible for more radical treatments.[117] However, there are several issues with the HKLC classification; for example, it uses nine substrata with significant overlap in survival between the different subgroups, and the system has not been validated in Western countries. Therefore, its use in clinical practice is limited.

Tissue and serum biomarkers predicting prognosis are less explored in patients with HCC compared to other solid tumors. Elevated AFP levels are shown to predict the risks of tumor recurrence after resection, dropout in patients on the liver transplantation waiting list, survival and tumor recurrence after liver transplantation, and the response to systemic therapies in advanced HCC.[118-121]

Treatment allocation

According to the BCLC staging system, patients with HCC can be classified into five stages (0, A, B, C, and D) [Figure 3]. The prognosis prediction in this model is defined by variables related to the tumor status (size and number of nodules, the presence/absence of invasion, nodal involvement, metastatic spread), the liver function (bilirubin level, presence/absence of portal hypertension, preservation of the liver function), and the ECOG PS of patients. The treatment allocation for every subclass is based on variables that are shown to impact the therapeutic outcome, such as bilirubin level, portal hypertension, symptomatology, and ECOG status.

BCLC stage 0: Very early HCC

BCLC stage 0 disease is characterized by the presence of a single tumor with a diameter of less than 2 cm without vascular invasion in patients with good health status (i.e., ECOG PS 0) and a preserved liver function (CPT A). Patients with very early HCC can be treated with either surgery or radiofrequency ablation (RFA). In two independent studies, the 5-year survival rate of patients with surgically resected solitary lesions <2 cm was reported at approximately 70%.[122,123] RFA is able to induce complete tumor necrosis with a safe margin. Therefore, RFA outcome is similar to what is achieved with surgery in this setting. In line with this, several cohort studies have shown a 70% 5-year survival rate when evaluating RFA in patients with very early HCC.[124] The Markov model analysis confirmed the comparable efficacy of RFA and surgery with an identical hazard ratio (HR) for OS in patients with BCLC stage 0.[125] A systematic review and meta-analysis pooling data from 17 studies also showed that RFA (N = 4,424) and surgery (N = 3,996) were associated with a similar life expectancy at 3 years and quality of life in patients with very early stage HCC. Of note, in this analysis, RFA proved to be more cost-effective than resection.[126] One potential advantage of surgery in this setting is that it facilitates a pathological evaluation of the recurrence

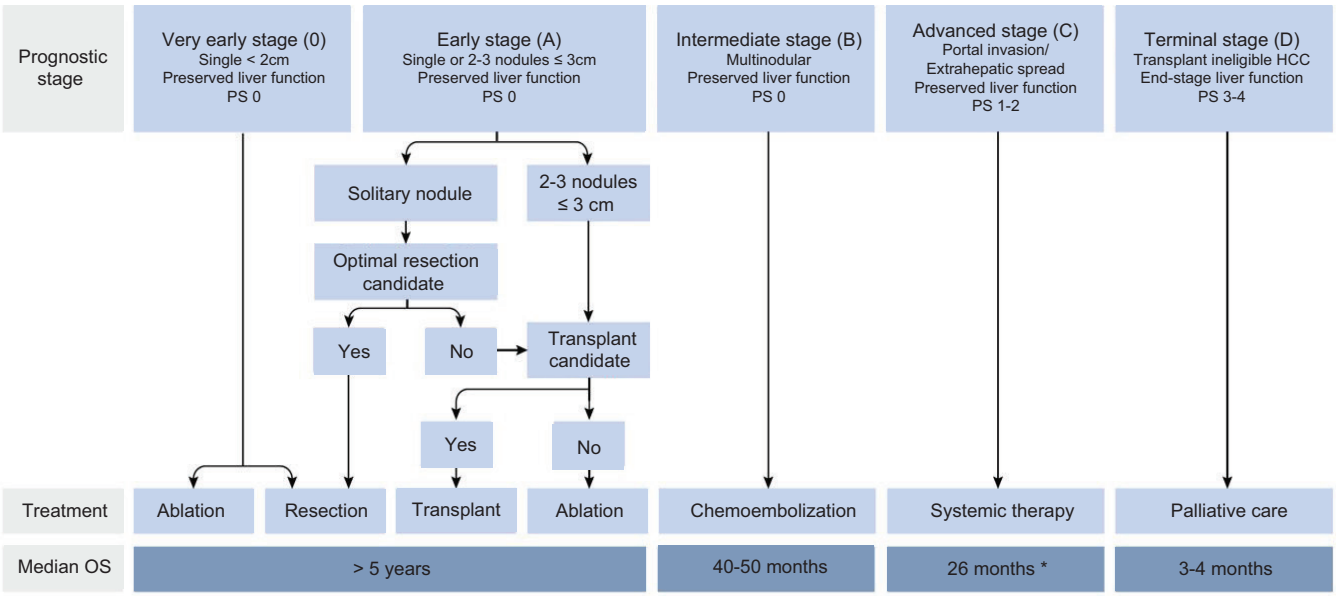


Figure 3: BCLC staging and subsequent treatment allocation for patients with HCC.[9] **the 26 months median OS obtained with sequential use of sorafenib and regorafenib*

risk (e.g., microvascular invasion, poor differentiation, etc.). However, this argument is only valid in patients who might become candidates for liver transplantation. In fact, when pathological examination of the surgical specimen reveals a high risk for recurrence, a transplant may be indicated. The choice for RFA or surgery in this situation is at the discretion of the treating center.

BCLC stage A: Early HCC

BCLC stage A encompasses patients with a single tumor >2 cm or three nodules <3 cm in diameter, with an ECOG PS of 0 and a preserved liver function. For these patients, the available treatment options consist of surgery, RFA, and transplantation.[127] With these treatment modalities, the 5-year survival rate of these patients ranges from 50 to 70%.[127] The absence of clinically relevant portal hypertension (defined as HVPG ≤10 mmHg) and normal bilirubin levels are key predictors for survival.[128-130] For patients with stage A disease, who do not present with a solitary lesion, liver transplantation or RFA is the preferred first-line treatment options.

BCLC stage B: Intermediate HCC

Patients with multiple nodules (i.e., more than three lesions), HCC without vascular invasion or extrahepatic spread, a preserved liver function and an ECOG PS of 0 are classified as BCLC stage B.[110,127] If left untreated, the 2-year survival rate of these patients is 49%.[131] Transarterial chemoembolization (TACE) is the initial treatment of choice in these patients. This recommendation is based on the results of two randomized controlled trials (RCT) and one meta-analysis.[132-134] If patients are adequately selected, and with the use of state-of-the-art TACE protocols, a median OS of 40–47 months can be achieved.[135,136]

BCLC stage C: Advanced HCC

Patients with advanced stage HCC disease (BCLC-C) have one or more of the following features: extrahepatic spread, macrovascular invasion, and mild cancer-related symptoms (ECOG PS 1-2). When left untreated, these patients have a poor prognosis with a median OS of only 6–8 months and only a quarter of patients being alive at the 2-year landmark.[131] Over the last decade, major advances were made in the treatment of these patients with the approval of several life-prolonging systemic treatments, such as the multi-tyrosine kinase inhibitor (TKI) sorafenib.[137] The positive results obtained with sorafenib in these patients paved the way for a long list of randomized trials evaluating novel targeted therapies in patients with advanced HCC. These studies will be discussed in detail in the systemic treatment section of these treatment guidelines.

BCLC stage D: Terminal stage HCC

Patients with end-stage HCC have a very poor functional status (ECOG PS 3-4), reflecting a severe tumor-related disability. The median OS for patients with end-stage HCC is only 3–4 months, with no more than 11% of patients surviving beyond 1 year.[131] In this setting, it is important to involve the palliative team at a very early stage, particularly because many physicians are reluctant to take adequate palliative measures (e.g., pain control) in patients with advanced cirrhosis, or a very impaired liver function because of concerns of side effects. More details on the optimal management of these patients can be found in the section on palliative treatment.

Summary: HCC staging

- Adequate cancer staging allows physicians to establish a prognosis for their patients and enables the selection of the best treatment for the individual patient.
- The prognostic ability of the BCLC classification has been validated in several populations and both EASL and AASLD have endorsed this staging system in their treatment guidelines.
- The BCLC staging system classifies HCC patients into five stages. The prognosis prediction in this model is defined by variables related to:
  - tumor status (size and number of nodules, the presence/absence of invasion, nodal involvement, metastatic spread).
  - liver function (bilirubin level, presence/absence of portal hypertension, preservation of the liver function).
  - ECOG PS of patients.
- The treatment allocation for every subclass is based on variables that were shown to impact the therapeutic outcome, such as bilirubin level, portal hypertension, symptomatology and ECOG status.

TREATMENT

HCC is a complex disease with a large number of potentially useful treatments. Therefore, patients should be managed by multidisciplinary teams involving hepatologists, surgeons, interventional radiologists, pathologists, and oncologists. In order to achieve the optimal therapeutic effectiveness and ideal outcome, careful selection of candidates for each treatment option is of pivotal importance.

Liver transplantation

From an oncologic perspective, liver transplantation is theoretically the best treatment option, since total hepatectomy eliminates unrecognized intrahepatic metastasis as well as the possibility of *de novo* HCC arising from the underlying liver disease, and it removes cirrhotic liver tissue.

Patient selection

Liver transplantation was established as an effective treatment for HCC in a landmark study by Mazzaferro *et al.* in 1996.[138] Transplantation when performed in the early stage of the disease (defined as one lesion ≤5 cm or 2–3 lesions ≤3 cm each, and absence of gross vascular invasion, metastases or lymph nodes involvement), leads to a 75% 4-year survival of patients, with a recurrence rate of less than 10–15%.[138] As such, the outcome with liver transplantation was comparable to what was obtained in non-HCC patients with cirrhosis. Following this publication, the so-called "Milan criteria" were widely accepted as the framework in which liver transplantation can be offered to patients with HCC. In other observational studies, the outcome of liver transplantation in HCC patients meeting the Milan criteria was excellent, with a 5-year OS rate ranging from 65 to 80%. Of note, this is significantly better than what was reported in patients beyond these criteria (OR[95%CI]: 1.68[1.38–2.03]).[139] Importantly, one should underscore that these criteria were developed in a time when the waiting list for liver transplantation was approximately six months. Over the years, these waiting times have become increasingly longer resulting in a high proportion of patients dropping off the waiting list (due to extrahepatic spread, increase in the size of the tumor beyond transplantation criteria, vascular invasion, etc.) and thus, decreasing the long-term outcome according to the intention-to-treat principle. In addition, many experts perceive the Milan criteria to be too restrictive, excluding a subset of patients who may benefit from liver transplantation, and proposed different expanded criteria.

It is beyond the scope of these guidelines to discuss all these criteria, but it is worthwhile to mention the criteria that have been externally validated. The University of California in San Francisco (UCSF) expanded beyond Milan criteria to include patients with a single nodule ≤6.5 cm or ≤3 nodules with the largest ≤4.5 cm and total sum of diameters ≤8 cm.[140] The outcome after liver transplantation in patients falling into these criteria was comparable to what was achieved with the Milan criteria. However, other studies failed to consistently reproduce this result.[141,142] For example, in a retrospective study, the 5-year OS rate was 45.6% for patients who met the UCSF criteria but not the Milan criteria, as compared to 60.1% for patients who met both criteria.[141] The up-to-seven criteria is another criterion that has expanded on the liver transplantation criteria for HCC patients. These criteria were based on the data of 1,112 patients who underwent liver transplantation for HCC at different centers worldwide, despite exceeding the Milan criteria. With these criteria, the cutoff value is set to seven, and the score is calculated by considering the total number of lesions plus the diameter (in cm) of the largest nodule (e.g., 4 nodules + larger diameter 3 cm corresponds to an up-to-seven score of 7). When compared with the Milan criteria, these up-to-seven scored patients showed no difference in survival after transplantation. Unfortunately, the up-to-seven score proved to be inadequate in patients with microvascular invasion, which limits its potential use

in clinical practice (as this cannot be assessed before the transplantation). A third noteworthy method to select HCC candidates for liver transplantation combines the total tumor volume (TTV) with the AFP level. In a prospective study, it was shown that candidate selection could safely be expanded to patients with a TTV ≤115 cm^3 and an AFP level ≤400 ng/ml, without macrovascular invasion or extrahepatic disease.[143]

A recent, large analysis from the European Liver Transplant registry demonstrated that vascular invasion is the most predictive variable of poor outcome after liver transplantation for patients with HCC. In this analysis (*N* = 23,124), HCC patients without evidence of microvascular invasion who fulfilled the Milan criteria had a 5-year OS of 73.2% after liver transplantation, while this was 70.7% if they fell within the up-to-seven criteria. However, patients who did not meet Milan or up-to-seven criteria, and who did not have vascular invasion had a 5-year OS rate of 65.8%, which is still acceptable for most liver transplant centers.[144]

Organ allocation and donor selection

The limited availability of donor livers determines the adoption of criteria, whereby the transplantation priority is based on the risk of waiting list mortality, which is based on the model for end-stage liver disease (MELD) score. This system takes into account the international normalized prothrombin ratio in combination with serum bilirubin and creatinine levels.[145] However, these criteria were originally designed in patients with cirrhosis rather than in patients with a liver malignancy. In fact, HCC patients often have a well-compensated liver function, which results in a low MELD score. In addition, the dropout risk from the waiting list in HCC patients is mainly related to tumor progression rather than the occurrence of liver failure. Therefore, modified scoring systems have been developed for patients with HCC on liver transplant lists. These "prioritization scores" for patients with HCC take into account characteristics of the tumor (size, number, and AFP level) and the waiting time (additional points are given to patients who have had long waiting periods).[146]

As indicated before, the major limiting factor of liver transplantation in HCC is the scarcity of donated organs, with the additional problem of balancing the distribution of available organs equally among cancer and non-cancer indications. Probably the most commonly used method to enlarge the organ pool consists of living donor liver transplantations (LDLT). This modality is especially valuable in regions where waiting lists are long, and patients are at a high risk of delisting due to tumor progression (like in the KSA). In fact, as LDLT can virtually be done without any delay, the risk for dropout due to progression is significantly lower. In this respect, Bhangui *et al.* reported a median waiting time for LDLT patients of 2.8 months, which is significantly shorter than the 7.9 months median waiting time seen with deceased donor liver transplantation (DDLT) in the same institution.[147] With respect to outcomes, a French multicenter study comparing LDLT (*N* = 79) and DDLT (*N* = 782) in cirrhotic HCC patients did not reveal a significant difference in 5-year OS (73.2% *vs.* 66.7%) or post-transplantation HCC recurrence (10.9% *vs.* 11.2%, respectively). Importantly, this study also revealed a significant difference in the delisting rate between both procedures: 20.7% for DDLT as compared to 0% with LDLT.[148] Living donors have become the main source for organ transplantation in the KSA. Early reports from the leading living donor center in the KSA revealed similar outcomes with LDLT compared to DDLT. In this analysis, data from 491 patients (222 LDLT, 269 DDLT) revealed a 5-year OS rate of 85% when the MELD score was below 25 (78% in patients with a MELD score above 25), with no difference between cadaveric and living donations.[149] In later reports (*N* = 642), higher biliary complication rates were reported with LDLT compared to DDLT (20% *vs.* 5%), but LDLT did induce a higher 5-year OS rate than cadaveric transplants ($P = 0.006$).[150] Liver grafts from living donors are typical of good quality, with minimal fat and reduced ischemic time. In 2019, Shimamura *et al.* formulated new, expanded criteria for the use of LDLT in patients with HCC.[151]

Neoadjuvant therapies and liver transplantation: Bridging and downstaging

Neoadjuvant therapy for HCC patients in the context of liver transplantation encompasses two treatment strategies: bridging therapy aims at mitigating the dropout of patients (estimated to be 10–20% of patients on liver transplantation waiting list[152,153]) that are on a liver transplantation waiting list, while downstaging treatment aims to bring patients whose tumor burden is outside the accepted criteria for liver transplantation to within an acceptable criterion.

Bridging therapy depends on the tumor location, size, number, and hepatic function and can consist of liver resection, percutaneous ethanol injection (PEI), RFA, microwave ablation (MWA), TACE, or stereotactic body radiotherapy (SBRT). Unfortunately, there are no randomized controlled data available in this setting. The overall results of bridging with TACE are rather inconsistent. A systematic review concluded that good

quality evidence was not available to indicate that TACE improves post-transplantation survival or decreases waiting list dropout rates.[154] In 2017, a retrospective review of 379 patients with HCC listed for liver transplant showed similar dropout rates with RFA, TACE, and SBRT, with similar rates of postoperative complications.[155] Overall, outcomes with these different treatment options in the bridging setting have been inconsistent. However, since beneficial effects were frequently reported, it seems wise to consider this option in HCC patients on waiting lists to undergo a bridge therapy (particularly for patients with ≥T2 disease and an excepted waiting time that exceeds 6 months).[156] Also, several studies suggest that a response to locoregional therapies for HCC patients while waiting for transplantation is correlated with a lower rate of post-liver transplantation cancer recurrence.[157]

In an attempt to offer more patients the potential curative option of liver transplantation, several locoregional therapies have been used to downstage patients with a higher tumor burden within the Milan criteria. Multiple studies have demonstrated that successful downstaging of HCC reduces tumor recurrence with a comparable survival rate after grafting compared to patients meeting the Milan criteria at the beginning.[158,159] There is no consensus on the optimal treatment modality that should be used for downstaging. However, most of the data in this setting were generated with TACE and RFA. A systematic review on downstaging for HCC, including the data of 950 patients, showed an overall success rate of 48% (no difference between TACE and RFA), while other reports suggest higher success rates (60%) when different strategies are combined (TACE plus either RFA or radioembolization).[160] During the 2019 annual AASLD meeting, Tabrizian *et al.* reported in a USA multicenter analysis (N = 2,529) the 10-year post-transplantation survival and recurrence rates were 60.5% and 14.3% in patients who met the Milan criteria (N = 2,086) as compared to 52% and 20.4% in the patient group downstaged to within Milan criteria (N = 330). In patients beyond Milan criteria who were not downstaged (N = 110), the 10-year OS rate was 38.8%, with 46.7% of patients having a recurrence during that timeframe. Thus, downstaging prior to liver transplantation can exhibits excellent 10-year survival outcomes for patients who are downstaged to within the Milan criteria.[161]

Post-transplantation disease recurrence

The recurrence rate of HCC after liver transplantation is estimated to range from 10 to 20%.[162,163] As indicated earlier, this risk of recurrence seems to increase with less stringent transplantation criteria.[139] Several factors are associated with post-transplantation recurrence, including microvascular invasion and elevated AFP levels. Different models have been developed to predict HCC recurrence after liver transplantation, of which the Risk Estimation of Tumor Recurrence after Transplant (RETREAT) score is most commonly used. The RETREAT score assigns 0–3 points for increasing AFP levels, 2 points for the presence of microvascular invasion, and 0–3 points for the increasing size of the largest viable tumor diameter plus the number of viable tumors for a total score of 8. A RETREAT score of 0 is predictive of a 1- and 5-year recurrence risk of only 1.0%, while a score of five or higher predicted 1- and 5-year recurrence rates of 39.3% and 75.2%, respectively.[164] Accurate models to predict HCC recurrence can help tailor surveillance after liver transplantation. In fact, high-risk patients can undergo more frequent surveillance imaging, while low-risk patients may be able to reduce or even avoid unnecessary surveillance imaging.

Data with inhibitors of the mammalian target of rapamycin (mTOR), such as sirolimus and everolimus, show that these agents can inhibit the growth and metastatic progression of HCC.[165] Thus, a meta-analysis showed that sirolimus-based immunosuppression significantly decreases the overall tumor recurrence and recurrence-related mortality in HCC patients who underwent liver transplantation.[166] However, a more recent prospective randomized controlled phase III trial comparing sirolimus with sirolimus-free immunosuppression after liver transplantation, failed to show a difference in 5-year disease-free survival between both arms.[167]

Studies on the use of systemic therapies (i.e., sorafenib) as adjuvant therapy for HCC patients who underwent liver transplantation failed to show an advantage in terms of recurrence risk reduction.[168]

Liver resection

Liver resection has been one of the main treatments for HCC for many decades. However, from the oncological perspective, it is inferior to transplantation in the sense that it cannot guarantee the removal of nonvisible tumor and microscopic satellite lesions. However, organ shortages leading to long transplantation waiting lists make liver resection a more practical treatment option for the majority of patients. Importantly, in well-selected candidates (patients with single tumors and well-preserved liver function), resection offers long-term survival comparable to liver transplantation, and at a lower cost.[9,169]

Hepatic resection is the treatment of choice for HCC patients without cirrhosis or in patients with well-compensated cirrhosis (CPT A without clinically relevant portal hypertension) in whom major resections

Recommendations: Liver transplantation

- For patients with HCC, we recommend using a multidisciplinary approach involving hepatologists, surgeons, radiologists (including interventional radiologists), pathologists, and oncologists. **(Strong recommendation, low-quality evidence)**.
- For HCC patients who meet the Milan criteria but unsuitable for resection (single nodule ≤5 cm or ≤3 lesions, none >3 cm and absence of gross vascular invasion, metastases or lymph nodes involvement), we recommend liver transplantation as a first-line treatment **(Strong recommendation, high-quality evidence)**.
- For patients who do not meet the Milan criteria but are successfully downstaged, we suggest assessing for liver transplantation **(Weak recommendation, moderate-quality evidence)**.
- For patients with extrahepatic tumor spread or macrovascular tumor invasion, we recommend against liver transplantation **(Strong recommendation, high-quality evidence)**.
- For HCC patients on the liver transplant waiting list, we recommend the use of locoregional treatments to reduce waiting list dropout **(Weak recommendation, low-quality evidence).**
- LDLT is a valuable alternative to DDLT, especially in regions where waiting lists are long, and patients are at a high risk of delisting due to tumor progression (as in the KSA) **(Strong recommendation, moderate-quality evidence)**.
- For HCC patients who underwent liver transplantation, we suggest against the use of adjuvant sorafenib systemic therapy **(Strong recommendation, moderate-quality evidence)**.
- For HCC patients who underwent liver transplantation, we suggest tailoring surveillance based on accurate models to predict HCC recurrence **(Weak recommendation, moderate-quality evidence)**.

can be done without life-threatening complications. In a small 2005 study, including 33 non-cirrhotic HCC patients without underlying viral hepatitis, the outcomes with liver resection were good with a 1- and 3-year OS rate of 87% and 50%, respectively.[170] Data from 77 patients undergoing liver resections in a tertiary center in KSA, showed a median OS of 13.2 months, with a 90-day postoperative mortality of 5.2%.[171] As indicated earlier, NAFLD-related HCC can develop in the absence of cirrhosis.[31] In this context, it is important to note that data on the use of liver resection in HCC patients with NAFLD or metabolic syndrome entails a significant rate of severe complications (13-20%). A possible explanation for this could lie in the fact that patients with NAFLD often present with comorbidities such as hypertension, diabetes, obesity, and cardiac problems. However, post-surgical mortality rates in this setting were low at only 2%.[172,173] With respect to outcome, the long-term survival after liver resection was shown to be higher in patients with NAFLD-related HCC than in patients with a viral etiology (5-year OS: 65.6% *vs*. 61.4%).[173]

In 2012, EASL formulated the following criteria to define an optimal cirrhotic HCC candidate for liver resection: a solitary tumor with a well-preserved liver function and a hepatic vein to portal system gradient of ≤10 mmHg or a platelet count of ≥100,000 platelets per ml.[68] While these criteria are still valid for less experienced centers, significant improvements in the (peri)operative management of HCC patients have led to a broadening of the liver resection indication beyond these stringent criteria.[174] CPT A patients may have CSPH that affects the outcome of resection of a small tumor.

Underlying liver function

One of the major factors impacting the feasibility of liver resection is the underlying liver function of the patient. CPT scoring remains the most commonly used method to measure the liver function, with stage A and well-compensated stage B patients being the population for whom liver resection can be considered. However, several other parameters can determine more accurately the risk of post-surgery liver failure. In Europe and the USA, portal hypertension and elevated bilirubin level (more than 1 mg/dl) are commonly used factors to assess the risk for post-resection liver decompensation.[68,89] In this setting, clinically significant portal hypertension (CSPH) is defined as the presence of an HVPG more than 10 mmHg. In a systematic review and meta-analysis from 2015, CSPH was shown to significantly increase the risk of 3- and 5-year mortality (OR[95CI]: 2.07[1.51-2.84]) and clinical decompensation (OR[95%CI]: 3.04[2.02–4.59]) after surgery for HCC.[130] Patients without CSPH and normal bilirubin levels achieve 70% survival at 5 years, whereas the survival is 50% or less when both adverse factors are present.[129] However, some nuance is needed with respect to the predictive value of CSPH. Studies indicate that CSPH *per se* should not be considered as an absolute contraindication for hepatic resection. In fact, limited resections in patients with a preserved liver function and moderate CSPH can result in competitive outcomes.[175] As such, the role of portal hypertension should always

be balanced with the extent of the hepatectomy and liver function indicators.

Hepatic indocyanine green kinetics (ICG) test (often used in Japan) offers an additional informative tool for liver resection planning. ICG is an inert, water-soluble, fluorescent tricarbocyanine dye with a high hepatic extraction rate in healthy individuals (usually above 70%).[176,177] The retention rate of ICG at 15 min (ICGR15) can be part of the decision making algorithm for liver resection in cirrhotic patients, limiting resection and segmentectomy to patients with an ICGR15 below 20–25% and 30–35%, respectively.[176] Finally, liver stiffness measurements with elastography to assess the fibrosis grade in the liver can be used to evaluate a patients' eligibility for liver resection. In this respect, higher liver stiffness (>12–14 kPa) was found to be associated with worse post-hepatectomy outcomes.[178] Recently, non-invasive markers of fibrosis, the AST–platelet ratio index (APRI) and the fibrosis-4 score, were also found to be associated with higher perioperative mortality.[179]

Tumoral spread and location

A first clear contraindication for liver resection consists of extrahepatic spread. In addition, most groups also restrict the indication for resection to patients with a single tumor, as multifocality is associated with a higher recurrence rate and impaired survival.[129] However, HCCs with multiple nodules are not a contraindication for liver resection *per se*, as long as the criteria with respect to liver function, PS and the remnant liver volume are met, particularly for patients with no more than three nodules with a diameter of ≤3 cm each for whom liver transplantation or RFA is not an option. In fact, several studies have yielded competitive survival results with liver resection in patients with multifocal disease.[180,181] In 1,066 cirrhotic patients with multinodular HCC treated with surgical resection, the 5-year OS rate was 34.6%, with a total tumor lesion size ≥8 cm and microvascular invasion being associated with a worse outcome.[182] Therefore, liver resection might also be an effective treatment option for BCLC A patients with multifocal tumors who meet the Milan criteria and have a sufficient liver function (CPT A and MELD ≤9) and a good PS (ECOG 0-1). The proximity of the different lesions also needs to be considered (i.e., can they be removed at the same time).

Vascular invasion

Vascular invasion, most commonly presenting as portal vein tumor thrombus (PVTT), is an ominous prognostic factor in HCC patients. It is often interpreted as metastatic disease, and hence most international guidelines recommend palliative treatment. HCCs with PVTT are often large in size and multifocal, with a limited remnant liver function and high level of serum AFP levels.[183] As a result, most centers will advise against offering aggressive surgical resection or liver transplantation to HCC patients with PVTT. The reported outcome of liver resection in this setting varies with 5-year OS rates ranging from 10 to 41%.[184] However, in recent years there have been important advances in the way HCC patients with PVTT are managed. PVTT can be graded as PV1 (segmentary), PV2 (secondary order branch), PV3 (first-order branch), or PV4 (main trunk/contralateral branch).[185] Japanese data demonstrate that as long as the PVTT is limited to the first-order branch, liver resection is associated with a longer survival outcome than non-surgical treatment, offering a median OS of more than 4 years.[186] In a retrospective Italian study, the 3- and 5-year OS rates were 30.1% and 20%, respectively, for HCC patients with major vascular invasion (all PV classes) undergoing liver resection.[187] Recently, two randomized trials indicated a significant survival benefit with (neo) adjuvant radiotherapy in resectable HCC patients with PVTT.[188,189] In the first trial, 52 HCC patients with PVTT, postoperative radiotherapy (50 Gy over 25 fractions) after an R0 resection showed a significant improvement in the 12-month disease-free survival (DFS) rate (15.3% *vs.* 3.7%; $P = 0.001$) and was associated with a significantly better 12-month OS rate (76.9% *vs.* 26.9%; $P = 0.005$).[189] In the second trial, a similar postoperative DFS and OS benefit was seen for HCC patients with PVTT receiving neoadjuvant radiotherapy compared to patients who only underwent surgery.[188]

However, in the absence of a head-to-head comparison of liver resection and systemic therapy or locoregional therapy in this setting, liver resection should not be considered to be a standard-of-care and should only be used in the context of a clinical trial.

Surgical procedures

The classical way to perform a liver resection consists of open, laparotomic surgery. However, in recent years, protocols have been developed for minimally invasive procedures (laparoscopic, robotic). In a meta-analysis, including data from 5,203 patients with HCC, laparoscopic, and open surgery were associated with comparable OS and recurrence rates, with a lower amount of blood loss and lower morbidity for the laparoscopic approach.[190] Laparoscopic surgery is of particular interest for the removal of smaller tumors (2 cm or less), located in superficial-peripheral areas of the liver. While in this setting, RFA is often the first-line treatment of choice (cost-effective, milder impact on liver 'function). Studies demonstrate that laparoscopic or robotic liver resection for very early and early HCC

located in superficial or anterolateral liver positions is associated with fewer complications and shorter hospital stays than a traditional open resection, while it achieves competitive oncologic outcomes as RFA.[191,192] Similar efficacy and safety outcomes were seen in a Saudi review when comparing laparoscopic liver resection with open surgery on patients with HCC.[193]

In the context of parenchyma-preserving resections, there is an ongoing discussion on the role of true anatomic (segment oriented) *vs*. non-anatomical resections (wedge resections) (particularly in the treatment of smaller lesions). Recently, at least two meta-analyses have addressed this issue and arrived at the same conclusion regarding the superiority of anatomic resections from an oncologic standpoint (higher 5-year DFS rates).[194,195] However, whether these findings should result in a general recommendation to always opt for an anatomic resection is subject to debate, especially given the fact that this procedure may result in a major resection with a small liver remnant. One could recommend performing an anatomic resection whenever possible, particularly when a parenchyma-preserving outcome is feasible. However, for patients with peripheral tumors, we suggest opting for a non-anatomic resection, given the fact that a complete resection (margin negative) with sparing of the liver parenchyma provides the best long-term results for this population.

Disease recurrence after liver resection

Unfortunately, tumor recurrence, including true recurrence due to dissemination and *de novo* tumors within the oncogenic liver, complicates 50–70% of cases at 5 years. Several strategies to prevent and treat HCC recurrences after surgery have been evaluated in different trials. Unfortunately, none of these trials yielded convincing results. For example, (neo)adjuvant systemic chemotherapy and chemoembolization did not show any efficacy. With respect to the latter, a meta-analysis even indicated that preoperative TACE could have a detrimental effect, as intra-tumoral necrosis induced by TACE can weaken the adhesive potential of the tumor. In turn, this can facilitate the release of cancer cells from the primary tumor and dislodgment into the bloodstream, which increases the risk for postoperative recurrence.[196] Adjuvant retinoids, ¹≥¹I-lipiodol' to'¹³¹I-lipiodol'. interferon can produce promising results but have not been studied further.[197] More recently, an RCT (STORM) comparing sorafenib with placebo as adjuvant therapy following liver resection or ablation failed to show any benefit.[168] Adoptive immunotherapy reduced HCC recurrence while increasing recurrence-free survival (RFS) and OS after curative treatment.[198-200] These studies require external validation but offer potential efficacy as immunotherapy, and currently, several ongoing phase III trials are exploring different immune checkpoints in this setting. Therefore, there is currently no scientific basis to support adjuvant therapy after liver resection.

Ablation

Tumor ablation is a widely accepted treatment option for patients with early stage HCC. This is mainly based on the fact that a large proportion of patients with HCC are unsuitable for surgical therapies due to the extent of the disease, poor hepatic reserve, or coexistent morbidities. Over the past 30 years, several methods for chemical or thermal tumor destruction have been developed. The primary objective of all the available ablation techniques is to induce complete necrosis of the liver tumors. This necrosis can be obtained by chemical (absolute alcohol or trichloracetic acid) or physical means (cryoablation, RFA, MWA, or injection of hot saline). In the majority of patients, ablation procedures can be performed with a

Recommendations: Liver resection

- For non-cirrhotic HCC patients, who are good surgical candidates, we recommend liver resection as the treatment of choice **(Strong recommendation, low-quality evidence)**.
- For cirrhotic patients with HCC, we recommend assessing liver function, the extent of the resection and vascular invasion to determine suitability for liver resection **(Strong recommendation, high-quality evidence)**.
- We recommend liver resection for single HCC of any size in selected cases and in particular for tumors between 2 and 5 cm, when hepatic function is preserved, and sufficient remnant liver volume is maintained **(Strong recommendation, moderate-quality evidence).**
- For HCC patients who underwent liver resection, we suggest against the use of adjuvant systemic therapy **(Strong recommendation, high-quality evidence)**.
- For patients who underwent liver resection with curative intent, we recommend follow-up every 3–4 months after resection because of high rates of treatable recurrence (**Strong recommendation, high-quality evidence)**.
- Since CPT A patients may have CSPH that affects the outcome of resection of a small tumor, we recommend assessing portal hypertension in patients with good liver function **(Ungraded statement)**.

percutaneous approach under image guidance, but in some cases, a laparoscopic procedure is warranted.[201] In these guidelines, the most widely available ablation techniques will be addressed in more detail: PEI, RFA, and MWA.

Percutaneous ethanol injection

PEI was the first ablation modality widely accepted in the management of HCC. With this technique, 95% absolute ethanol is injected into the tumor under US or CT guidance, which induces coagulative necrosis of the lesion as a result of cellular dehydration, protein denaturation, and chemical occlusion of small tumor vessels. Its wide acceptance is based on the ease of treatment, minimal and inexpensive therapeutic equipment required, and good clinical results. In fact, PEI is associated with an excellent performance in the treatment of smaller HCC lesions (<2 cm), where necrosis rates of >90% are achieved.[202] More recently, PEI was associated with a comparable 5-year OS rate as RFA in patients with HCCs <2 cm, despite higher recurrence rates (5-year recurrence-free survival: 73.3% *vs.* 49%; $P = 0.023$).[203] In larger tumors, however, the performance of PEI is suboptimal. In fact, in most HCCs, PEI is only able to induce incomplete necrosis, resulting in high local recurrence rates. Thus, several meta-analyses comparing PEI with RFA have indicated a superior OS and RFS with RFA, particularly for tumors >2 cm.[204-206] Therefore, RFA has largely replaced PEI as the preferred ablation technique in the treatment of HCC. However, RFA cannot be applied in all patients (e.g., RFA is not suitable in HCCs in proximity to the gallbladder, stomach, colon, or other viscera) depending on the local experience and in these situations, PEI represents a feasible alternative (in addition to laparoscopic RFA in some cases).

Radiofrequency ablation

RFA causes cellular death by thermocoagulation necrosis. With this technique, frictional heat is generated using high-frequency alternating current. Depending on the size and the shape of the needle tip that is used, a spherical ablated area with a diameter of 2–5 cm is generated in about 10–30 min. Importantly, the zone of active tissue heated by RFA is limited to just a few millimeters surrounding the active electrode, while the remainder of the ablation zone is heated via thermal conduction.[207] As such, it is not surprising to see that the efficacy of the treatment reduces with an increase in the size of the target area (the maximum result is obtained for diameter less than 3.5 cm).

RFA has been extensively studied as a first-line treatment for patients with early HCC. In a retrospective study, 162 cirrhotic HCC patients with a maximum tumor diameter of 5 cm (CPT A or B) undergoing RFA, had a 5-year OS rate of 67.9%, with a quarter of patients being recurrence-free at the 5-year landmark. Several studies have compared the efficacy of RFA to surgical resection in patients with early HCC. Similar OS results were obtained (although the 3-year DFS rate was higher with resection than with RFA: 53% *vs.* 24.7%) in a retrospective analysis comparing the outcome of 129 HCC patients treated with surgical resection with 57 patients treated with RFA.[208] A second retrospective analysis also demonstrated showed that both treatment (liver resection $N = 273$ and RFA $N = 331$) strategies were associated with a comparable OS (5- and 10-year OS rates of 87.6% *vs.* 82.1% and 59% *vs.* 61.2%, respectively), despite the fact that liver resection induced a lower rate of HCC recurrence than RFA (5- and 10-year RFS: 60.6% *vs.* 39.4% and 37.5% *vs.* 25.1%, respectively) in 604 patients with a single HCC < 3 cm.[209] Overall, these studies indicate that although RFA carries a higher risk of recurrence than hepatic resection, it provides similar OS probabilities in patients with a single small HCC tumor. A recent Cochrane review also concluded there to be no evidence for a difference in mortality at maximal follow-up between RFA and surgery, while the proportion of patients with HCC recurrence was lower with liver resection.[210]

In the absence of a survival difference between RFA and surgery, it is important to assess which of the two procedures is most cost-effective. For very early HCC and in the presence of two or three nodules ≤3 cm, RFA is more cost-effective than resection. In contrast, for single, larger early stage HCCs, surgical resection remains the best strategy to adopt as survival rates are better at an acceptable increase in cost.[126] With respect to prognosis, surgery and ablation are influenced by the same factors, namely liver dysfunction and tumor size. However, the weight of these two factors differs significantly between treatment modalities. In fact, while the prognosis after surgery is more heavily affected by the progression of liver dysfunction, RFA suffers a more abrupt drop in effectiveness with increasing tumor size than surgery.[211] Based on the available literature, RFA should be considered as a preferred first-line treatment for patients with HCC ≤2 cm. However, when the tumor is larger, particularly >3 cm, RFA is characterized by high incomplete ablation and high local recurrence rates. This statement is supported by a meta-analysis of 95 studies, including 5,224 liver tumors treated by RFA, which showed an overall local recurrence rate of 12.4%. However, local recurrence was substantially more common following the treatment of tumors >3–5 cm (24.1%) or >5 cm (58.1%) in diameter.[212]

The use of RFA in HCC patients raises a debate when treating subcapsular HCCs. In fact, initial studies suggest

lower effectiveness in these patients, with a higher risk for complications. However, results of a propensity score-matched study, including 508 patients, did not show a difference in OS, local tumor progression, or complication rate with RFA in patients with subcapsular or non-subcapsular tumors.[213]

Microwave ablation

MWA is based on dielectric heating, a phenomenon that occurs when an imperfect dielectric material is exposed to an alternating electromagnetic field.[214] Compared to RFA, MWA has some theoretical benefits: the target that can be treated is larger because MWA produces a larger area of necrosis, the time of the treatment is shorter, and MWA is less influenced by inhibitory effects of neighboring tissues (as it is not dependent on thermal conduction of surrounding tissue).[214] One of the largest studies to evaluate the performance of MWA in the treatment of HCC consists of a single-center retrospective analysis of 219 HCC patients treated with MWA, in which a total of 340 tumors with a median tumor size of 3.2 cm were treated, and MWA (laparoscopic in 97%) induced a complete ablation in 97.1%. At 2 years, 61.5% of patients were still alive and the rates of local recurrences were low (8.5% at 10.9 months of median follow-up).[215] Importantly, MWA is a well-tolerated technique with a low rate of major complications (2.6% among 1,136 patients over a 13-year period).[216]

Recently, a meta-analysis confirmed that MWA could significantly shorten operative time, reduce intraoperative blood loss, and have fewer complications compared with hepatic resection. However, the OS, DFS, and local tumor recurrence proved to be significantly better with resection than with MWA. Suggesting that MWA can be an effective and safe alternative to liver resection for tumors that are not amenable to resection.[217]

Several studies show no difference between MWA and RFA in terms of OS,[207] with some studies suggesting a decrease in local recurrence with MWA.[207] However, two meta-analyses did not see this lower rate of recurrence with MWA compared to RFA but showed similar efficacy of both techniques in terms of OS and RFS.[218,219] One study did detect a signal for superiority of MWA in patients with larger tumors (>3 cm).[219] Finally, a recent phase II RCT ($N = 152$) also failed to show a difference in efficacy for MWA and RFA in the treatment of HCC lesions of 4 cm or smaller.[220] Importantly, both ablation techniques in this study were associated with a low rate of local tumor progression at two years (6% with MWA *vs.* 12% with RFA; RR[95%CI]: 1.62[0.66-3.94]; $P = 0.27$).[220]

Recommendations: Ablation

- For HCC patients undergoing ablation therapy, we recommend using RFA technique over PEI technique **(Strong recommendation, high-quality evidence)**.
- For patients with small HCC tumor ≤2 cm, very early HCC (BCLC 0), or in the presence of two or three nodules ≤3 cm (BCLC A), we recommend using RFA over liver resection **(Strong recommendation, moderate-quality evidence)**.
- For patients with HCC in proximity to the gallbladder, stomach, colon, or other viscera, we recommend performing PEI or surgical resection (if feasible) over RFA **(Strong recommendation, low-quality evidence)**.

Transarterial therapies

Transarterial therapies aim to induce tumor necrosis by exploiting the predominant arterial vascularization of HCCs compared to the surrounding liver parenchyma. This difference in vascularization enables the selective intravascular delivery of drugs, embolic particles, or radioactive devices.

Transarterial chemoembolization

The rationale for TACE is that the intra-arterial infusion of a cytotoxic agent followed by embolization of the tumor-feeding blood vessels will result in a strong cytotoxic and ischemic effect targeted at the tumor. In fact, the tumor tends to be fed entirely by arterial inflow, unlike the surrounding parenchyma, which receives the majority of inflow through the portal system. With conventional TACE, an emulsion of chemotherapy (usually doxorubicin, epirubicin, cisplatin, or miriplatin) and lipiodol is injected via a catheter into the segmental hepatic artery supplying the tumor, followed by vascular stagnation and particle embolization by tumor cells.

The acceptance of TACE as the standard of care for patients with intermediate stage HCC (BCLC B) was based on two phase III RCTs. The first study that showed TACE was associated with a significantly better OS than symptomatic treatment (2-year OS rate: 63% *vs.* 27%, $P = 0.009$) in 112 stringently selected patients with unresectable HCC.[133] The second RCT yielded similar results with a 2-year OS rate of 31% for TACE compared to 11% with symptomatic treatment only in an Asian population of newly diagnosed unresectable HCC.[134] Several meta-analyses have confirmed these findings.[132,221] More recently, a systemic review on conventional TACE

in HCC generated data on more than 10,000 patients found that TACE induced an objective response in 52.5% of patients, with 70% of patients being alive at 1-year (dropping to 51.8%, 40.4% and 32.4% at 2, 3 and 4 years, respectively).[222] In addition to these efficacy data, the most common side effects after TACE were liver enzyme abnormalities (18.1%), fever (17.2%), hematological/bone marrow toxicity (13.5%), pain (11%), and vomiting (6%). These adverse events (AEs) are commonly referred to as postembolization syndrome.

Stringent patient selection is key to the success of TACE when treating HCC. In this respect, patients with an ECOG PS (2 or more), or with severe hepatic decompensation (CPT C or decompensated CPT B) will not benefit from TACE. In fact, TACE may even induce detrimental effects in these patients. The main contraindication to TACE treatment is the presence of poor venous blood supply from the portal vein (mostly due to chemical or neoplastic thrombosis of the main portal vein or its lobar and segmental branches, as well as porto-systemic anastomosis and hepatofugal portal flow). These patients have an increased risk of ischemic necrosis of the liver and, thus, liver failure. Similarly, patients with advanced hepatic disease (CPT B and C) should not be considered for TACE due to their increased risk of liver failure.[223] Based on the available evidence, TACE should primarily be reserved for patients with a compensated liver function and an asymptomatic multifocal or large HCC, without vascular invasion, who are not amenable for a resection,[9] which can result in an excellent median survival ranging from 40 to 50 months.[135,136]

Only a small percentage of patients will obtain a complete response after the first TACE treatment. Therefore, TACE can be performed more than once. However, there is no consensus on the optimal number of TACE treatments or on the time interval between TACE sessions. As a result, the choice is the decision of the individual operator, with the experts suggesting "on-demand" treatments with a 1- or 2-month interval between sessions and ceasing TACE after 2-3 unsuccessful sessions.[224] Additionally, TACE should not be repeated in patients who develop 'untreatable progression.' These untreatable progressions may include major progressions with extensive liver involvement, extrahepatic metastasis or vascular invasion, and also smaller intrahepatic progressions that are associated with an impaired liver function and/or PS.[225]

Several attempts have been made to improve the outcomes of TACE, including the development of TACE with drug-eluting beads (TACE-DEB), which involves the controlled release of chemotherapeutic agents from these microbeads and may result in a more sustained and tumor-selective drug delivery and permanent embolization. However, an RCT and meta-analysis failed to show a convincing survival benefit from TACE-DEB over conventional TACE, nor did they indicate a difference in tumor response, number of procedures, or in-hospital stay.[226-228] A somewhat concerning observation with TACE-DEB came from a retrospective analysis demonstrating a higher risk for therapy-related hepatic locoregional complications (e.g., biliary injury, intrahepatic biloma, and global liver damage) compared to conventional TACE.[229]

Conventional TACE has also been combined with other treatment modalities to improve its outcome, such as TACE with a percutaneous ablation technique, which was associated with a significantly lower 3-year mortality than TACE alone.[230] Another study tested the combination of RFA and TACE in 40 cirrhotic HCC patients with a single large HCC (>3 cm), which resulted in a significantly lower 2-year recurrence rate (48.1% *vs.* 78.2%) and a significantly higher 2-year OS (91.1% *vs.* 60.6%).[231]

As TACE induces local hypoxia and ischemic necrosis, resulting in the activation of hypoxia-inducible factors and increased levels of vascular endothelial growth factor (VEGF), some have combined TACE with anti-angiogenic agents, such as sorafenib, brivanib or orantinib to evaluate its therapeutic benefit; however, clinical trials have not yet shown a clinical benefit over TACE alone.[232-235] One exception to this rule is from a recent meta-analysis ($N = 2,538$) demonstrating a significant improvement in the time to progression and OS when adding sorafenib to TACE in Asian patients (HR[95%CI]: 0.66[0.48–0.89] and 0.57[0.45–0.72], respectively), but in non-Asian patients, the addition of sorafenib did not provide any clinical benefit.[236] Recently, patients with unresectable HCC were randomized to TACE plus sorafenib ($N = 80$) or TACE alone ($N = 76$). The median progression-free survival (PFS) was significantly longer in the TACE plus sorafenib than in the TACE alone group (25.2 *vs.* 13.5 months; $P = 0.006$). Regrettably, OS was not analysed because the study did not reach the pre-planned number of events.[237]

Transarterial radioembolization

Transarterial radioembolization (TARE), also known as selective internal radiation therapy (SIRT), consists of the selective intra-arterial percutaneous administration of microspheres loaded with a radioactive compound (yttrium-90 [Y90] or lipiodol labeled with

iodine[131] or rhenium[188]). Currently, the most popular technique uses resin or glass microspheres coated with Y90, a ß-emitting isotope. Similar to TACE, delivery of treatment relies upon the hepatic arterial predominant blood supply of HCCs (80%) to reduce its effect on normal hepatic parenchyma. From a technical point of view, radioembolization comprises several stages. The first stage consists of identifying potentially eligible patients for the procedure, according to a multidisciplinary assessment, after which a diagnostic angiography is performed to evaluate the vascular anatomy and establish the most appropriate site of access. At the same time, labeled macroaggregates of albumin are injected; their diffusion is similar to that of radioembolization microspheres and, therefore, can be studied using single-photon emission CT to predict the actual diffusion of TARE microspheres. This diffusion simulation measures hepatopulmonary shunt and can predict the response to TARE and, therefore, plays a crucial role in the selection of patients and the personalization of the treatment. The next stage calculates the amount of radiation compound (mostly Y90) specifically needed for each patient to achieve the desired activity. Finally, microspheres are injected by a catheter within four weeks from the first visit.[238]

Two small prospective studies have compared TARE to TACE in patients with intermediate stage HCC. In the randomized phase II PREMIERE trial, 43 patients with unresectable HCC who were deemed ineligible for ablation were randomly assigned to TARE or TACE. TARE was associated with a significantly longer time to progression ($P = 0.00019$) compared to TACE, but this did not result in a better OS.[239] In the SIRTACE trial, 28 patients with unresectable HCC (CPT no higher than B7, ECOG PS 0-2, no more than five lesions with a total diameter of ≤20 cm) were treated with either TACE (with 6-weekly intervals until tumor enhancement) or a single session of Y90 TARE.[240] Similar efficacy and health-related quality of life results were reported with both procedures. A meta-analysis reported comparable OS and complication rates with TARE and TACE, and also, a Cochrane database review concluded that there is insufficient evidence to assume a beneficial effect of TARE over TACE.[241,242] In contrast, one retrospective study ($N = 80$) did demonstrate a survival advantage for TARE over TACE (2-year OS: 59% *vs*. 47%) in patients with BCLC stage B-C HCC.[243]

TARE has also been evaluated in patients with locally advanced HCC and compared with sorafenib treatment in two RCTs. Both trials failed to demonstrate a survival benefit of TARE over sorafenib, despite a higher rate of tumor responses with TARE. In one of these trials (SIRveNIB), TARE was associated with a significantly longer PFS, while the other trial (SARAH) demonstrated a significantly lower rate of AEs with radioembolization.[244,245] Finally, in the SORAMIC trial, 216 patients were randomized to TARE plus sorafenib and 208 to sorafenib alone. Although this combination was not associated with a higher rate of AEs, the median OS was 12.1 months in the TARE plus sorafenib arm, and 11.4 months in the sorafenib arm (HR[95%CI]: 1.01[0.81-1.25]; $P = 0.9529$).[246]

In general, indications for TARE are similar to what was described for TACE, with one important exception wherein because of the minimally embolic effect of Y90 microspheres, TARE can be safely used in patients with portal vein thrombosis. Severe complications such as ulceration can be caused by the spread of the microspheres to the gastrointestinal tract. Careful mapping of the blood vessels to identify aberrant vasculature from the branches of the hepatic artery that supply the gastrointestinal tract can prevent this. Radiation pneumonitis has been shown to occur when the lung shunt function is greater than 13%.

TARE could hold the potential as a bridge, or downstaging strategy, as data from a small study showed patients treated with TARE had better tumor control, and a higher proportion received liver transplantation than those with TACE, leading to speculation that SIRT could reduce dropout from transplant waiting lists.[247] A small Saudi study has also reported promising findings supporting TARE as a therapeutic tool for downstaging and bridging of HCC patients before liver transplantation.[248]

Stereotactic body radiation therapy

Several studies have assessed a potential role for SBRT in patients with HCC and as an alternative for RFA. In a recent retrospective analysis, including a total of 773 HCC patients, similar rates of freedom from local progression (FFLP) were reported with SBRT and RFA. After propensity score matching, the 2-year FFLP rates were 74.9% and 64.9% for patients treated with SBRT and RFA, respectively.[249] Interestingly, in larger tumors (>2 cm), SBRT was associated with a higher rate of local control, compared to RFA ($P = 0.036$), but this was not the case in patients with smaller tumors (≤2 cm) ($P = 0.635$). Among the patients treated with RFA, a subphrenic tumor location correlated with a significantly worse local control ($P = 0.003$), but no difference in OS was seen between RFA and SBRT.[249] Similar results were seen in a retrospective analysis of 224 HCC patients treated with either RFA ($N = 161$) or SBRT ($N = 83$) between 2004 and 2012. SBRT and RFA were associated with similar control rates, with larger tumors being less likely to be controlled with RFA (no size-outcome relation with SBRT).[250] Thus,

Recommendations: Transarterial therapies

- We recommend TACE as the preferred treatment for BCLC B patients **(Strong recommendation, high-quality evidence)**.
- Contraindications for TACE include ECOG PS (2 or more), severe hepatic decompensation (CPT C or decompensated CPT B), and portal vein thrombosis. **(Strong recommendation, high-quality evidence)**.
- There is no consensus on the optimal number of TACE sessions or on the time interval between sessions **(Ungraded statement)**.
- We recommend using TACE alone compared to using sorafenib in combination with TACE **(Strong recommendation, high-quality evidence)**.
- TARE may be used as an alternative to TACE in treatment of intermediate stage HCC if associated with portal vein thrombosis **(Weak recommendation, low-quality evidence)**.

SBRT represents a reasonable alternative option for RFA in HCC patients with larger tumors (>2 cm) or in patients with a challenging tumor location.

To evaluate SBRT as an alternative to TACE, a retrospective study[251] analysed 209 patients with HCC and 1-2 tumors, of which 84 were treated with TACE (114 tumors) and 125 with SBRT (173 tumors). Interestingly, the 1- and 2-year local control rates were significantly higher with SBRT (96.5% and 91.3%, respectively) than with TACE (47.1% and 22.9%), respectively ($P < 0.001$), and the data for FFLP significantly favored SBRT (HR[95%CI]: 3.55[1.94-6.52]; $P < 0.001$). Moreover, SBRT was associated with a lower rate of grade ≥3 AEs compared to TACE (8% *vs*. 13%). Suggesting that SBRT is a safe and effective alternative for TACE in patients with 1 to 2 HCC tumors, with superior local and liver control compared to TACE.[251] In a recently reported prospective RCT, SBRT was also tested as salvage therapy after TACE. Forty patients with BCLC stage A (18%) and B (82%) HCC and an incomplete response after one cycle of TACE were randomly assigned to SBRT ($N = 21$), or the second cycle of TACE ($N = 19$).[252] The use of SBRT as a salvage therapy resulted in a significantly longer median time to a loss of local control ($P = 0.0002$) compared to the second round of TACE. No difference was seen between both arms in terms of toxicity.[252]

Overall, these data indicate that SBRT can be considered as an alternative treatment option for RFA or TACE in selected, inoperable HCC patients. Opting for SBRT comes with several theoretical advantages, as it is a non-invasive treatment modality that is not limited by tumor location, tumor size, or involvement of major vessels. In addition, SBRT is cost-effective, it does not require sedation, and the treatment time is short. Finally, SBRT is generally well-tolerated with a low rate of high-grade AEs. With respect to the type of radiotherapy, a recent retrospective analysis demonstrated that, compared to photon-based radiotherapy, proton radiation therapy was associated with improved survival. This survival benefit is likely driven by a decreased incidence of post-treatment liver decompensation with proton-based radiotherapy.[253] Based on these findings, it is probably better to avoid photon-based radiotherapy in patients with an advanced CPT score.

Finally, SBRT could also play a role in patients with oligometastatic disease. As will be discussed subsequently, systemic therapy is the standard of care for patients with extrahepatic metastases. Recently, however, studies suggest that local therapies might be of use in select patients with a limited metastatic spread. In a Canadian phase II RCT, the addition of SBRT resulted in a clinically relevant improvement in both PFS and OS in 99 patients with a controlled, primary tumor and 1-5 metastatic lesions randomly assigned to standard of palliative care with or without SBRT to all metastatic lesions.[254]

Systemic therapies

Unfortunately, the majority (>50%) of patients with HCC are diagnosed at (or eventually evolve towards) an advanced disease stage, defined as a multifocal disease with portal vein invasion and/or extrahepatic lesions and/or mild cancer-related symptoms.[127] If left untreated, patients with advanced HCC have a dismal prognosis with a median OS of only 7 months.[255] In this context, systemic treatment is the only therapeutic option, provided that liver function is sufficiently preserved.[9] Advanced HCC is a disease that is notoriously difficult to treat due to its intrinsic high chemo-resistance and the constant threat of a decline in liver function rendering further treatment impossible. Prior to 2008, no systemic drug was recommended for patients with advanced HCC, an unparalleled situation in oncology. However, in recent years, increased knowledge of the molecular events that govern tumor initiation and progression in HCC patients has permitted the development of targeted therapies aimed to abrogate disrupted molecular pathways.[9] After 30 years of research, sorafenib emerged as the first effective systemic treatment for patients with advanced HCC and rapidly became the reference therapy in this setting.[137]

Unfortunately, this major breakthrough was followed by a decade of disappointments with a long list of failed phase III RCT. This stream of negative trials came to an end in 2017, when the oral multi-TKI regorafenib was shown to prolong the survival of patients who progressed under sorafenib.[256] Since 2017, several positive trials with targeted therapies followed in quick succession (i.e., ramucirumab and cabozantinib in second-line, lenvatinib in first-line treatments, promising findings with immune checkpoint inhibition [ICI]).[257-263] Recently, the phase III IMbrave150 trial showed that the combination of atezolizumab and bevacizumab was associated with a significantly longer OS and PFS compared to sorafenib,[264] which is likely to cause an important shift in the treatment paradigm of patients with advanced HCC.[264]

First-line therapy

Sorafenib

Sorafenib was the first drug to show a survival benefit in patients with advanced HCC.[137] It is an oral multi-TKI targeting a broad spectrum of protein kinases (such as VEGFR, PDGFR, c-KIT, RAF), resulting in both anti-angiogenic and anti-proliferative effects. In the pivotal phase III SHARP trial, 602 patients with advanced HCC were randomly assigned to sorafenib (at a dose of 400 mg twice daily) or placebo. Patients who received sorafenib had a median OS of 10.7 months, which was significantly longer than the 7.9 months median OS seen among placebo-treated patients, corresponding to a 31% reduced death risk for patients in the sorafenib arm (HR[95%CI]: 0.69[0.55-0.87]; $P < 0.001$).[137] In addition, the sorafenib-treated patients had a significantly higher disease control rate (43% *vs*. 32%, $P = 0.002$) and a longer time to radiological progression (5.5 *vs*. 2.8 months; HR 0.58%; 95% CI 0.45-0.74; $P < 0.001$). In a parallel, phase III trial ($N = 226$) performed in the Asia-Pacific region, similar results were obtained with a median OS of 6.5 and 4.2 months for sorafenib and placebo, respectively (HR[95%CI]: 0.68[0.50-0.93]; $P = 0.014$). The most common grade 3/4 AEs with sorafenib include diarrhea (8–9%), hand-foot-skin reactions (8–16%), and fatigue (3–4%).[137,265] Nevertheless, the initial rate of treatment discontinuations due to AEs was relatively high with sorafenib (e.g., 38% in SHARP), which has decreased over the years as clinicians have gained more experience with the drug (e.g., 22.4% in a large retrospective [$N = 3,094$] study reported in 2017).[137,266] Investigators have retrospectively evaluated the effect of treatment initiation at a lower sorafenib dose (<800 mg/day) to reduce AE-related dropout.[266] The initiation of sorafenib therapy at reduced dosages was not only associated with a reduced pill burden and lower treatment costs, but it also led to a lower rate of sorafenib discontinuation due to AEs. Importantly, reduced dosing was not associated with inferior OS relative to standard dosing. Another common strategy to prevent sorafenib-related AEs consists of the prophylactic use of a corticosteroid-based topical cream (e.g., clobetasol) to avoid hand-foot syndrome.[267]

Most patients enrolled in the two RCTs discussed above had a well-preserved liver function (95% in the SHARP and 97% in the Asia-Pacific study had CPT A disease). In clinical practice, however, many patients presented with hepatic dysfunction (CPT B or C). Thus, patients with CPT A disease had a better OS than patients with CPT B (median OS 13 *vs*. 4.5 months) when evaluating the efficacy and safety of sorafenib in relation to CPT score.[268] In an observational HCC registry (GIDEON), the median OS was 5.2 months in CPT B patients treated with sorafenib,[269] and 6.5 months in CPT B patients in a separate prospective study. Despite a high prevalence of severe AEs in CPT B patients, the rate of treatment interruptions in the latter cohort was relatively low at 27.7% (*vs*. 30.1% in CPT A patients). Thus, these data indicate that selected CPT B patients benefit from sorafenib therapy, with a tolerable safety profile.[270]

Lenvatinib

Lenvatinib is an oral multi-kinase inhibitor that targets VEGFR1-3; FGFR1-4; PDGFRa, RET, and KIT.[271] In phase III REFLECT trial, lenvatinib was shown to be non-inferior to sorafenib as first-line therapy, with a median OS of 13.6 *vs*. 12.3 months (HR[95%CI]: 0.92[0.79–1.06]) in advanced HCC patients without portal vein invasion, and a tumor that occupied no more than 50% of the total liver volume. In addition to the non-inferior OS, lenvatinib also showed a significant improvement for all secondary efficacy endpoints, including a longer median PFS (7.3 *vs*. 3.6 months; HR[95%CI]: 0.64[0.55–0.75; $P < 0.0001$) and a higher objective response rate (ORR) (40.6% *vs*. 12.4%; OR[95%CI]: 3.34[2.17-5.15]; $P < 0.0001$). This PFS and ORR benefit with lenvatinib did come at the cost of a higher rate of grade ≥3 treatment-related AEs (TRAEs) (57% *vs*. 49%), which were hypertension (23% *vs*. 14%), weight loss (8% *vs*. 3%), and thrombocytopenia (6% *vs*. 3%). Of note, the rate of grade 3/4 hand-foot syndrome was lower with lenvatinib than with sorafenib (3% *vs*. 11%).[257] As such, these data indicate that lenvatinib is a feasible alternative for sorafenib in the first-line treatment for patients with advanced HCC.

Atezolizumab + bevacizumab

Apart from their effect on angiogenesis, anti-angiogenic agents also have immunomodulatory properties. In fact, these agents can reverse tumor-immunosuppression, which

makes the combination of anti-angiogenic molecules and ICIs a very logical and rational strategy.[272] The phase III IMbrave 150 trial compared the combination of atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) *vs*. sorafenib in untreated advanced HCC patients. The atezolizumab-bevacizumab combination outperformed sorafenib with a significant and clinically meaningful improvement in OS (median OS not reached *vs*. 13.2 months; HR[95%CI]: 0.58[0.42–0.79]; $P = 0.006$). At 12 months, OS was 67.2% for patients treated with atezolizumab-bevacizumab, 12% higher than the 54.6% OS rate at 12-month with sorafenib. In addition, the median PFS was 6.8 months with atezolizumab-bevacizumab compared to 4.3 months with sorafenib (HR[95%CI]: 0.59[0.47–0.76]; $P < 0.0001$). The safety and tolerability profile compiled with known side effects of both components and a delayed deterioration of quality of life for patients randomized to the combination arm was reported.[264] With the atezolizumab-bevacizumab combination having the potential to prolong life and improve the quality of life, it could radically change the way we treat advanced HCC. Further follow-up of this trial is needed, but these results clearly mark this combination as a treatment regimen with the potential to shake up the current standard of care for patients with advanced HCC (i.e., sorafenib or lenvatinib followed by regorafenib, cabozantinib, or ramucirumab in high-AFP patients). Based on these findings, the U.S. Food and Drug Administration (FDA) recently (May 2020) approved the atezolizumab-bevacizumab combination for treating patients with unresectable HCC who did not receive prior systemic therapy. In addition, the European Society for Medical Oncology updated their HCC guidelines and endorsed the atezolizumab-bevacizumab combination as a regimen that can be considered as a first-line treatment option for advanced HCC patients.[273]

Second-line therapy

Regorafenib

Regorafenib is an oral multi-kinase inhibitor that blocks the activity of several proteins involved in angiogenesis (VEGFR1, 2, and 3; FGFR1 and 2;TIE2; and PDGFRα and β),oncogenesis (RAF-1, RET, KIT), and the tumor microenvironment(CSF1R).[274] In 2017, the phase III RESORCE RCT trial, evaluating regorafenib in advanced HCC patients with disease progression on sorafenib, proved to be the first trial in over a decade to demonstrate a survival benefit.[256] In this study, 573 CPT A patients with advanced HCC who tolerated (≥400 mg/day for ≥20 of last 28 days of treatment) and progressed on sorafenib were randomly assigned to regorafenib (160 mg/daily) or best supportive care (BSC). Regorafenib was associated with a significantly longer OS (median 10.6 months) compared to BSC (median 7.8 months) (HR[95%CI]: 0.63[0.50-0.79]; $P < 0.0001$). Regorafenib also showed significant improvements in the secondary endpoints such as PFS, time to progression, disease control rate and ORR. The AEs observed with regorafenib were manageable and in line with previous reports, with hand-foot-skin reaction (13% *vs*. 1%), fatigue (9% *vs*. 5%) and hypertension (15% *vs*. 5%) as the leading AEs.[256] An analysis of the OS from the start of sorafenib treatment to death showed a median duration of 26 months in the regorafenib arm as compared to 19 months in the placebo arm. As such, the sorafenib-regorafenib sequence can provide a significant survival benefit for patients with advanced HCC.

Cabozantinib

Cabozantinib is a small, multi-target TKI molecule that inhibits VEGFRs 1-3, MET and AXL, and has been evaluated in previously treated advanced HCC patients. In a phase III CELESTIAL trial, 707 progressive advanced HCC patients (CPT A, ECOG PS 0-1) who previously received up to two lines of systemic therapy (including sorafenib) were randomly assigned to receive cabozantinib (60 mg/day) or matching placebo.[258] At the second interim analysis, a significantly longer OS was reported with cabozantinib compared to placebo, with an HR for death of 0.76 (median OS: 10.2 *vs*. 8.0 months; HR[95%CI]: 0.76[0.63-0.92]; $P = 0.005$). The median PFS was significantly prolonged from 1.9 months with placebo to 5.2 months with cabozantinib (HR[95%CI]: 0.44[0.36-0.52]; $P < 0.001$). This clinical benefit did come at the cost of an increased rate of grade 3/4 AEs (68% *vs*. 36%), the most common were hand-foot syndrome (17% *vs*. 0%), hypertension (16% *vs*. 2%), increased AST (12% *vs*. 7%), fatigue (10% *vs*. 4%), and diarrhea (10% *vs*. 2%).[258] Following these results, both the FDA and the European Medicines Agency (EMA) approved cabozantinib for the treatment of advanced HCC patients who were previously treated with sorafenib.

Ramucirumab

Ramucirumab is a monoclonal antibody directed against VEGFR-2. The Phase III REACH trial randomized 565 patients with advanced HCC who had previously received sorafenib and stopped because of disease progression (86%) or intolerance (14%), to receive ramucirumab (intravenous 8 mg/kg every 2 weeks) or placebo plus BSC. In the overall study population, REACH did not meet its primary endpoint as the difference in OS did not reach statistical significance (median OS: 9.2 *vs*. 7.6 months; HR[95%CI]: 0.87[0.72-1.05]; $P = 0.14$). However, in a subsequent, prespecified subgroup analysis of REACH-1 patients with a baseline AFP level of ≥400 ng/ml,

showed a significant OS benefit induced by ramucirumab over placebo (median OS of 7.8 and 4.2 months for ramucirumab and placebo, respectively (HR[95%CI]: 0.67[0.51-0.90], $P = 0.006$).[275] A dedicated phase III trial (REACH-2) was set up to evaluate advanced HCC patients with an AFP level of 400 ng/ml or higher.[259] Eligible patients were previously treated with sorafenib, had CPT A liver disease, an ECOG PS of 0-1 and a baseline AFP concentration of ≥400 ng/ml. In total, 292 patients were randomized (2:1) to receive 8 mg/kg intravenous ramucirumab every 2 weeks or placebo. The median OS in patients treated with ramucirumab was 8.5 months, which was significantly longer than the 7.3 median OS seen with placebo (HR[95%CI]: 0.710[0.531-0.949]; $P = 0.0199$). In addition, the PFS was significantly improved with ramucirumab (median PFS: 2.8 *vs*. 1.6 months; HR[95%CI]: 0.452[0.339-0.603]; $P < 0.001$).[259] A pooled analysis, including all 542 patients with a baseline AFP level of ≥400 ng/ml, confirmed this finding (median OS: 8.1 *vs*. 5.0 months; HR[95%CI]: 0.694[0.571-0.842]; $P = 0.0002$).[259] With respect to safety, ramucirumab was well-tolerated across the two phase III trials. In REACH-2, the most frequently reported AEs of any grade in the ramucirumab group were fatigue (27%), peripheral edema (25%), hypertension (25%), and a decreased appetite (23%). Importantly, these AEs rarely reached grade 3 in severity (hypertension and hyponatremia were the only grade 3 or worse TRAEs that were noted in at least 5% of patients).[259,275]

These trials prompted the EMA and FDA to approve ramucirumab as a second-line treatment option for sorafenib-pretreated advanced HCC patients with a baseline AFP level of ≥400 ng/ml. As such, this makes ramucirumab the first, and to date the only, biomarker-driven therapy for patients with advanced HCC.

Immune checkpoint inhibition

Over the last few years, immunotherapy has revolutionized the therapeutic landscape of various types of cancers. More specifically, ICIs targeting cytotoxic T-lymphocyte protein 4 (anti-CTLA4) or programmed cell death protein 1 and its ligand (anti-PD-1/PD-L1) have yielded impressive results. As discussed previously, HCC predominantly develops in a background of cirrhosis. This inflammatory milieu is particularly immunosuppressive, which makes immunotherapy an attractive treatment strategy for patients with HCC.[276] The two most relevant phase III clinical trials in advanced HCC were performed with the PD-1 antibodies nivolumab and pembrolizumab.

ICI monotherapy

Nivolumab (anti-PD-1) monotherapy in first- and second-line therapy have provided promising results in an extended phase I/II trial, leading to an accelerated FDA-approval of nivolumab as a second-line treatment for advanced HCC patients.[277] However, the subsequent phase III CHECKMATE-459 trial, comparing nivolumab to sorafenib in the first-line treatment of advanced HCC patients, did not reach statistical significance in its primary endpoint of OS (median OS: 16.4 *vs*. 14.7 months; HR[95%CI]: 0.85[0.72-1.02]; $P = 0.0752$). Nevertheless, a clear subset of patients seemed to derive a durable response on nivolumab. In fact, the ORR with nivolumab was reported to be 15%, which is more than twice as much as the 7% seen with sorafenib (complete response rate: 4% *vs*. 1%). This difference in ORR was even more pronounced in the subgroup of patients with a PD-L1 expression of ≥1%, where nivolumab induced a response in 28% of patients as compared to 9% with sorafenib. However, PD-L1 expression did not seem to be a prerequisite for a response to nivolumab, as 12% of patients with PD-L1 expression <1% had a response to nivolumab.[260,278] More studies are needed to better identify the patients that are likely to respond to this agent.

After promising results from the phase I/II trials, the phase III Keynote-240 trial randomly compared pembrolizumab to BSC as a second-line treatment for patients with advanced HCC. While the 13.9 months median OS reported with pembrolizumab was numerically longer than the 10.6 median OS seen with BSC, this difference did not meet the prespecified threshold for statistical significance at the first interim analysis (HR[95%CI]: 0.775[0.609-0.987]; $P = 0.0186$).[261,279]

As such, despite promising signals during earlier stages of their clinical development, both pembrolizumab (second-line) and nivolumab (first-line) have failed to induce a survival benefit in their respective phase III trials in advanced HCC. Before a definitive recommendation for the use of ICI as monotherapy can be made, it is necessary to wait for the final results of these phase III trials with a more specific follow-up.

Several other ICIs are being evaluated as a monotherapy in patients with advanced HCC. Durvalumab is an anti-PD-L1 monoclonal antibody, tested in a phase I-II trial, with acceptable safety profile and ORR of 10% and a median OS of 13.2 months.[280] Camrelizumab (anti-PD-1) showed an ORR of 13.8% in a randomized phase II study in second-line treatment of advanced HCC in China.[281] Similar results for tislelizumab (anti-PD-1) led to the ongoing phase III trial of tislelizumab monotherapy in the first-line setting.[282]

Table 2: Systemic therapy recommendations for different HCC stages

Drug	Mechanism of action	Previous clinical trial	Adverse events	Patient HCC stage	Recommendations or observations	Publications
First-line therapies						
Atezolizumab + bevacizumab combination	Monoclonal antibody of IgG1 isotope, target PD-L1 + monoclonal antibody target VEGF-A, respectively	IMbrave 150 phase III compared this combination (atezolizumab 1200 mg IV on day 1 of each 21-day cycle and bevacizumab IV 15 mg/kg on day 1 of each 21 day cycle) with sorafenib: better OS at 12 months and PFS	Similar AEs to sorafenib-treated	Unresectable HCC or patients who have not received prior systemic therapy	For patients with BCLC C HCC, we recommend atezolizumab-bevacizumab as a first-line alternative to sorafenib or Lenvatinib. Approved by the FDA in May 2020 as an alternative first-line treatment for patients with advanced HCC	[263], [271]
Sorafenib	Multi-TKI	SHARP phase III – 400 mg twice daily: longer OS, better disease control rate. Asia-Pacific phase III improved OS	Some grade 3/4: Diarrhea Hand-foot-skin reactions Fatigue	Advanced HCC with preserved liver function (CPT A) and some patients with CPT B	We recommend sorafenib as a first-line treatment for advanced HCC (BCLC C and well-preserved liver) function (CPT A). AEs are reduced in patients given <800 mg per day	[136], [263]
Lenvatinib	Multi-TKI	REFLECT phase III – 12 mg/day for bodyweight ≥60 kg or 8 mg/day for bodyweight ≤60 kg. Non-inferior to sorafenib with OS 13.6 months. Improved PFS and ORR	More grade 3 TRAEs: Hypertension Weight loss Thromocytopenia	Advanced HCC	We recommend for patients with BCLC C HCC, lenvatinib as an alternative to sorafenib as a first-line therapy	[255]
Second-line therapies						
Regorafenib	Multi-TKI	RESORCE phase III – CPT A advanced HCC patients tolerated ≥400 mg/day for ≥20 days of sorafenib + 160 mg/day of regorafenib. Longer OS vs. BSC. Improved PFS, time to progression, disease control rate and ORR	Similar AEs as reported with sorafenib: Hand-foot-skin reactions Fatigue Hypertension	Advanced HCC patients with sorafenib disease progression	Sorafenib-regorafenib sequence can provide significant survival benefit with advanced HCC. We recommend this in patients with well-preserved liver function.	[254]
Cabozantinib	Multi-TKI	CELESTIAL phase III – 60 mg/day to advanced HCC patients already received 2 lines of systemic therapy. OS improved vs. placebo. PFS prolonged	Increased AEs: Hand-foot syndrome Hypertension Increased AST Fatigue Diarrhea	Advanced HCC (CPT A, ECOG PS 0-1) already received two systemic therapies	Cabozantinib can be considered for patients who have progressive disease on one or two systemic therapies with well-preserved liver function. FDA and EMA approved cabozantinib as a second-line treatment to advanced patients previously treated with sorafenib	[256]
Ramucirumab	Monoclonal antibody target VEGFR-2	REACH phase III, 8 mg/kg IV every 2 weeks to advanced HCC with disease progression or intolerance with sorafenib. OS has not improved. REACH-1 trial showed subgroup of patients with baseline AFP ≥400 ng/ml with improved OS. REACH-2 used advanced HCC patients with CPT A, ECOG PS 0-1, baseline AFP ≥400 ng/ml: improved OS and PFS vs. placebo	Well-tolerated, fewer grade 3 AEs. AEs reported: Fatigue Peripheral edema Hypertension Decreased appetite	Advanced HCC with CPT A, ECOG PS 0-1 and baseline AFP ≥400 ng/ml	Ramucirumab can be considered for patients in second-line therapy with a baseline AFP ≥400 ng/ml and a well-preserved liver function. FDA and EMA approved ramucirumab as a second-line treatment option for sorafenib-pretreated advanced HCC patients with a baseline AFP ≥400 ng/ml	[257], [273]

Contd...

Table 2: Contd...

Drug	Mechanism of action	Previous clinical trial	Adverse events	Patient HCC stage	Recommendations or observations	Publications
Immune checkpoint inhibitors						
Nivolumab	IgG4 monoclonal antibody target PD-1	CHECKMATE-459 phase III as first-line treatment in advanced HCC. OS non-inferior to sorafenib but ORR improved			More studies needed to identify patients that'll respond to this treatment	[258], [275], [276]
Pembrolizumab	IgG4 antibody target PD-1	Keynote-240 phase III randomly compared pembrolizumab vs. BSC as a second-line treatment. Slightly improved OS but did not reach prespecified first interim analysis			No survival benefit with current trials, further trials needed	[259], [277]

TKI, Tyrosine kinase inhibitor; OS, Overall survival; PFS, Progression-free survival; ORR, Objective response rate; AEs, Adverse events; TRAEs, Treatment-related adverse events; PD-L1, Programmed cell death ligand 1, VEGF-A, Vascular endothelial growth factor A; BSC, Best supportive care; ECOG PS, European Cooperative Oncology Group performance status

ICI combination strategies

To improve on the outcomes seen with ICI monotherapy in advanced HCC patients, several combination strategies are being explored. Previously, we discussed the IMbrave150 trial evaluating the atezolizumab-bevacizumab combination as first-line therapy. However, in addition to this, several other ICI-based combinations are also being evaluated in patients with advanced HCC.

Dual targeting of the CTLA-4 and the PD-1/PD-L1 axis is the first logical combination. In fact, blocking the PD-1/PD-L1 pathway does not induce antitumor immunity if there are no cytotoxic T-cells in cancer tissues. Simultaneous blocking of the CTLA-4 pathway leads to priming and activation of cytotoxic T-cells in the lymph nodes and improves the tumoral infiltration of cytotoxic T-lymphocytes.[283] In this context, the combination of durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA-4) induced an ORR of 15% with manageable AEs in phase I/II trial including advanced HCC patients who were progressive and/or intolerant to sorafenib.[284] This led to the design of the phase III HIMALAYA trial comparing durvalumab/tremelimumab to sorafenib monotherapy and durvalumab monotherapy in the first-line treatment of advanced HCC patients. Also, the combination of nivolumab and ipilimumab (anti-CTLA-4) was found to induce a favorable OS and ORR in sorafenib-treated patients with advanced HCC (mean OS 22.8 months, ORR 32%).[262] However, toxicity with this combination (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg) raised concerns as the CHECKMATE-040 trial reported TRAEs in 94% of patients, with grade 3-4 AEs in 53% of patients. Particularly concerning is the 20% grade 3/4 hepatitis that was reported with this combination.[285] Based on these findings, the FDA granted accelerated approval to this ICI combination as a second-line treatment option for sorafenib-pretreated advanced HCC patients. Currently, a phase III trial is comparing the combination of nivolumab/ipilimumab to a standard-of-care (sorafenib or lenvatinib) in the first-line treatment of advanced HCC patients.

Lastly, a combination therapy consisting of ICI pembrolizumab and the multi-kinase inhibitor lenvatinib resulted in an ORR of 44.8%, including a complete response in 6% of patients in the phase Ib KEYNOTE-524 study, where 104 newly diagnosed HCC patients (BCLC B ineligible for TACE or BCLC C; ECOG PS ≤1; CPT A) were treated with this combination. Based on these results, this combination was granted an FDA breakthrough designation for newly diagnosed, unresectable HCC.[286]

Biomarkers

With this new arsenal of potential therapeutic options, clinicians now face the challenge of selecting the right treatment for the right patient. To date, ramucirumab is the only biomarker-driven therapy for advanced HCC. As we evolve towards the era of 'personalized medicine,' the search for biomarkers is urgent. For example, a clear subset of patients are durable responders to treatment with ICIs, but for the moment, we are unable to identify them before the start of the treatment. In this respect, data from 956 patients showed that a quarter of patients express markers of an inflammatory response (high expression levels of PD-L1/PD-1; markers of cytolytic activity, fewer chromosomal aberrations). Within this group, two different HCC subclasses were identified, characterized by either an adaptive or an exhausted immune response. As such, these findings indicate that some HCCs might be susceptible to therapeutic agents designed to block the regulatory pathways in T-cells, such as inhibitors of the PD1/PD-L1 immune checkpoint.[287] More research is needed to assess

whether these markers can be used to select patients for treatment with an ICI. Given the continuous threat of a declining liver function in advanced HCC patients, there is a clinical need for predictive and early response biomarkers that can guide clinicians in their therapeutic decisions and avoid missed opportunities.

Table 2 depicts the systemic therapy recommendations for various HCC stages.

Palliative treatment

Patients with end-stage or terminal HCC are those presenting with tumors leading to a very poor PS (ECOG PS 3–4) or CPT C stage with tumors beyond the transplantation threshold. Patients with advanced HCC have a very dismal prognosis, with a median OS of only 3-4 months and a 1-year survival rate of approximately 10%.[131,288] Given this very poor life expectancy, the management of end-stage liver disease is only symptomatic, and no tumor-directed treatment is indicated. These patients should receive palliative support, including management of pain, nutrition, and psychological support. HCC patients suffer from cancer symptoms, and complications that arise in addition to the underlying chronic liver disease making their needs more complex than other patients. Moreover, managing HCC patients comes with additional safety concerns on the use of certain medications, given their hepatic metabolism.

A systematic review compared the impact of early palliative care *vs.* standard cancer care on the quality of life in patients with advanced cancer. In this analysis, early palliative care intervention proved to be more beneficial in the quality of life of patients and led to better symptom control.[289] In line with this, the American Society of Clinical Oncology (ASCO) guidelines recommend early integration of palliative care in the treatment of cancer patients, as soon as the diagnosis is established.[290] However, evidence shows that access to palliative care for patients with advanced HCC is suboptimal, despite their great symptom burden. In fact, Poonja *et al.* demonstrated that only 10% of cirrhotic HCC patients who were removed from a transplantation list received adequate palliative care.[291] Similar results were obtained in a study from AASLD, indicating that only 7.5% of patients with the end-stage liver disease received palliative care in the last year before they died.[292] Barriers to receiving palliative care in HCC are multiple, including uncertainty about disease course, complications and prognosis, inadequate communication, and discussion about end of life. Other factors include misconception and stigma about palliative care that make it difficult to discuss with primary teams.[292]

Recommendations: Systemic therapy

- For patients with BCLC C HCC and well-preserved liver function (CPT A), we recommend atezolizumab-bevacizumab as a first-line therapy **(Strong recommendation, high-quality evidence).**
- For patients with BCLC C HCC and a well-preserved liver function (CPT A), we recommend sorafenib or lenvatinib, a first-line alternative for atezolizumab-bevacizumab **(Strong recommendation, high-quality evidence)**.
- For selected CPT B advanced HCC patients, we suggest using sorafenib over other agents **(Weak recommendation, low-quality evidence)**.
- Several life-prolonging second-line treatment options are available:
  - Regorafenib is the standard of care for patients with advanced HCC who have tolerated sorafenib but progressed. It is recommended in patients with well-preserved liver function **(Strong recommendation, high-quality evidence)**.
  - Cabozantinib can be considered for patients who have progressive disease on one or two systemic therapies with well-preserved liver function **(Strong recommendation, high-quality evidence)**.
  - Ramucirumab can be considered for patients in second-line therapy with a baseline AFP ≥400 ng/ml and a well-preserved liver function **(Strong recommendation, high-quality evidence)**.
  - Nivolumab plus ipilimumab combination therapy can be considered as second-line therapy for patients with HCC (CPT A) who were previously treated with sorafenib **(Weak recommendation, moderate-quality evidence)**.

Although there is no specific palliative care model in HCC, palliative care provides an extra layer of support to the multidisciplinary team approach. Importantly, the role of palliative care should not be restricted to advanced stages of the disease, but it is also important during earlier disease stages.[293] The role of palliative care in the early stage goes beyond symptom management and includes psychosocial and spiritual support, functional support, and discussions about treatment options and preferences. In addition to this, the treatment goals and important decisions like future resuscitations and intubations should be discussed. Palliative care helps the patient and the family to cope with and understand the current medical situation and finally helps to address, coordinate and plan

the patients' care outside the hospital, including homecare needs and follow-up.[294] Continuous longitudinal palliative care support is essential to patients with HCC throughout the disease trajectory. However, palliative care needs are variable from one patient to another depending on the stage of the disease, the age of the patient, comorbidities, and the disease course. As such, the importance of palliative care in the management of patients increases when the disease approaches the terminal stage of HCC (BCLC stage D).

Effective symptom management allows patients and their families to focus on maintaining hope and help them to attain a sense of completion.[295] One of the most common symptoms that are reported by patients with end-stage HCC consists of pain, as it can be related to disease or the treatment, but irrespective of the cause, it represents a significant cause of morbidity. A numeric pain scale should be used to assess pain and, recognizing its often-transient nature, requires it to be reassessed frequently. For mild pain, acetaminophen (paracetamol) is the preferred drug, up to a total dose of 3 g/day. Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk of gastrointestinal bleeding, decompensation of ascites, and nephrotoxicity and should be avoided.[295,296] For patients with more severe pain, paracetamol is usually insufficient. In this setting, opioids are the treatment of choice. Importantly, opioid-treated patients with cirrhosis are at an increased risk of constipation. Therefore, a purging program (preferably with naltrexone) should be started together with the use of opioids (do not wait for severe constipation).[68] Finally, for the alleviation of pain originating from well-defined bone metastasis, palliative radiotherapy can be used.[297]

A second common symptom of end-stage HCC patients, especially in cases of decompensated cirrhosis, consists of weight loss and muscle wasting, which has clinical implications as muscle volume loss is associated with shorter survival in patients with advanced HCC.[298] Nutritional intervention should be considered in cases of low energy intake for a longer period. As terminal HCC patients may also have fluid retention and ascites, oral supplementation is preferred. Home enteral and parenteral nutrition not only allows the patients to be at home but is also more cost-effective than in-patient care.[295] The assistance of a dietician experienced in liver disease could be highly valuable. However, any choice with respect to nutrition should consider the individual situation and needs of the patient.

Fatigue is also a common distressing symptom in HCC, especially in advanced disease stages. Fatigue is multifactorial and can be related to correctable causes such as anemia, metabolic or Electrolyte disturbance, drugs, or infections. Other causes include anorexia, depression, or uncontrolled symptoms.[299] To adequately address fatigue in patients, it is important to make an appropriate assessment of the underlying cause and try to correct it. Importantly, treating fatigue should not ignore non-pharmacological measures like exercise, physiotherapy, and psychological support.[300] With respect to pharmacological interventions, methylphenidate as a psychostimulant may give the patient some energy, reduce fatigue and depression (recommended dose: 5 mg oral once or twice daily).[301]

Psychosocial and spiritual concerns are nearly universal among patients who are conscious as they near the end of life. However, this appears to be particularly pronounced in patients with terminal HCC. In fact, patients with HCC were described to show the third-highest reported level of psychological distress or depression among patients diagnosed with 14 other types of cancer.[302] Cancer patients with an adjustment disorder may respond to brief psychotherapy that addresses cancer-related stressors by teaching coping skills and focusing upon immediate problems. Finally, successful treatment of depression or

Recommendations: Palliative treatment

- For patients with end-stage HCC, we recommend palliative support, including management of pain, nutrition, and psychological support **(Best practice statement)**.
- Pain in HCC can be related to disease or the treatment, but irrespective of the cause it represents a significant cause of morbidity **(Ungraded statement)**:
  - For mild pain, acetaminophen (paracetamol) is the preferred drug. NSAIDs should be avoided.
  - For more severe pain, opioids are the treatment of choice (in combination with adequate purging program).
  - For bone metastasis-related pain, palliative radiotherapy can be used.
- Nutritional interventions should be considered in cases of low energy intake for a longer period of time **(Strong recommendation, low-quality evidence)**.
- Psychosocial support is advised in patients with end-stage HCC. If a pharmacological intervention is considered, caution is needed when using benzodiazepines in patients with cirrhosis **(Strong recommendation, low-quality evidence)**.

anxiety in cancer patients often requires a combination of pharmacologic and non-pharmacologic interventions.[295]

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Wild CP, Weiderpass E, Steward BW, editors. World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on cancer; 2020.
2. Abdo AA, Hassanain M, AlJumah A, Al Olayan A, Sanai FM, Alsuhaibani HA, *et al*. Saudi guidelines for the diagnosis and management of hepatocellular carcinoma: Technical review and practice guidelines. Ann Saudi Med 2012;32:174-99.
3. The Global Cancer Observatory, Cancer Today [Internet]. Lyon: Fact Sheet Liver cancer: c2019 Available from: https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf. [Last cited on 2020 Aug 26].
4. White DL, Thrift AP, Kanwal F, Davila J, El-Serag HB. Incidence of hepatocellular carcinoma in all 50 United States, from 2000 through 2012. Gastroenterology 2017;152:812-20.
5. Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, *et al*. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: Results from the Global Burden of Disease Study 2015. JAMA Oncol 2017;3:1683-91.
6. Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. Gastroenterology 2019;156:477-91.
7. Saudi Health Council, National Health Information Centre [Internet]. Riyadh: Cancer Incidence report Saudi Arabia 2015. c2020:50-1. Available from: https://nhic.gov.sa/eServices/Documents/E%20SCR%20final%206%20NOV.pdf. [Last updated on 2018 Sep; Last cited on 2020 Aug 26].
8. Sharafi H, Alavian SM. The rising threat of hepatocellular carcinoma in the middle east and north Africa region: Results from Global Burden of Disease Study 2017. Clin Liver Dis (Hoboken) 2020;14:219-23.
9. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301-14.
10. Ioannou GN, Splan MF, Weiss NS, McDonald GB, Beretta L, Lee SP. Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2007;5:938-45.
11. West J, Card TR, Aithal GP, Fleming KM. Risk of hepatocellular carcinoma among individuals with different aetiologies of cirrhosis: A population-based cohort study. Aliment Pharmacol Ther 2017;45:983-90.
12. Massarweh NN, El-Serag HB. Epidemiology of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Cancer Control 2017;24:1073274817729245. doi: 10.1177/1073274817729245.
13. Ioannou GN, Green P, Lowy E, Mun EJ, Berry K. Differences in hepatocellular carcinoma risk, predictors and trends over time according to etiology of cirrhosis. PLoS One 2018;13:e0204412.
14. Baecker A, Liu X, La Vecchia C, Zhang ZF. Worldwide incidence of hepatocellular carcinoma cases attributable to major risk factors. Eur J Cancer Prev 2018;27:205-12.
15. Shi J, Zhu L, Liu S, Xie WF. A meta-analysis of case-control studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma in China. Br J Cancer 2005;92:607-12.
16. Sanai FM, Alghamdi H, Alswat KA, Babatin MA, Ismail MH, Alhamoudi WK, *et al*. Greater prevalence of comorbidities with increasing age: Cross-sectional analysis of chronic hepatitis B patients in Saudi Arabia. Saudi J Gastroenterol 2019;25:194-200.
17. Abdo AA, Al-Jarallah BM, Sanai FM, Hersi AS, Al-Swat K, Azzam NA, *et al*. Hepatitis B genotypes: Relation to clinical outcome in patients with chronic hepatitis B in Saudi Arabia. World J Gastroenterol 2006;12:7019-24.
18. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, *et al*. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65-73.
19. Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, *et al*. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168-74.
20. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006;130:678-86.
21. Fattovich G, Giustina G, Schalm SW, Hadziyannis S, Sanchez-Tapias J, Almasio P, *et al*. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. The EUROHEP Study Group on Hepatitis B Virus and Cirrhosis. Hepatology 1995;21:77-82.
22. Sanai FM, Sobki S, Bzeizi KI, Shaikh SA, Alswat K, Al-Hamoudi W, *et al*. Assessment of alpha-fetoprotein in the diagnosis of hepatocellular carcinoma in Middle Eastern patients. Dig Dis Sci 2010;55:3568-75.
23. Chayanupatkul M, Omino R, Mittal S, Kramer JR, Richardson P, Thrift AP, *et al*. Hepatocellular carcinoma in the absence of cirrhosis in patients with chronic hepatitis B virus infection. J Hepatol 2017;66:355-62.
24. Alswat KA, Sanai FM, Altuwaijri M, Albenmousa A, Almadi M, Al-Hamoudi WK, *et al*. Clinical characteristics of patients with hepatocellular carcinoma in a middle eastern population. Hepat Mon 2013;13:e7612.
25. Qari YA, Mosli MH. Epidemiology and clinical features of patients with hepatocellular carcinoma at a tertiary hospital in Jeddah. Niger J Clin Pract 2017;20:43-7.
26. Aljumah AA, Kuriry H, AlZunaitan M, Al Ghobain M, Al Muaikeel M, Al Olayan A, *et al*. Clinical presentation, risk factors, and treatment modalities of hepatocellular carcinoma: A single tertiary care center experience. Gastroenterol Res Pract 2016;2016:1989045. doi: 10.1155/2016/1989045.
27. Alavian SM, Haghbin H. Relative importance of Hepatitis B and C Viruses in hepatocellular carcinoma in EMRO countries and the middle east: A systematic review. Hepat Mon 2016;16:e35106.
28. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, *et al*. Morbidity and mortality in compensated cirrhosis type C: A retrospective follow-up study of 384 patients. Gastroenterology 1997;112:463-72.
29. Waziry R, Hajarizadeh B, Grebely J, Amin J, Law M, Danta M, *et al*. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression. J Hepatol 2017;67:1204-12.
30. White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. Clin Gastroenterol Hepatol 2012;10:1342-59.
31. Ertle J, Dechêne A, Sowa JP, Penndorf V, Herzer K, Kaiser G, *et al*. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. Int J Cancer 2011;128:2436-43.
32. Hassan MM, Abdel-Wahab R, Kaseb A, Shalaby A, Phan AT, El-Serag HB, *et al*. Obesity early in adulthood increases risk but does not affect outcomes of hepatocellular carcinoma. Gastroenterology 2015;149:119-29.
33. Alswat K, Aljumah AA, Sanai FM, Abaalkhail F, Alghamdi M, Al Hamoudi WK, *et al*. Nonalcoholic fatty liver disease burden-Saudi Arabia and United Arab Emirates, 2017-2030. Saudi J Gastroenterol 2018;24:211-9.
34. DeNicola E, Aburizaiza OS, Siddique A, Khwaja H, Carpenter DO. Obesity and public health in the Kingdom of Saudi Arabia. Rev Environ Health 2015;30:191-205.

35. Turati F, Galeone C, Rota M, Pelucchi C, Negri E, Bagnardi V, *et al*. Alcohol and liver cancer: A systematic review and meta-analysis of prospective studies. Ann Oncol 2014;25:1526-35.
36. Rushing BR, Selim MI. Aflatoxin B1: A review on metabolism, toxicity, occurrence in food, occupational exposure, and detoxification methods. Food Chem Toxicol 2019;124:81-100.
37. Strosnider H, Azziz-Baumgartner E, Banziger M, Bhat RV, Breiman R, Brune MN, *et al*. Workgroup report: Public health strategies for reducing aflatoxin exposure in developing countries. Environ Health Perspect 2006;114:1898-903.
38. Kew MC. Aflatoxins as a cause of hepatocellular carcinoma. J Gastrointestin Liver Dis 2013;22:305-10.
39. Farag M, AlAyobi D, Kwon H, El-Ansary A. Relationship between aflatoxin B1 exposure and etiology of liver disease in Saudi Arabian patients. J Pure Appl Microbiol 2018;12:1147-53.
40. Elzupir A, Alamer AS, Alrajhi M, Idriss H. Assessment of health risks from aflatoxins in rice commercialised in Riyadh, Kingdom of Saudi Arabia. Qual Assur Saf Crop 2018;10:255-60.
41. Lee YC, Cohet C, Yang YC, Stayner L, Hashibe M, Straif K. Meta-analysis of epidemiologic studies on cigarette smoking and liver cancer. Int J Epidemiol 2009;38:1497-511.
42. Elmberg M, Hultcrantz R, Ekbom A, Brandt L, Olsson S, Olsson R, *et al*. Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives. Gastroenterology 2003;125:1733-41.
43. Ioannou GN, Bryson CL, Weiss NS, Miller R, Scott JD, Boyko EJ. The prevalence of cirrhosis and hepatocellular carcinoma in patients with human immunodeficiency virus infection. Hepatology 2013;57:249-57.
44. Alhuraiji A, Alaraj A, Alghamdi S, Alrbiaan A, Alrajhi AA. Viral hepatitis B and C in HIV-infected patients in Saudi Arabia. Ann Saudi Med 2014;34:207-10.
45. Al-Faleh FZ, Ayoola EA, Arif M, Ramia S, Al-Rashed R, Al-Jeffry M, *et al*. Seroepidemiology of hepatitis B virus infection in Saudi Arabian children: A baseline survey for mass vaccination against hepatitis B. J Infect 1992;24:197-206.
46. Madani TA. Hepatitis C virus infections reported in Saudi Arabia over 11 years of surveillance. Ann Saudi Med 2007;27:191-4.
47. Ayoola EA, Gadour MO. Hepatocellular carcinoma in Saudi Arabia: Role of hepatitis B and C infection. J Gastroenterol Hepatol 2004;19:665-9.
48. Chang MH, You SL, Chen CJ, Liu CJ, Lai MW, Wu TC, *et al*. Long-term effects of hepatitis b immunization of infants in preventing liver cancer. Gastroenterology 2016;151:472-80.
49. Chien YC, Jan CF, Chiang CJ, Kuo HS, You SL, Chen CJ. Incomplete hepatitis B immunization, maternal carrier status, and increased risk of liver diseases: A 20-year cohort study of 3.8 million vaccinees. Hepatology 2014;60:125-32.
50. Qu C, Chen T, Fan C, Zhan Q, Wang Y, Lu J, *et al*. Efficacy of neonatal HBV vaccination on liver cancer and other liver diseases over 30-year follow-up of the qidong hepatitis b intervention study: A cluster randomized controlled trial. PLOS Med 2015;11:e1001774.
51. Al Ghamdi SS, Fallatah HI, Fetyani DM, Al-Mughales JA, Gelaidan AT. Long-term efficacy of the hepatitis B vaccine in a high-risk group. J Med Virol 2013;85:1518-22.
52. Al-Faleh FZ, Al-Jeffri M, Ramia S, Al-Rashed R, Arif M, Rezeig M, *et al*. Seroepidemiology of Hepatitis B virus infection in Saudi children 8 years after a mass hepatitis B vaccination programme. J Infect 1999;38:167-70.
53. Al-Faleh F, Al-Shehri S, Al-Ansari S, Al-Jeffri M, Al-Mazrou Y, Shaffi A, *et al*. Long- term protection of hepatitis b vaccine 18 years after vaccination. J Infect 2008;57:404-9.
54. Aljumah AA, Babatin M, Hashim A, Abaalkhail F, Bassil N, Safwat M, *et al*. Hepatitis B care pathway in Saudi Arabia: Current situation, gaps and actions. Saudi J Gastroenterol 2019;25:73-80.
55. Alkhayyat S, Fallatah HI, Akbar HO, Ahwal MSA, Ghamdi WSA. Causes and stages of hepatocellular carcinoma at patient presentation at a tertiary medical center in western Saudi Arabia. J Cancer Ther 2014;5:1303-10.
56. Alsohaibani F, Porter G, Al-Ashgar H, Walsh M, Berry R, Molinari M, *et al*. Comparison of cancer care for hepatocellular carcinoma at two tertiary-care referral centers from high and low endemic regions for viral hepatitis. J Gastrointest Cancer 2011;42:228-35.
57. Nouh MS, Bashi SA, Laajam MA, Mofleh IA, al-Aska A. Hepatitis B virus vs schistosomiasis and hepatocellular carcinoma in Saudi Arabia. East Afr Medical J 1990;67:139-45.
58. Varbobitis I, Papatheodoridis GV. The assessment of hepatocellular carcinoma risk in patients with chronic hepatitis B under antiviral therapy. Clin Mol Hepatol 2016;22:319-26.
59. Papatheodoridis GV, Idilman R, Dalekos GN, Buti M, Chi H, van Boemmel F, *et al*. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology 2017;66:1444-53.
60. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, *et al*. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584-93.
61. 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;158:329-37.
62. D'Ambrosio R, Della Corte C, Colombo M. Hepatocellular carcinoma in patients with a sustained response to anti-Hepatitis C therapy. Int J Mol Sci 2015;16:19698-712.
63. Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, *et al*. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol 2016;65:719-26.
64. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, *et al*. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016;65:727-33.
65. Aljumah AA, Abaalkhail F, Al-Ashgar H, Assiri A, Babatin M, Al Faleh F, *et al*. Epidemiology, disease burden, and treatment strategies of chronic hepatitis C virus infections in Saudi Arabia in the new treatment paradigm shift. Saudi J Gastroenterol 2016;22:269-81.
66. Altraif I. Can hepatitis C virus be eliminated by 2030? Saudi Arabia as an example. Saudi Med J 2018;39:842-5.
67. Aleksandrova K, Bamia C, Drogan D, Lagiou P, Trichopoulou A, Jenab M, *et al*. The association of coffee intake with liver cancer risk is mediated by biomarkers of inflammation and hepatocellular injury: Data from the European Prospective Investigation into Cancer and Nutrition. Am J Clin Nutr 2015;102:1498-508.
68. European Association for the Study of the Liver. Electronic address: European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
69. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: Special emphasis on disease progression and prognostic factors. J Hepatol 2008;48:335-52.
70. Yang HI, Yuen MF, Chan HL, Han KH, Chen PJ, Kim DY, *et al*. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): Development and validation of a predictive score. Lancet Oncol 2011;12:568-74.
71. Lok AS, Seeff LB, Morgan TR, di Bisceglie AM, Sterling RK, Curto TM, *et al*. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. Gastroenterology 2009;136:138-48.
72. Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. J Hepatol 2003;39:1076-84.
73. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, *et al*. Meta-analysis: Surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30:37-47.

74. Gambarin-Gelwan M, Wolf DC, Shapiro R, Schwartz ME, Min AD. Sensitivity of commonly available screening tests in detecting hepatocellular carcinoma in cirrhotic patients undergoing liver transplantation. Am J Gastroenterol 2000;95:1535-8.
75. Biselli M, Conti F, Gramenzi A, Frigerio M, Cucchetti A, Fatti G, *et al*. A new approach to the use of α-fetoprotein as surveillance test for hepatocellular carcinoma in patients with cirrhosis. Br J Cancer 2015;112:69-76.
76. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, *et al*. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358-80.
77. Di Bisceglie AM, Sterling RK, Chung RT, Everhart JE, Dienstag JL, Bonkovsky HL, *et al*. Serum alpha-fetoprotein levels in patients with advanced hepatitis C: Results from the HALT-C Trial. J Hepatol 2005;43:434-41.
78. Marrero JA, Feng Z, Wang Y, Nguyen MH, Befeler AS, Roberts LR, *et al*. Alpha-fetoprotein, des-gamma carboxyprothrombin, and lectin-bound alpha-fetoprotein in early hepatocellular carcinoma. Gastroenterology 2009;137:110-8.
79. Lok AS, Sterling RK, Everhart JE, Wright EC, Hoefs JC, Di Bisceglie AM, *et al*. Des-gamma-carboxy prothrombin and alpha-fetoprotein as biomarkers for the early detection of hepatocellular carcinoma. Gastroenterology 2010;138:493-502.
80. Capurro M, Wanless IR, Sherman M, Deboer G, Shi W, Miyoshi E, *et al*. Glypican-3: A novel serum and histochemical marker for hepatocellular carcinoma. Gastroenterology 2003;125:89-97.
81. Shen Q, Fan J, Yang XR, Tan Y, Zhao W, Xu Y, *et al*. Serum DKK1 as a protein biomarker for the diagnosis of hepatocellular carcinoma: A large-scale, multicentre study. Lancet Oncol 2012;13:817-26.
82. Farag RMA, Al Ayobi D, Alsaleh KA, Kwon HJ, EL-Ansary A, Dawoud EA. Studying the impact of golgi protein 73 serving as a candidate biomarker in early diagnosis for hepatocellular carcinoma among Saudi patients. Asian Pac J Cancer Prev 2019;20:215-20.
83. Trinchet JC, Chaffaut C, Bourcier V, Degos F, Henrion J, Fontaine H, *et al*. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: A randomized trial comparing 3-and 6-month periodicities. Hepatology 2011;54:1987-97.
84. Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P, *et al*. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol 2010;53:291-7.
85. Trevisani F, Santi V, Gramenzi A, Di Nolfo MA, Del Poggio P, Benvegnù L, *et al*. Surveillance for early diagnosis of hepatocellular carcinoma: Is it effective in intermediate/advanced cirrhosis? Am J Gastroenterol 2007;102:2448-57.
86. Hanna RF, Miloushev VZ, Tang A, Finklestone LA, Brejt SZ, Sandhu RS, *et al*. Comparative 13-year meta-analysis of the sensitivity and positive predictive value of ultrasound, CT, and MRI for detecting hepatocellular carcinoma. Abdom Radiol (NY) 2016;41:71-90.
87. Lee YJ, Lee JM, Lee JS, Lee HY, Park BH, Kim YH, *et al*. Hepatocellular carcinoma: Diagnostic performance of multidetector CT and MR imaging-A systematic review and meta-analysis. Radiology 2015;275:97-109.
88. Chou R, Cuevas C, Fu R, Devine B, Wasson N, Ginsburg A, *et al*. Imaging techniques for the diagnosis of hepatocellular carcinoma: A systematic review and meta-analysis. Ann Intern Med 2015;162:697-711.
89. Aube C, Oberti F, Lonjon J, Pageaux G, Seror O, N'Kontchou G, *et al*. EASL and AASLD recommendations for the diagnosis of HCC to the test of daily practice. Liver Int 2017;37:1515-25.
90. Guo J, Seo Y, Ren S, Hong S, Lee D, Kim S, *et al*. Diagnostic performance of contrast-enhanced multidetector computed tomography and gadoxetic acid disodium-enhanced magnetic resonance imaging in detecting hepatocellular carcinoma: Direct comparison and a meta-analysis. Abdom Radiol (NY) 2016;41:1960-72.
91. Duncan JK, Ma N, Vreugdenburg TD, Cameron AL, Maddern G. Gadoxetic acid-enhanced MRI for the characterization of hepatocellular carcinoma: A systematic review and meta-analysis. J Magn Reson Imaging 2017;45:281-90.
92. Ayuso C, Forner A, Darnell A, Rimola J, García-Criado Á, Bianchi L, *et al*. Prospective evaluation of gadoxetic acid magnetic resonance for the diagnosis of hepatocellular carcinoma in newly detected nodules≤2 cm in cirrhosis. Liver Int 2019;39:1281-91.
93. Paisant A, Vilgrain V, Riou J, Oberti F, Sutter O, Laurent V, *et al*. Comparison of extracellular and hepatobiliary MR contrast agents for the diagnosis of small HCCs. J Hepatol 2020;72:937-45.
94. Vilana R, Forner A, Bianchi L, García-Criado A, Rimola J, de Lope CR, *et al*. Intrahepatic peripheral cholangiocarcinoma in cirrhosis patients may display a vascular pattern similar to hepatocellular carcinoma on contrast-enhanced ultrasound. Hepatology 2010;51:2020-9.
95. Galassi M, Iavarone M, Rossi S, Bota S, Vavassori S, Rosa L, *et al*. Patterns of appearance and risk of misdiagnosis of intrahepatic cholangiocarcinoma in cirrhosis at contrast enhanced ultrasound. Liver Int 2013;33:771-9.
96. Piscaglia F, Wilson SR, Lyshchik A, Cosgrove D, Dietrich CF, Jang HJ, *et al*. American College of Radiology Contrast Enhanced Ultrasound Liver Imaging Reporting and Data System (CEUS LI-RADS) for the diagnosis of Hepatocellular Carcinoma: A pictorial essay. Ultraschall Med 2017;38:320-4.
97. Terzi E, Iavarone M, Pompili M, Veronese L, Cabibbo G, Fraquelli M, *et al*. Contrast ultrasound LI-RADS LR-5 identifies hepatocellular carcinoma in cirrhosis in a multicenter restropective study of 1,006 nodules. J Hepatol 2018;68:485-92.
98. Forner A, Vilana R, Ayuso C, Bianchi L, Sole M, Ayuso JR, *et al*. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology 2008;47:97-104.
99. Chotipanich C, Kunawudhi A, Promteangtrong C, Tungsuppawattanakit P, Sricharunrat T, Wongsa P. Diagnosis of hepatocellular carcinoma using C11 Choline PET/CT: Comparison with F18 FDG, Contrast Enhanced MRI and MDCT. Asian Pac J Cancer Prev 2016;17:3569-73.
100. Lopci E, Torzilli G, Poretti D, de Neto LJ, Donadon M, Rimassa L, *et al*. Diagnostic accuracy of ^{11}C-choline PET/CT in comparison with CT and/or MRI in patients with hepatocellular carcinoma. Eur J Nucl Med Mol Imaging 2015;42:1399-407.
101. El Jabbour T, Lagana SM, Lee H. Update on hepatocellular carcinoma: Pathologists' review. World J Gastroenterol 2019;25:1653-65.
102. Koehne de Gonzalez AK, Salomao MA, Lagana SM. Current concepts in the immunohistochemical evaluation of liver tumors. World J Hepatol 2015;7:1403-11.
103. Di Tommaso L, Destro A, Seok JY, Balladore E, Terracciano L, Sangiovanni A, *et al*. The application of markers (HSP70 GPC3 and GS) in liver biopsies is useful for detection of hepatocellular carcinoma. J Hepatol 2009;50:746-54.
104. The International Consensus Group for Hepatocellular Neoplasia. Pathologic diagnosis of early hepatocellular carcinoma: A report of the international consensus group for hepatocellular neoplasia. Hepatology 2009;49:658-64.
105. Uthamalingam P, Das A, Behra A, Kalra N, Chawla Y. Diagnostic value of glypican3, heat shock protein 70 and glutamine synthetase in hepatocellular carcinoma arising in cirrhotic and non-cirrhotic livers. J Clin Exp Hepatol 2018;8:173-80.
106. Roskams T, Kojiro M. Pathology of early hepatocellular carcinoma: Conventional and molecular diagnosis. Semin Liver Dis 2010;30:17-25.
107. Kim H, Choi GH, Na DC, Ahn EY, Kim GI, Lee JE, *et al*. Human hepatocellular carcinomas with "Stemness"-related marker expression: Keratin 19 expression and a poor prognosis. Hepatology 2011;54:1707-17.
108. Chan AW, Tong JH, Chan SL, Lai PB, To KF. Expression of stemness markers (CD133 and EpCAM) in prognostication of hepatocellular carcinoma. Histopathology 2014;64:935-50.
109. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver

biopsy. Hepatology 2009;49:1017-44.
110. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology 2016;150:835-53.
111. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, *et al*. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56:918-28.
112. Chan AC, Fan ST, Poon RT, Cheung TT, Chok KS, Chan SC, *et al*. Evaluation of the seventh edition of the American Joint Committee on Cancer tumour-node-metastasis (TNM) staging system for patients undergoing curative resection of hepatocellular carcinoma: Implications for the development of a refined staging system. HPB (Oxford) 2013;15:439-48.
113. Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G, *et al*. Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol 2006;44:723-31.
114. Chen CH, Hu FC, Huang GT, Lee PH, Tsang YM, Cheng AL, *et al*. Applicability of staging systems for patients with hepatocellular carcinoma is dependent on treatment method--analysis of 2010 Taiwanese patients. Eur J Cancer 2009;45:1630-9.
115. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, *et al*. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723-50.
116. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: The BCLC staging classification. Semin Liver Dis 1999;19:329-38.
117. Yau T, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology 2014;146:1691-700.
118. Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, *et al*. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 2003;38:200-7.
119. Vibert E, Azoulay D, Hoti E, Iacopinelli S, Samuel D, Salloum C, *et al*. Progression of alphafetoprotein before liver transplantation for hepatocellular carcinoma in cirrhotic patients: A critical factor. Am J Transplant 2010;10:129-37.
120. Merani S, Majno P, Kneteman NM, Berney T, Morel P, Mentha G, *et al*. The impact of waiting list alpha-fetoprotein changes on the outcome of liver transplant for hepatocellular carcinoma. J Hepatol 2011;55:814-9.
121. Notarpaolo A, Layese R, Magistri P, Gambato M, Colledan M, Magini G, *et al*. Validation of the AFP model as a predictor of HCC recurrence in patients with viral hepatitis-related cirrhosis who had received a liver transplant for HCC. J Hepatol 2017;66:552-9.
122. Hasegawa K, Kokudo N, Makuuchi M, Izumi N, Ichida T, Kudo M, *et al*. Comparison of resection and ablation for hepatocellular carcinoma: A cohort study based on a Japanese nationwide survey. J Hepatol 2013;58:724-9.
123. Roayaie S, Obeidat K, Sposito C, Mariani L, Bhoori S, Pellegrinelli A, *et al*. Resection of hepatocellular cancer≤2 cm: Results from two Western centers. Hepatology 2013;57:1426-35.
124. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, *et al*. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? Hepatology 2008;47:82-9.
125. Cho YK, Kim JK, Kim WT, Chung JW. Hepatic resection versus radiofrequency ablation for very early stage hepatocellular carcinoma: A Markov model analysis. Hepatology 2010;51:1284-90.
126. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Ercolani G, Bolondi L, *et al*. Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. J Hepatol 2013;59:300-7.
127. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: The BCLC update and future prospects. Semin Liver Dis 2010;30:61-74.
128. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: Resection versus transplantation. Hepatology 1999;30:1434-40.
129. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, *et al*. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology 2008;134:1908-16.
130. Berzigotti A, Reig M, Abraldes JG, Bosch J, Bruix J. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: A systematic review and meta-analysis. Hepatology 2015;61:526-36.
131. Cabibbo G, Enea M, Attanasio M, Bruix J, Craxì A, Cammà C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology 2010;51:1274-83.
132. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003;37:429-42.
133. Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, *et al*. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. Lancet 2002;359:1734-9.
134. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, *et al*. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-71.
135. Takayasu K, Arii S, Kudo M, Ichida T, Matsui O, Izumi N, *et al*. Superselective transarterial chemoembolization for hepatocellular carcinoma. Validation of treatment algorithm proposed by Japanese guidelines. J Hepatol 2012;56:886-92.
136. Burrel M, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, *et al*. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. J Hepatol 2012;56:1330-5.
137. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, *et al*. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
138. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, *et al*. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-9.
139. Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R, *et al*. Milan criteria in liver transplantation for hepatocellular carcinoma: An evidence-based analysis of 15 years of experience. Liver Transpl 2011;17:S44-57.
140. Yao FY, Xiao L, Bass NM, Kerlan R, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: Validation of the UCSF-expanded criteria based on preoperative imaging. Am J Transplant 2007;7:2587-96.
141. Decaens T, Roudot-Thoraval F, Hadni-Bresson S, Meyer C, Gugenheim J, Durand F, *et al*. Impact of UCSF criteria according to pre- and post-OLT tumor features: Analysis of 479 patients listed for HCC with a short waiting time. Liver Transpl 2006;12:1761-9.
142. Abdelfattah MR, Elsiesy H, Al-Manea H, Broering DC. Liver transplantation for hepatocellular carcinoma within the Milan criteria versus the University of California San Francisco criteria: A comparative study. Eur J Gastroenterol Hepatol 2018;30:398-403.
143. Toso C, Meeberg G, Hernandez-Alejandro R, Dufour JF, Marotta P, Majno P, *et al*. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: A prospective validation. Hepatology 2015;62:158-65.
144. Pommergaard HC, Rostved AA, Adam R, Thygesen LC, Salizzoni M, Gómez Bravo MA, *et al*. Vascular invasion and survival after liver transplantation for hepatocellular carcinoma: A study from the European Liver Transplant Registry. HPB (Oxford) 2018;20:768-75.
145. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular

intrahepatic portosystemic shunts. Hepatology 2000;31:864-71.
146. Toso C, Mazzaferro V, Bruix J, Freeman R, Mentha G, Majno P. Toward a better liver graft allocation that accounts for candidates with and without hepatocellular carcinoma. Am J Transplant 2014;14:2221-7.
147. Bhangui P, Vibert E, Majno P, Salloum C, Andreani P, Zocrato J, *et al*. Intention-to-treat analysis of liver transplantation for hepatocellular carcinoma: Living versus deceased donor transplantation. Hepatology 2011;53:1570-9.
148. Azoulay D, Audureau E, Bhangui P, Belghiti J, Boillot O, Andreani P, *et al*. Living or brain-dead donor liver transplantation for hepatocellular carcinoma: A multicenter, western, intent-to-treat cohort study. Ann Surg 2017;266:1035-44.
149. Al Sebayel M, Abaalkhail F, Hashim A, Al Bahili H, Alabbad S, Shoukdy M, *et al*. Living donor liver transplant versus cadaveric liver transplant survival in relation to model for end-stage liver disease score. Transplant Proc 2015;47:1211-3.
150. Al Sebayel M, Abaalkhail F, Al Abbad S, AlBahili H, Elsiesy H, Aleid M, *et al*. Liver transplantation in the Kingdom of Saudi Arabia. Liver Transpl 2017;23:1312-7.
151. Shimamura T, Akamatsu N, Fujiyoshi M, Kawaguchi A, Morita S, Kawasaki S, *et al*. Expanded living-donor liver transplantation criteria for patients with hepatocellular carcinoma based on the Japanese nationwide survey: The 5-5-500 rule-A retrospective study. Transpl Int 2019;32:356-68.
152. Yao FY, Bass NM, Nikolai B, Merriman R, Davern TJ, Kerlan R, *et al*. A follow-up analysis of the pattern and predictors of dropout from the waiting list for liver transplantation in patients with hepatocellular carcinoma: Implications for the current organ allocation policy. Liver Transpl 2003;9:684-92.
153. Majno P, Lencioni R, Mornex F, Girard N, Poon RT, Cherqui D. Is the treatment of hepatocellular carcinoma on the waiting list necessary? Liver Transpl 2011;17:S98-108.
154. Lesurtel M, Müllhaupt B, Pestalozzi BC, Pfammatter T, Clavien PA. Transarterial chemoembolization as a bridge to liver transplantation for hepatocellular carcinoma: An evidence-based analysis. Am J Transplant 2006;6:2644-50.
155. Sapisochin G, Barry A, Doherty M, Fischer S, Goldaracena N, Rosales R, *et al*. Stereotactic body radiotherapy vs. TACE or RFA as a bridge to transplant in patients with hepatocellular carcinoma. An intention-to-treat analysis. J Hepatol 2017;67:92-9.
156. Samuel D, Coilly A. Management of patients with liver diseases on the waiting list for transplantation: A major impact to the success of liver transplantation. BMC Med 2018;16:113.
157. Montalti R, Mimmo A, Rompianesi G, Di Gregorio C, Serra V, Cautero N, *et al*. Absence of viable HCC in the native liver is an independent protective factor of tumor recurrence after liver transplantation. Transplantation 2014;97:220-6.
158. Ravaioli M, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, *et al*. Liver transplantation for hepatocellular carcinoma: Results of down-staging in patients initially outside the Milan selection criteria. Am J Transplant 2008;8:2547-57.
159. Yao FY, Mehta N, Flemming J, Dodge J, Hameed B, Fix O, *et al*. Downstaging of hepatocellular cancer before liver transplant: Long-term outcome compared to tumors within Milan criteria. Hepatology 2015;61:1968-77.
160. Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: A systematic review and pooled analysis. Liver Transpl 2015;21:1142-52.
161. Tabrizian P, Holzner M, Halazum K, Agopian V, Busutill R. A US multicenter analysis of 2528 HCC patients undergoing liver transplantation: 10-year outcome assessing the role of downstaging to within Milan criteria. Hepatology 2019;70:10A (Suppl S1).
162. Sotiropoulos GC, Molmenti EP, Lösch C, Beckebaum S, Broelsch CE, Lang H. Meta-analysis of tumor recurrence after liver transplantation for hepatocellular carcinoma based on 1,198 cases. Eur J Med Res 2007;12:527-34.
163. Silva MF, Sherman M. Criteria for liver transplantation for HCC: What should the limits be? J Hepatol 2011;55:1137-47.
164. Mehta N, Heimbach J, Harnois DM, Sapisochin G, Dodge JL, Lee D, *et al*. Validation of a Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score for hepatocellular carcinoma recurrence after liver transplant. JAMA Oncol 2017;3:493-500.
165. Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, *et al*. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: Involvement of vascular endothelial growth factor. Nat Med 2002;8:128-35.
166. Menon KV, Hakeem AR, Heaton ND. Meta-analysis: Recurrence and survival following the use of sirolimus in liver transplantation for hepatocellular carcinoma. Aliment Pharmacol Ther 2013;37:411-9.
167. Geissler EK, Schnitzbauer AA, Zulke C, Lamby PE, Proneth A, Duvoux C, *et al*. Sirolimus use in liver transplant recipients with hepatocellular carcinoma: A randomized, multicenter, open-label phase 3 trial. Transplantation 2016;100:116-25.
168. Bruix J, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, *et al*. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): A phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2015;16:1344-54.
169. Vitale A, Huo TL, Cucchetti A, Lee YH, Volk M, Frigo AC, *et al*. Survival benefit of liver transplantation versus resection for hepatocellular carcinoma: Impact of MELD score. Ann Surg Oncol 2015;22:1901-7.
170. Lang H, Sotiropoulos GC, Dömland M, Frühauf NR, Paul A, Hüsing J, *et al*. Liver resection for hepatocellular carcinoma in non-cirrhotic liver without underlying viral hepatitis. Br J Surg 2005;92:198-202.
171. Al-Alem F, Mattar RE, Fadl OA, Alsharabi A, Al-Saif F, Hassanain M. Morbidity and mortality and predictors of outcome following hepatectomy at a Saudi tertiary care center. Ann Saudi Med 2016;36:414-21.
172. Cauchy F, Zalinski S, Dokmak S, Fuks D, Farges O, Castera L, *et al*. Surgical treatment of hepatocellular carcinoma associated with the metabolic syndrome. Br J Surg 2013;100:113-21.
173. Vigano L, Conci S, Cescon M, Fava C, Capelli P, D'Errico A, *et al*. Liver resection for hepatocellular carcinoma in patients with metabolic syndrome: A multicenter matched analysis with HCV-related HCC. J Hepatol 2015;63:93-101.
174. Roayaie S, Jibara G, Tabrizian P, Park JW, Yang J, Yan L, *et al*. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology 2015;62:440-51.
175. Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, Ramacciato G, *et al*. Is portal hypertension a contraindication to hepatic resection? Ann Surg 2009;250:922-8.
176. Zipprich A, Kuss O, Rogowski S, Kleber G, Lotterer E, Seufferlein T, *et al*. Incorporating indocyanin green clearance into the Model for End Stage Liver Disease (MELD-ICG) improves prognostic accuracy in intermediate to advanced cirrhosis. Gut 2010;59:963-8.
177. De Gasperi A, Mazza E, Prosperi M. Indocyanine green kinetics to assess liver function: Ready for a clinical dynamic assessment in major liver surgery? World J Hepatol 2016;8:355-67.
178. Wong JS, Wong GL, Chan AW, Wong VW, Cheung YS, Chong CN, *et al*. Liver stiffness measurement by transient elastography as a predictor on posthepatectomy outcomes. Ann Surg 2013;257:922-8.
179. Maegawa FB, Shehorn L, Aziz H, Kettelle J, Jie T, Riall TS. Association between noninvasive fibrosis markers and postoperative mortality after hepatectomy for hepatocellular carcinoma. JAMA Netw Open 2019;2:e187142.
180. Yin L, Li H, Li AJ, Lau WY, Pan ZY, Lai EC, *et al*. Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan Criteria: A RCT. J Hepatol 2014;61:82-8.
181. Zhong JH, Xiang BD, Gong WF, Ke Y, Mo QG, Ma L, *et al*. Comparison of long-term survival of patients with BCLC stage B hepatocellular

carcinoma after liver resection or transarterial chemoembolization. PLoS One 2013;8:e68193.
182. Li ZL, Yu JJ, Guo JW, Sui CJ, Dai BH, Zhang WG, *et al*. Liver resection is justified for multinodular hepatocellular carcinoma in selected patients with cirrhosis: A multicenter analysis of 1,066 patients. Eur J Surg Oncol 2019;45:800-7.
183. Chan SL, Chong CC, Chan AW, Poon DM, Chok KS. Management of hepatocellular carcinoma with portal vein tumor thrombosis: Review and update at 2016. World J Gastroenterol 2016;22:7289-300.
184. Guglielmi A, Ruzzenente A, Conci S, Valdegamberi A, Vitali M, Bertuzzo F, *et al*. Hepatocellular carcinoma: Surgical perspectives beyond the barcelona clinic liver cancer recommendations. World J Gastroenterol 2014;20:7525-33.
185. Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, *et al*. A new classification for hepatocellular carcinoma with portal vein tumor thrombus. J Hepatobiliary Pancreat Sci 2011;18:74-80.
186. Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, *et al*. Liver resection for hepatocellular carcinoma associated with hepatic vein invasion: A Japanese nationwide survey. Hepatology 2017;66:510-7.
187. Pesi B, Ferrero A, Grazi GL, Cescon M, Russolillo N, Leo F, *et al*. Liver resection with thrombectomy as a treatment of hepatocellular carcinoma with major vascular invasion: Results from a retrospective multicentric study. Am J Surg 2015;210:35-44.
188. Wei X, Jiang Y, Zhang X, Feng S, Zhou B, Ye X, *et al*. Neoadjuvant three-dimensional conformal radiotherapy for resectable hepatocellular carcinoma with portal vein tumor thrombus: A randomized, open-label, multicenter controlled study. J Clin Oncol 2019;37:2141-51.
189. Sun J, Yang L, Shi J, Liu C, Zhang X, Chai Z, *et al*. Postoperative adjuvant IMRT for patients with HCC and portal vein tumor thrombus: An open-label randomized controlled trial. Radiother Oncol 2019;140:20-5.
190. Sotiropoulos GC, Prodromidou A, Kostakis ID, Machairas N. Meta-analysis of laparoscopic vs open liver resection for hepatocellular carcinoma. Updates Surg 2017;69:291-311.
191. Morise Z, Ciria R, Cherqui D, Chen KH, Belli G, Wakabayashi G. Can we expand the indications for laparoscopic liver resection? A systematic review and meta-analysis of laparoscopic liver resection for patients with hepatocellular carcinoma and chronic liver disease. J Hepatobiliary Pancreat Sci 2015;22:342-52.
192. Takahara T, Wakabayashi G, Beppu T, Aihara A, Hasegawa K, Gotohda N, *et al*. Long-term and perioperative outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma with propensity score matching: A multi-institutional Japanese study. J Hepatobiliary Pancreat Sci 2015;22:721-7.
193. Al-Saif FA, Aldekhayel MK, Al-Alem F, Hassanain MM, Mattar RE, Alsharabi A. Comparison study between open and laparoscopic liver resection in a Saudi tertiary center. Saudi Med J 2019;40:452-7.
194. Zhou Y, Xu D, Wu L, Li B. Meta-analysis of anatomic resection versus nonanatomic resection for hepatocellular carcinoma. Langenbecks Arch Surg 2011;396:1109-17.
195. Ye JZ, Miao ZG, Wu FX, Zhao YN, Ye HH, Li LQ. Recurrence after anatomic resection versus nonanatomic resection for hepatocellular carcinoma: A meta-analysis. Asian Pac J Cancer Prev 2012;13:1771-7.
196. Ha TY, Hwang S, Lee YJ, Kim KH, Ko GY, Ii Gwon D, *et al*. Absence of benefit of Transcatheter Arterial Chemoembolization (TACE) in patients with resectable solitary hepatocellular carcinoma. World J Surg 2016;40:1200-10.
197. Lu LC, Cheng AL, Poon RT. Recent advances in the prevention of hepatocellular carcinoma recurrence. Semin Liver Dis 2014;34:427-34.
198. Takayama T, Sekine T, Makuuchi M, Yamasaki S, Kosuge T, Yamamoto J, *et al*. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: A randomised trial. Lancet 2000;356:802-7.
199. Lee JH, Lee JH, Lim YS, Yeon JE, Song TJ, Yu SJ, *et al*. Adjuvant immunotherapy with autologous cytokine-induced killer cells for hepatocellular carcinoma. Gastroenterology 2015;148:1383-91.
200. Lee JH, Lee JH, Lim YS, Yeon JE, Song TJ, Yu SJ, *et al*. Sustained efficacy of adjuvant immunotherapy with cytokine-induced killer cells for hepatocellular carcinoma: An extended 5-year follow-up. Cancer Immunol Immunother 2019;68:23-32.
201. Knavel EM, Brace CL. Tumor ablation: Common modalities and general practices. Tech Vasc Interv Radiol 2013;16:192-200.
202. Livraghi T, Giorgio A, Marin G, Salmi A, de Sio I, Bolondi L, *et al*. Hepatocellular carcinoma and cirrhosis in 746 patients: Long-term results of percutaneous ethanol injection. Radiology 1995;197:101-8.
203. Pompili M, De Matthaeis N, Saviano A, De Sio I, Francica G, Brunello F, *et al*. Single hepatocellular carcinoma smaller than 2 cm: Are ethanol injection and radiofrequency ablation equally effective? Anticancer Res 2015;35:325-32.
204. Germani G, Pleguezuelo M, Gurusamy K, Meyer T, Isgrò G, Burroughs AK. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocelullar carcinoma: A meta-analysis. J Hepatol 2010;52:380-8.
205. Orlando A, Leandro G, Olivo M, Andriulli A, Cottone M. Radiofrequency thermal ablation vs. percutaneous ethanol injection for small hepatocellular carcinoma in cirrhosis: Meta-analysis of randomized controlled trials. Am J Gastroenterol 2009;104:514-24.
206. Cho YK, Kim JK, Kim MY, Rhim H, Han JK. Systematic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. Hepatology 2009;49:453-9.
207. Izzo F, Granata V, Grassi R, Fusco R, Palaia R, Delrio P, *et al*. Radiofrequency ablation and microwave ablation in liver tumors: An update. Oncologist 2019;24:e990-1005.
208. Park EK, Kim HJ, Kim CY, Hur YH, Koh YS, Kim JC, *et al*. A comparison between surgical resection and radiofrequency ablation in the treatment of hepatocellular carcinoma. Ann Surg Treat Res 2014;87:72-80.
209. Kim GA, Shim JH, Kim MJ, Kim SY, Won HJ, Shin YM, *et al*. Radiofrequency ablation as an alternative to hepatic resection for single small hepatocellular carcinomas. Br J Surg 2016;103:126-35.
210. Majumdar A, Roccarina D, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Management of people with early- or very early-stage hepatocellular carcinoma: An attempted network meta-analysis. Cochrane Database Syst Rev 2017;3:Cd011650.
211. Cucchetti A, Piscaglia F, Cescon M, Serra C, Colecchia A, Maroni L, *et al*. An explorative data-analysis to support the choice between hepatic resection and radiofrequency ablation in the treatment of hepatocellular carcinoma. Dig Liver Dis 2014;46:257-63.
212. Mulier S, Ni Y, Jamart J, Ruers T, Marchal G, Michel L. Local recurrence after hepatic radiofrequency coagulation: Multivariate meta-analysis and review of contributing factors. Ann Surg 2005;242:158-71.
213. Kang TW, Lim HK, Lee MW, Kim YS, Rhim H, Lee WJ, *et al*. Long-term therapeutic outcomes of radiofrequency ablation for subcapsular versus nonsubcapsular hepatocellular carcinoma: A propensity score matched study. Radiology 2016;280:300-12.
214. Sun Y, Wang Y, Ni X, Gao Y, Shao Q, Liu L, *et al*. Comparison of ablation zone between 915- and 2,450-MHz cooled-shaft microwave antenna: Results in *in vivo* porcine livers. AJR Am J Roentgenol 2009;192:511-4.
215. Baker EH, Thompson K, McKillop IH, Cochran A, Kirks R, Vrochides D, *et al*. Operative microwave ablation for hepatocellular carcinoma: A single center retrospective review of 219 patients. J Gastrointest Oncol 2017;8:337-46.
216. Liang P, Wang Y, Yu X, Dong B. Malignant liver tumors: Treatment with percutaneous microwave ablation--complications among cohort of 1136 patients. Radiology 2009;251:933-40.
217. Glassberg MB, Ghosh S, Clymer JW, Wright GWJ, Ferko N, Amaral JF. Microwave ablation compared with hepatic resection for the treatment of hepatocellular carcinoma and liver metastases: A systematic review and meta-analysis. World J Surg Oncol 2019;17:98.
218. Poulou LS, Botsa E, Thanou I, Ziakas PD, Thanos L. Percutaneous

microwave ablation vs radiofrequency ablation in the treatment of hepatocellular carcinoma. World J Hepatol 2015;7:1054-63.
219. Facciorusso A, Di Maso M, Muscatiello N. Microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma: A systematic review and meta-analysis. Int J Hyperthermia 2016;32:339-44.
220. Vietti Violi N, Duran R, Guiu B, Cercueil JP, Aubé C, Digklia A, *et al*. Efficacy of microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma in patients with chronic liver disease: A randomised controlled phase 2 trial. Lancet Gastroenterol Hepatol 2018;3:317-25.
221. Cammà C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, *et al*. Transarterial chemoembolization for unresectable hepatocellular carcinoma: Meta-analysis of randomized controlled trials. Radiology 2002;224:47-54.
222. Lencioni R, de Baere T, Soulen MC, Rilling WS, Geschwind JF. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: A systematic review of efficacy and safety data. Hepatology 2016;64:106-16.
223. Brown DB, Nikolic B, Covey AM, Nutting CW, Saad WE, Salem R, *et al*. Quality improvement guidelines for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy. J Vasc Interv Radiol 2012;23:287-94.
224. Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, *et al*. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: Proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012;32:348-59.
225. Forner A, Gilabert M, Bruix J, Raoul JL. Treatment of intermediate-stage hepatocellular carcinoma. Nat Rev Clin Oncol 2014;11:525-35.
226. Golfieri R, Giampalma E, Renzulli M, Cioni R, Bargellini I, Bartolozzi C, *et al*. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 2014;111:255-64.
227. Gao S, Yang Z, Zheng Z, Yao J, Deng M, Xie H, *et al*. Doxorubicin-eluting bead versus conventional TACE for unresectable hepatocellular carcinoma: A meta-analysis. Hepatogastroenterology 2013;60:813-20.
228. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, *et al*. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: Results of the PRECISION V study. Cardiovasc Intervent Radiol 2010;33:41-52.
229. Monier A, Guiu B, Duran R, Aho S, Bize P, Deltenre P, *et al*. Liver and biliary damages following transarterial chemoembolization of hepatocellular carcinoma: Comparison between drug-eluting beads and lipiodol emulsion. Eur Radiol 2017;27:1431-9.
230. Li L, Tian J, Liu P, Wang X, Zhu Z. Transarterial chemoembolization combination therapy vs monotherapy in unresectable hepatocellular carcinoma: A meta-analysis. Tumori 2016;2016:301-10.
231. Iezzi R, Pompili M, La Torre MF, Campanale MC, Montagna M, Saviano A, *et al*. Radiofrequency ablation plus drug-eluting beads transcatheter arterial chemoembolization for the treatment of single large hepatocellular carcinoma. Dig Liver Dis 2015;47:242-8.
232. Kudo M, Han G, Finn RS, Poon RT, Blanc JF, Yan L, *et al*. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: A randomized phase III trial. Hepatology 2014;60:1697-707.
233. Lencioni R, Llovet JM, Han G, Tak WY, Yang J, Guglielmi A, *et al*. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. J Hepatol 2016;64:1090-8.
234. Meyer T, Fox R, Ma YT, Ross PJ, James MW, Sturgess R, *et al*. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): A randomised placebo-controlled, double-blind, phase 3 trial. Lancet Gastroenterol Hepatol 2017;2:565-75.
235. Kudo M, Cheng AL, Park JW, Park JH, Liang PC, Hidaka H, *et al*. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma (ORIENTAL): A randomised, double-blind, placebo-controlled, multicentre, phase 3 study. Lancet Gastroenterol Hepatol 2018;3:37-46.
236. Jin PP, Shao SY, Wu WT, Zhao XY, Huang BF, Fu QH, *et al*. Combination of transarterial chemoembolization and sorafenib improves outcomes of unresectable hepatocellular carcinoma: An updated systematic review and meta-analysis. Jpn J Clin Oncol 2018;48:1058-69.
237. Kudo M, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, *et al*. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut 2020;69:1492-501.
238. Sacco R, Conte C, Tumino E, Parisi G, Marceglia S, Metrangolo S, *et al*. Transarterial radioembolization for hepatocellular carcinoma: A review. J Hepatocell Carcinoma 2016;3:25-9.
239. Gordon A, Lewandowski R, Hickey R, Kallini J, Gabr A, Sato K, *et al*. Prospective randomized phase 2 study of chemoembolization versus radioembolization in hepatocellular carcinoma: Results from the PREMIERE trial. J Vasc Interv Radiol 2016;27:S61-2.
240. Kolligs FT, Bilbao JI, Jakobs T, Iñarrairaegui M, Nagel JM, Rodriguez M, *et al*. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. Liver Int 2015;35:1715-21.
241. Lobo L, Yakoub D, Picado O, Ripat C, Pendola F, Sharma R, *et al*. Unresectable hepatocellular carcinoma: Radioembolization versus chemoembolization: A systematic review and meta-analysis. Cardiovasc Intervent Radiol 2016;39:1580-8.
242. Abdel-Rahman OM, Elsayed Z. Yttrium-90 microsphere radioembolisation for unresectable hepatocellular carcinoma. Cochrane Database Syst Rev 2016;2:Cd011313.
243. Soydal C, Arslan MF, Kucuk ON, Idilman R, Bilgic S. Comparison of survival, safety, and efficacy after transarterial chemoembolization and radioembolization of Barcelona clinic liver cancer stage B-C hepatocellular cancer patients. Nucl Med Commun 2016;37:646-9.
244. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, *et al*. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): An open-label randomised controlled phase 3 trial. Lancet Oncol 2017;18:1624-36.
245. Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, *et al*. SIRveNIB: Selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. J Clin Oncol 2018;36:1913-21.
246. Ricke J, Klümpen HJ, Amthauer H, Bargellini I, Bartenstein P, de Toni EN, *et al*. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. J Hepatol 2019;71:1164-74.
247. Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, *et al*. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2016;151:1155-63.e2.
248. Abdelfattah MR, Al-Sebayel M, Broering D, Alsuhaibani H. Radioembolization using yttrium-90 microspheres as bridging and downstaging treatment for unresectable hepatocellular carcinoma before liver transplantation: Initial single-center experience. Transplant Proc 2015;47:408-11.
249. Kim N, Kim HJ, Won JY, Kim DY, Han KH, Jung I, *et al*. Retrospective analysis of stereotactic body radiation therapy efficacy over radiofrequency ablation for hepatocellular carcinoma. Radiother Oncol 2019;131:81-7.
250. Wahl DR, Stenmark MH, Tao Y, Pollom EL, Caoili EM, Lawrence TS, *et al*. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. J Clin Oncol 2016;34:452-9.
251. Sapir E, Tao Y, Schipper MJ, Bazzi L, Novelli PM, Devlin P, *et al*. Stereotactic body radiation therapy as an alternative to transarterial chemoembolization for hepatocellular carcinoma. Int J Radiat Oncol

Biol Phys 2018;100:122-30.
252. Comito T, Loi M, Franzese C, Clerici E, Pedicini V, Poretti D, *et al*. SBRT vs TAE/TACE in hepatocellular carcinoma: Results from a phase III trial (NTC02323360). J Hepatol 2020 73 (Suppl 1);Abstract PB02-02.
253. Sanford NN, Pursley J, Noe B, Yeap BY, Goyal L, Clark JW, *et al*. Protons versus photons for unresectable hepatocellular carcinoma: Liver decompensation and overall survival. Int J Radiat Oncol Biol Phys 2019;105:64-72.
254. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, *et al*. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomised, phase 2, open-label trial. Lancet 2019;393:2051-8.
255. Giannini EG, Farinati F, Ciccarese F, Pecorelli A, Rapaccini GL, Di Marco M, *et al*. Prognosis of untreated hepatocellular carcinoma. Hepatology 2015;61:184-90.
256. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, *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;389:56-66.
257. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, *et al*. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-73.
258. Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, *et al*. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018;379:54-63.
259. Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, *et al*. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:282-96.
260. Yau T, Park J, Finn R, Cheng A, Mathurin P, Edeline J, *et al*. CheckMate 459: A randomized, multi-center phase 3 study of nivolumab vs sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma. Ann Oncol 2019;30:v851-934.
261. Finn R, Ryoo B-Y, Merle P. Results of KEYNOTE-240: Phase 3 study of pembrolizumab (Pembro) vs best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC). J Clin Oncol 2019;37:Abstract 4004.
262. Yau T, Kang Y, Kim T. Nivolumab+ipilimumab combination therapy in patients with advanced hepatocellular carcinoma: Results from CheckMate 040. J Clin Oncol 2019;37:Abstract 4012.
263. Cheng A, Qin S, Ikeda M. IMbrave150: Efficacy and safety results from a Ph 3 study evaluating atezolizumab (atezo)+bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). Ann Oncol 2019;30:Abstract LBA3.
264. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, *et al*. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894-905.
265. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, *et al*. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
266. Reiss KA, Yu S, Mamtani R, Mehta R, D'Addeo K, Wileyto EP, *et al*. Starting dose of sorafenib for the treatment of hepatocellular carcinoma: A retrospective, multi-institutional study. J Clin Oncol 2017;35:3575-81.
267. Cuesta L, Betlloch I, Toledo F, Latorre N, Monteagudo A. Severe sorafenib-induced hand-foot skin reaction. Dermatol Online J 2011;17:14.
268. Hollebecque A, Cattan S, Romano O, Sergent G, Mourad A, Louvet A, *et al*. Safety and efficacy of sorafenib in hepatocellular carcinoma: The impact of the child-pugh score. Aliment Pharmacol Ther 2011;34:1193-201.
269. Marrero JA, Kudo M, Venook AP, Ye SL, Bronowicki JP, Chen XP, *et al*. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. J Hepatol 2016;65:1140-7.
270. Leal CRG, Magalhães C, Barbosa D, Aquino D, Carvalho B, Balbi E, *et al*. Survival and tolerance to sorafenib in Child-Pugh B patients with hepatocellular carcinoma: A prospective study. Invest New Drugs 2018;36:911-8.
271. Matsui J, Funahashi Y, Uenaka T, Watanabe T, Tsuruoka A, Asada M. Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGF-R3 kinase. Clin Cancer Res 2008;14:5459-65.
272. Khan KA, Kerbel RS. Improving immunotherapy outcomes with anti-angiogenic treatments and vice versa. Nat Rev Clin Oncol 2018;15:310-24.
273. ESMO Guidelines Committee [Internet]. Lugano: c2020. eUpdate – Hepatocellular carcinoma treatment recommendations. Available from: https://www.esmo.org/guidelines/gastrointestinal-cancers/hepatocellular-carcinoma/eupdate-hepatocellular-carcinoma-treatment-recommendations3. [Last updated on 2020 Jun 19; Last cited on 2020 Jul 20].
274. Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, *et al*. Regorafenib (BAY 73-4506): A new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer 2011;129:245-55.
275. Zhu AX, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D, *et al*. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): A randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2015;16:859-70.
276. Johnston MP, Khakoo SI. Immunotherapy for hepatocellular carcinoma: Current and future. World J Gastroenterol 2019;25:2977-89.
277. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, *et al*. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492-502.
278. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, *et al*. CheckMate 459: A randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). Ann Oncol 2019;30:v874-5.
279. Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, *et al*. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: A randomized, double-blind, phase III trial. J Clin Oncol 2020;38:193-202.
280. Wainberg Z, Segal N, Jaeger D. Safety and clinical activity of durvalumab monotherapy in patients with hepatocellular carcinoma (HCC). J Clin Oncol 2017;35:4071.
281. Qin S, Ren Z, Meng Z. A randomized multicentered phase II study to evaluate SHR-1210 (PD-1 antibody) in subjects with advanced hepatocellular carcinoma (HCC) who failed or intolerable to prior systemic treatment. Ann Oncol 2018;29:LBA27.
282. Qin S, Finn R, Kudo M. phase 3, randomized, open-label, multicenter study to compare the efficacy and safety of tislelizumab, an anti-PD-1 antibody, versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma. J Clin Oncol 2018;36:TPS3110.
283. Kudo M. Scientific rationale for combination immunotherapy of hepatocellular carcinoma with anti-PD-1/PD-L1 and anti-CTLA-4 antibodies. Liver Cancer 2019;8:413-26.
284. Kelley RK, Abou-Alfa GK, Bendell JC, Kim T-Y, Borad MJ, Yong W-P, *et al*. Phase I/II study of durvalumab and tremelimumab in patients with unresectable hepatocellular carcinoma (HCC): Phase I safety and efficacy analyses. J Clin Oncol 2017;35:4073.
285. Yau T, Kang Y-K, Kim T-Y, El-Khoueiry AB, Santoro A, Sangro B, *et al*. Nivolumab (NIVO)+ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results

from CheckMate 040. J Clin Oncol 2019;37:4012.
286. Finn RS, Ikeda M, Zhu AX, Sung MW, Baron AD, Kudo M, *et al*. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol 2020;38:2960-70.
287. Sia D, Jiao Y, Martinez-Quetglas I, Kuchuk O, Villacorta-Martin C, Castro de Moura M, *et al*. Identification of an immune-specific class of hepatocellular carcinoma, based on molecular features. Gastroenterology 2017;153:812-26.
288. Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, *et al*. Natural history of untreated nonsurgical hepatocellular carcinoma: Rationale for the design and evaluation of therapeutic trials. Hepatology 1999;29:62-7.
289. Haun MW, Estel S, Rücker G, Friederich HC, Villalobos M, Thomas M, *et al*. Early palliative care for adults with advanced cancer. Cochrane Database Syst Rev 2017;6:Cd011129.
290. Ferrell BR, Temel JS, Temin S, Alesi ER, Balboni TA, Basch EM, *et al*. Integration of palliative care into standard oncology care: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017;35:96-112.
291. Poonja Z, Brisebois A, van Zanten SV, Tandon P, Meeberg G, Karvellas CJ. Patients with cirrhosis and denied liver transplants rarely receive adequate palliative care or appropriate management. Clin Gastroenterol Hepatol 2014;12:692-8.
292. Rakoski MO, Volk ML. Palliative care for patients with end-stage liver disease: An overview. Clin Liver Dis (Hoboken) 2015;6:19-21.
293. Woodrell CD, Hansen L, Schiano TD, Goldstein NE. Palliative care for people with hepatocellular carcinoma, and specific benefits for older adults. Clin Ther 2018;40:512-25.
294. Back AL, Park ER, Greer JA, Jackson VA, Jacobsen JC, Gallagher ER, *et al*. Clinician roles in early integrated palliative care for patients with advanced cancer: A qualitative study. J Palliat Med 2014;17:1244-8.
295. Kumar M, Panda D. Role of supportive care for terminal stage hepatocellular carcinoma. J Clin Exp Hepatol 2014;4:S130-9.
296. Imani F, Motavaf M, Safari S, Alavian SM. The therapeutic use of analgesics in patients with liver cirrhosis: A literature review and evidence-based recommendations. Hepat Mon 2014;14:e23539.
297. Hayashi S, Tanaka H, Hoshi H. Palliative external-beam radiotherapy for bone metastases from hepatocellular carcinoma. World J Hepatol 2014;6:923-9.
298. Hiraoka A, Hirooka M, Koizumi Y, Izumoto H, Ueki H, Kaneto M, *et al*. Muscle volume loss as a prognostic marker in hepatocellular carcinoma patients treated with sorafenib. Hepatol Res 2017;47:558-65.
299. Mock V. Evidence-based treatment for cancer-related fatigue. J Natl Cancer Inst Monogr 2004;(32):112-8.
300. Puetz TW, Herring MP. Differential effects of exercise on cancer-related fatigue during and following treatment: A meta-analysis. Am J Prev Med 2012;43:e1-24.
301. Bruera E, Valero V, Driver L, Shen L, Willey J, Zhang T, *et al*. Patient-controlled methylphenidate for cancer fatigue: A double-blind, randomized, placebo-controlled trial. J Clin Oncol 2006;24:2073-8.
302. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. Psychooncology 2001;10:19-28.