



Clinical Practice Guidelines

Argentinian clinical practice guideline for surveillance, diagnosis, staging and treatment of hepatocellular carcinoma



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ABSTRACT

The A.A.E.E.H has developed this guideline for the best care of patients with hepatocellular carcinoma (HCC) from Argentina. It was done from May 2018 to March 2020. Specific clinical research questions were systematically searched. The quality of evidence and level of recommendations were organized according to GRADE. HCC surveillance is strongly recommended with abdominal ultrasound (US) every six months in the population at risk for HCC (cirrhosis, hepatitis B or hepatitis C); it is suggested to add alpha-feto protein (AFP) levels in case of inexperienced sonographers. Imaging diagnosis in patients at risk for HCC has high specificity and tumor biopsy is not mandatory. The Barcelona Clinic Liver Cancer algorithm is strongly recommended for HCC staging and treatment-decision processes. Liver resection is strongly recommended for patients without portal hypertension and preserved liver function. Composite models are suggested for liver transplant selection criteria. Therapies for HCC with robust clinical evidence include transarterial chemoembolization (TACE) and first to second line systemic treatment options (sorafenib, lenvatinib, regorafenib, cabozantinib and ramucirumab). Immunotherapy with nivolumab and pembrolizumab has failed to show statistical benefit but the novel combination of atezolizumab plus bevacizumab has recently shown survival benefit over sorafenib in frontline.

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Abbreviations

AFP	alpha-feto protein
AFP-L3	lens-culinaris AFP
ALT	alanine amino transferase
APHE	arterial phase hyperenhancement
AST	aspartate amino transferase
AUROC	area under the receiving operator curve
CI	confidence interval 95%
CR	complete response
CSPH	clinically significant portal hypertension
CT	computed axial tomography
DCP	desgamma carboxyprothrombin
DCR	disease control rate
DEB	drug-eluting beads
DFS	disease free survival
ECOG	Eastern Cooperative Oncology Group
FDGF	fibroblast derived growth factor
HCC	hepatocellular carcinoma
HBV	hepatitis B virus
HCV	hepatitis C virus
HFSR	hand-foot skin reaction
HR	hazard ratio
irAEs	immune-related adverse events
LR	likelihood ratio
LR	liver resection
LSM	liver stiffness measure
LT	liver transplantation
MRI	magnetic resonance image
NAFLD	non-alcoholic fatty liver disease
OR	odds ratio
ORR	objective response rate
PD	progressive disease
PDGF	platelet derived growth factor
PEI	percutaneous ethanol injection
PR	partial response
RR	relative risk
RRR	relative risk reduction
RA	absolute risk
RCT	randomized clinical trial
RECIST	Response Evaluation Criteria for Solid Tumors
RFA	radiofrequency ablation
RFS	recurrence free survival
Se	sensitivity
Sp	specificity
TACE	transarterial chemoembolization
TARE	transarterial radioembolización
TKI	tirosin kinase inhibitor
TTP	time to progression
US	ultrasound
VEGF	vascular endothelial growth factor

1. Introduction

With the advent of new diagnostic and treatment tools for hepatocellular carcinoma (HCC) during the last decade, the Argentinian Association for the Study of Liver Diseases (A.A.E.E.H) has developed this clinical practice guideline. The aim of the A.A.E.E.H was to develop a simple clinical tool, not a rigid *dogma*, applicable to national general physicians, hepatologists, gastroenterologists, oncologists, radiologist, and surgeons, for the best care of patients with HCC.

2. Materials and methods

This guideline has been focused on epidemiology, surveillance, diagnosis, staging and treatment for patients with HCC. It has been carried out by a multidisciplinary board from May to December 2018 and up-dated in March 2020. Teams were invited to develop a synthesis of specific clinical research questions ([Appendix 1](#)), which were structured according to Population, Intervention/Exposure, Comparison and Outcomes (PICO). The evidence was systematically searched using Medline-Pubmed (MESH terms) and other databases (Trip-database, Lilacs) including original articles; editorial comments, personal opinions, reviews among others, were excluded.

The quality of the evidence and level of recommendations followed the *Grade of Recommendation Assessment, Development and Evaluation* (GRADE), including quality of evidence (High, Moderate, Low and Very Low) [1,2] using other guidelines for randomized clinical trials (RCT) [3], systematic reviews [4] and observational studies [5]. The strength of each recommendation followed a) balance between risks and benefits, b) precision of estimations (95% confidence intervals –CI), c) values and preferences of the patients and d) costs of interventions. For strong recommendations this guideline uses the term “*it is recommended*” and for conditional or weak ones “*it is suggested*” [1] ([Appendix 1](#)).

3. Evidenced-based statements

3.1. Epidemiology

HCC is an increasing public health issue around the world, being the fifth most common cancer and the second leading cancer-related death [6,7]. In Asian countries, 60% of HCC cases are attributable to chronic hepatitis B virus (HBV) infection and vaccination with anti-HBV has dramatically reduced the incidence of HCC [8]. On the contrary, chronic hepatitis C virus (HCV) infection, followed by chronic alcohol consumption are the leading causes of HCC, with increasing HCC incidence and mortality rates in Western populations [9]. An increasing etiology of HCC during the last decade is non-alcoholic fatty liver disease (NAFLD) [10–15]. In Argentina, the HCC incidence rate is lower than 5.6 cases per 100.000 persons/year, equivalent to intermediate rates around the world [6].

This cancer originates in a cirrhotic liver or in the context of chronic liver injury in more than 90% of the cases [6,16]. In North America, HCV and alcoholic liver disease have been historically the most frequent causes of HCC but more recently, NAFLD has become a leading cause of HCC [10–12,17,18]. In Latin America, the most frequent etiology of HCC is HCV, followed by alcohol consumption [19,20]. Regional disparities have been reported, HBV in Brazil [21] and NAFLD in Chile. In Argentina, main etiologies are HCV in transplant centers and alcoholic liver disease in non-transplant centers [22,23]; whereas NAFLD has become an increasing etiology [23].

3.1.1. Population at risk and HCC prevention

An estimated threshold of high risk for HCC was established in 1.5%/year [14,15]. Patients with cirrhosis of any etiology, or with chronic HBV or HCV infection are those with the highest risk of developing HCC [14,15]. Persistence of chronic infection [24–27], the degree of liver fibrosis and inflammation [28,29] and the presence of clinically significant portal hypertension (CSPH) are risk factors for HCC in HCV patients [30]. The risk of HCC decreases but it is not completely eliminated following HCV eradication, particularly in patients with advanced fibrosis (F3 or F4) [31–35] and CSPH [28,36].

Oncogenic pathways associated with HBV are independent from fibrosis grades. Presence of “e” antigen (Age), persistence of chronic inflammation, higher viral load in Age negative, pre-core mutants and the presence of advanced fibrosis have all been associated with higher risk [37]. On the contrary, asymptomatic carriers might be at lower risk, unless they present advanced fibrosis [38]. The REVEAL study cohort, including Age negative cohort, showed increasing HCC risk with higher viral loads [37]. Quantification of AgS levels might be another tool in Age- patients with lower viral load (<2000 IU/ml) [39,40]. On the other hand, genotype C and pre-core mutants have been associated with higher risk of HCC [41]. More recently, values of liver stiffness measurement (LSM) have been associated with increasing Hazard Ratios (HR) of HCC, particularly with >18 kPa HR 5.5 (CI 1.5;20.0) and >23 kPa HR 6.6 (CI 1.8;23.8) [42]. Finally, some scoring models assessing the risk of HCC in treated patients with entecavir/tenofovir have been published, including the REACH (age, ALT levels, viral load and Age status) [43] and the PAGE score (age, gender and platelet count) [44]. A PAGE score of ≤9 points in non-cirrhotic HBV patients has a high negative predictive value for HCC [45].

The risk of HCC increases with alcohol consumption, particularly in the context of advanced fibrosis grades [46,47]. Moreover, it is a co-factor of HCC for other chronic liver diseases [48–50]. The risk of HCC in non-cirrhotic NAFLD is not clearly defined [10,12,17,23,51].

Primary Prevention. The most effective measure is the universal vaccination of HBV [8]. Other unspecific measures include biosecurity of health procedures, sexual protective measures, avoidance of recreational drugs and alcohol consumption. Also, promotion of healthy lifestyle habits to avoid obesity and metabolic syndrome are recommended.

Secondary Prevention. The most effective measures are viral eradication in chronic HBV [45,52–55] and HCV [24–26,31–34], stopping alcohol consumption [48,50,56,57] and promoting healthy lifestyle habits [58,59]. Direct-acting antivirals have shown decreasing incidence of HCC in those achieving HCV eradication [31,34,35,60]. Treatment of HBV has been associated with a RRR of 51% for HCC in a meta-analysis [53]. This effect was observed even in patients with cirrhosis [45], although the risk was not completely abolished [55]. The rate in which the risk of HCC decreases in patients who present treatment-related fibrosis reversion is uncertain [52,53]. Some meta-analyses have shown that coffee consumption may decrease the risk of HCC in patients with chronic liver disease [61,62]. However, the low quality of the evidence does not support any strong recommendation.

Tertiary Prevention. In HBV, viral load has been associated with higher HCC recurrence after ablative therapies or LR [63,64]; treatment with interferon alfa 2b following resection did not reduce HCC recurrence rate [65] but opposite results were observed using nucleotide/nucleoside analogs [66]. In HCV, interferon-based regimens following ablation or liver resection did not reduce HCC recurrence in two RCT [67,68] and controversial data has been reported following direct-acting antivirals [69,70]. A higher tumor progression rate was not observed in HCV patients listed for liver transplantation (LT) treated with direct-acting antivirals [71,72] (Table 1).

3.2. Surveillance for HCC

3.2.1. Rational and evidence supporting HCC surveillance

Surveillance is the sequencing or repetitive application of a cost-effective screening tool on a population at risk for a specific health problem, aiming at reducing its mortality rate avoiding the so-called *lead and length-time* bias. Surveillance failure is not the same as screening failure. Whereas the first one refers to the failure of any procedure associated with the surveillance program (e.g. non

adherence), screening failure refers to false-negative tests associated with each screening tool.

Among HBV patients, the evidence comes from prospective observational studies [73,74] and three RCT with different risk of bias [75–77]. In cirrhosis, the evidence is even less robust [78–84]. Some meta-analyses with significant heterogeneity [85,86] and Markov modeling approaches have evaluated its cost-effectiveness [87–92]. Despite these unrobust data, it is strongly recommended to perform HCC surveillance in the population at risk (Table 1).

This panel considers that the aim of screening tool is to detect a single HCC of <3 cm because it is associated with higher likelihood for curative therapies and better survival [78,93–99]. Screening tools for HCC that have been explored are abdominal ultrasound (US), CT or MRI scans and different biomarkers.

3.2.2. Comparison of screening tools for HCC

US is the most cost-effective screening tool [100,101]; though it has low sensitivity (range 30–70%), it is operator dependent and a negative test does not completely rule out HCC. On the contrary, it has elevated specificity (>90%). US accuracy should be analyzed within the framework of serial repetition over time, ideally a 6-month interval [96,99]. In this context, a 34% rate of US screening failure is expected, higher when performed by inexperienced operators [98] or inconsistent repetition [97,98,102]. In Argentina the rate of “surveillance failure” has been reported to be 42% [103]; whereas “screening failure” was observed between 26–32% of the cases [103].

The use of alpha-fetoprotein (AFP) alone or in combination with abdominal US has been less effective for detection of single <3 cm HCC [75,79,96,99]. There is lack of consensus on AFP thresholds with different sensitivities (Se) and specificities (Sp): AFP >20 ng/ml: Se 60% Sp 90%, AFP >100 ng/ml Se 31% Sp 98.8%, AFP >200 Se 22% Sp 99.4%, AFP >400 Se 17% Sp 99% [79]. The panel suggests to include AFP values at different thresholds to avoid US screening failure by inexperienced operators [98] (Fig. 1). Other biomarkers including *lens-culinaris* fraction of AFP (AFP-L3) and desgamma carboxiprotrombin (DCP) have not been better than AFP as screening tools either alone or in combination with US [104–106].

3.3. Diagnosis of HCC based on imaging and pathological features

3.3.1. Imaging HCC diagnosis

Imaging HCC diagnosis can be performed with high specificity and tumor biopsy is not mandatory in the population at risk [107–112]. Triphasic scans including arterial, portal and delayed phases, either with computed axial tomography (CT) or magnetic resonance imaging (MRI) accurately perform HCC diagnosis. Specificities range from 85% to 100% for liver nodules ≥10 mm showing imaging hallmarks including homogenous (non-rim) arterial phase hyperenhancement (APHE) and washout (non-peripheral) in portal phase [107–112]. Typical hallmarks may not be present in all HCCs. The presence of enhancing pseudocapsule during the late phase or increasing diameter of pre-existing nodule with APHE are additional criteria [113]. Reported sensitivities for nodules >20 mm of diameter are similar with CT 92% and MRI 95%; however, MRI has superior accuracy for nodules <20 mm with sensitivity of 70% and specificity of 83% (67% and 76% for CT, respectively) [114,115].

Liver nodules <10 mm are not specific for HCC even showing hallmarks in MRI or CT scans. APHE is more frequently observed in these tiny lesions, whereas washout may not be present in nodules between 10 and 20 mm of diameter [115]. In this regard, MRI with hepatobiliary contrast agents (Gadoxetic acid) may be useful to rule out malignancy, but it may decrease HCC specificity [107,108,112,116] (Fig. 1).

Table 1
Quality of evidence and level of recommendations for HCC prevention, surveillance, diagnosis and staging.

Topic	Statement	Grade of Recommendation	Quality of the evidence
Primary Prevention	It is recommended universal vaccination for HBV, to reduce alcohol consumption, avoid illicit recreational drugs, to promote biosecurity and healthy life styles.	Strong	High
Secondary Prevention	It is recommended to eradicate/treat HBV or HCV chronic infections, to stop alcohol abuse.	Strong	Moderate to high
	It is uncertain to recommend coffee consumption in patients with chronic liver disease.	Conditional	Low
Tertiary Prevention	It is suggested to eradicate/treat HCV chronic infection after curative therapies.	Conditional	Low
	It is recommended to eradicate/treat HBV chronic infection after curative therapies.	Strong	Moderate
	It is recommended for patients with cirrhosis and preserved liver function irrespective of etiology.	Strong	Low
Surveillance	It is recommended for patients with decompensated cirrhosis listed for liver transplantation.	Strong	Low to very low
	It is recommended for patients with chronic HBV, previous family history of HCC ¹ .	Strong	Moderate
	It is recommended for patients with chronic HCV and F > 2.	Strong	Low
	It is suggested for any chronic liver disease with F > 2.	Conditional	Very Low
	It is recommended after viral eradication of HBV or HCV in patients with F > 2.	Strong	Low to moderate
	It is recommended to use abdominal ultrasound every 6 months; performed by expert sonographers.	Strong	Low to Moderate
	It is suggested to use alpha-feto protein (AFP) as additional tool for HCC surveillance (Fig. 1).	Weak	Low to very low
	It is recommended to perform HCC diagnosis either with CT or MRI when specific hallmarks are observed in the population at risk (APHE plus washout in delay portal phase).	Strong	High
Diagnosis	A tumor biopsy is not recommended for HCC diagnosis confirmation in cases with imaging hallmarks.	Strong	High
	It is recommended to include LIRADS in radiological reports as well as detailed descriptions.	Strong	Very low
	AFP or other biomarkers are not recommended for HCC diagnosis.	Strong	High
	PET CT is not recommended for HCC diagnosis, staging or prognosis.	Strong	Low to moderate
Staging	The Barcelona Clinic Liver Cancer staging is recommended for staging and therapeutic clinical-decision-making.	Strong	High
	It is recommended to perform clinical-decision-making in the context of multidisciplinary working teams.	Strong	Low
	It is not suggested to support BCLC-B sub-staging classification.	Conditional	Low to very low

Notes: 1 – Among patient with chronic HBV, in the absence of fibrosis grade >2 or family history, it is suggested to assess risk of HCC and need for surveillance using the PAGE-B score. A PAGE-B score ≤ 9 points can exclude patients for surveillance.

Abbreviations: APHE: arterial phase hyper-enhancement; CT: computed axial tomography; F: fibrosis; MRI: magnetic resonance image.

Radiological reports should be described in detail and include the LI-RADS system (liver imaging reporting and data system) [108,117]. LI-RADS is not applicable to patients without cirrhosis, without chronic HBV or HCV, or with vascular liver disorders (e.g. Budd Chiari syndrome, portal vein thrombosis, cardiac congestion and diffuse nodular regenerative hyperplasia) [108,118]. LI-RADS categorizes liver nodules in definitely benign (LI-RADS 1), probably benign (LI-RADS 2), with intermediate probability of HCC (LI-RADS 3), probable HCC (LI-RADS 4), definitely HCC (LI-RADS 5), probably or definitely malignant but unspecific for HCC (LI-RADS M) and definite HCC with tumor in vein (LI-RADS-TIV) [130–133]. Although LI-RADS has been validated in retrospective cohort studies [119], it has not been validated in RCT (Table 1).

3.3.2. Pathological HCC diagnosis

Pathological diagnosis of HCC should be reserved for unconfirmed imaging diagnosis through fine needle biopsy, core needle biopsy or explant pathological analysis (Fig. 1). Cytological criteria for probable HCC include the presence of moderate to high cellularity, polygonal cells with dense cytoplasm, prominent nucleolus and surrounding sinusoidal cells, absence of biliary ducts cells, among other features. Guided core needle biopsy should be cautiously

done for subcapsular liver lesions due to the risk of bleeding or tumor seeding. Histological features of HCC include cells grouped in trabeculae of 3 or more cells, cytological atypia, vascular invasion and loss of reticulin trama. Nuclear grading and histological classification should be assessed according to Edmondson and Steiner and WHO 2010 criteria, respectively. There is no pathognomonic immunohistochemistry but the presence of at least 2 out of 3 signs, Glypican 3 or Heat Shock Protein 70 or Glutamine Sintetase, has 60% sensitivity and 100% specificity for HCC [120]. Molecular evaluation of HCC may be used for research purposes.

3.3.3. Biomarkers for HCC diagnosis and prognostic purposes

Serum AFP has been extensively studied as HCC biomarker. Although a threshold of 200 ng/ml was shown to be the best cut-off [121], most of the patients show AFP values <20 ng/ml at HCC diagnosis [80,104,122]. Also, AFP is not completely specific for HCC. For this reason, AFP is not considered a requisite for HCC diagnosis. Nevertheless, AFP has been associated with recurrence risk in patients receiving liver resection (LR) [123,124] or radiofrequency ablation (RFA) [125–127], with tumor progression following transarterial chemoembolization (TACE) [128–131] and as a prognostic marker with systemic therapies [132–134]. Extensive evidence has been

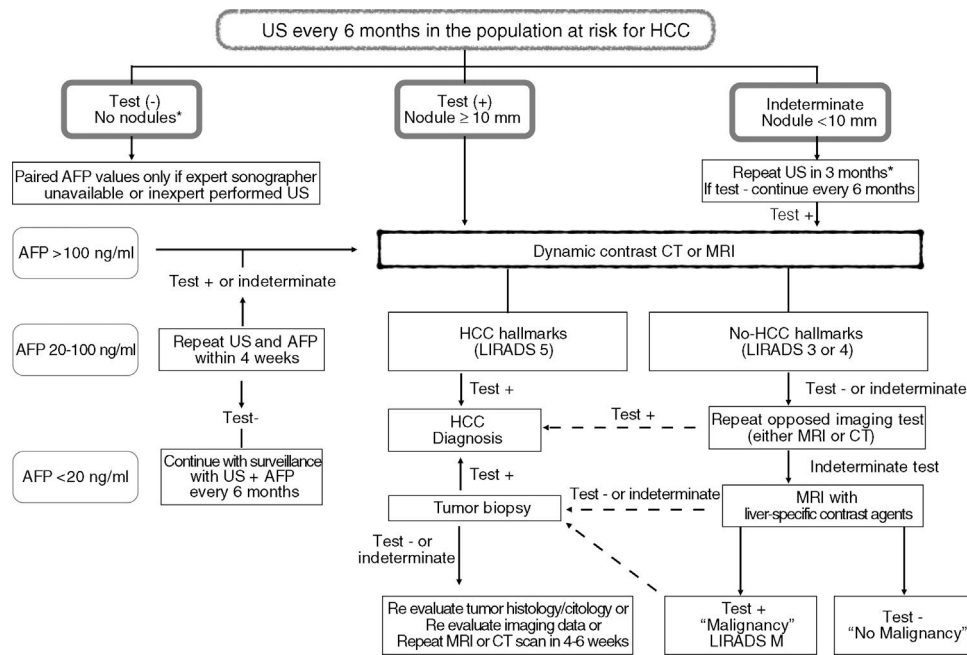


Fig. 1. Surveillance and diagnostic algorithm for hepatocellular carcinoma.

Note: See additional information in Appendix 2.

published regarding AFP values as a selection tool for LT [135–138]. Other biomarkers have not been included in the daily practice except in Asian countries [104–106] (Table 1).

3.4. Staging

Different staging algorithms have been proposed including the Okuda system [139], the GRETCH score [140], the CLIP (Cancer of the Liver Italian Program) [141], CUPI [142], JIS (Japan Integrated System) [143], HKLC (Hong-Kong Liver Cancer) [144] and the BCLC staging (Barcelona-Clinic Liver Cancer) [145].

The BCLC was originally proposed according to the best available evidence, was externally validated in cohort studies [146–148] and adopted in international guidelines (Fig. 2). It includes five different stages according to baseline prognostic variables and the best evidenced-based therapeutic approach. Very early HCC or BCLC stage 0 includes patients with *Eastern Cooperative Oncology Group* (ECOG) 0, preserved liver function and single HCC <20 mm and the best approach is RFA or LR [149–152]. Early HCC or BCLC-A corresponds to patients with preserved liver function, ECOG 0–1 and tumors including (a) single lesion without limit on diameter and (b) up-to 3 nodules less or equal than 30 mm. Either CSPH or total bilirubin level >1 mg/dl are prognostic variables that preclude LR, whereas these patients are candidates for LT if remaining within transplant criteria [154,155]. Intermediate BCLC-B stage are those patients with ECOG 0–1, preserved liver function with or without evidence of portal hypertension and multinodular tumors or those beyond BCLC-A stage. TACE is the treatment of choice [156–158], whereas in particular cases TARE might be indicated. Advanced HCC or BCLC-C stage includes patients with preserved liver function, with or without evidence of portal hypertension, ECOG 0–2 and tumor progressing or not responding after 2 TACEs or those with macrovascular invasion or extrahepatic spread. First and second-line sequencing therapy has achieved a median survival above 26 months in this group of patients [158]. Finally, BCLC-D stage includes patients with unpreserved liver function with any tumor burden or patients with ECOG 2–3; in these patients best supportive care is the treatment of choice. In this latter group, LT is the treatment of choice only if tumor burden is within transplant

criteria or other co-morbidities do not exclude them for LT. Preserved liver function should be addressed including biochemical (total bilirubin, prothrombin time, serum creatinine and albumin) and clinical assessment (presence of CSPH including ascites and its complications, hepatic encephalopathy among other complications associated with portal hypertension). Scoring models like Child–Pugh or MELD score may be additional tools [159].

It is important to underline that the BCLC is not a rigid algorithm and some patients may be treated with subsequent recommended therapy (“*treatment stage-migration*”) [160]. Moreover, dynamic changes over time on liver function before or after each treatment should be considered. Finally, it includes the feasibility of each treatment. Other sub-staging algorithms for BCLC-B have been proposed (score ITALICA, HKLC) [144,161,162] or those avoiding ascites or hepatic encephalopathy grades (ALBI grade score) [163]. Adherence to the BCLC algorithm has been reported between 40% and 60% around the world [164–169] and 53% in Argentina [103].

3.5. Locoregional treatments for HCC

3.5.1. Locoregional-ablative therapies

The most frequently used locoregional ablative therapies include RFA, PEI and microwave ablation (MWA), either percutaneously or laparoscopically [127,170,171]. PEI consists of the injection of ethanol solution generating tumor coagulative necrosis [151,172,173]. RFA and MWA generate thermal tissue damage through radiofrequency or microwave mechanisms; the effect of MWA does not decrease when applied near blood vessels (as it happens with RFA). PEI’s main limitation is tumor diameter and fibrosis septa and may be an alternative when RFA is unfeasible (e.g. subcapsular or peri-biliary or vascular lesions) [174]. RFA is more effective than PEI for local tumor control, HCC recurrence [173] and overall survival [151] with similar hospital stay and fewer adverse events [172]. In a metaanalysis with moderate quality, RFA and MWA presented similar overall survival, recurrence rates and local tumor control but MWA presented fewer adverse events [175]. Other ablative techniques such as cryoablation [176], irreversible electroporation (IRE) [177] and stereotaxic body radiation therapy (SBRT) have been developed but evidence-based supporting the

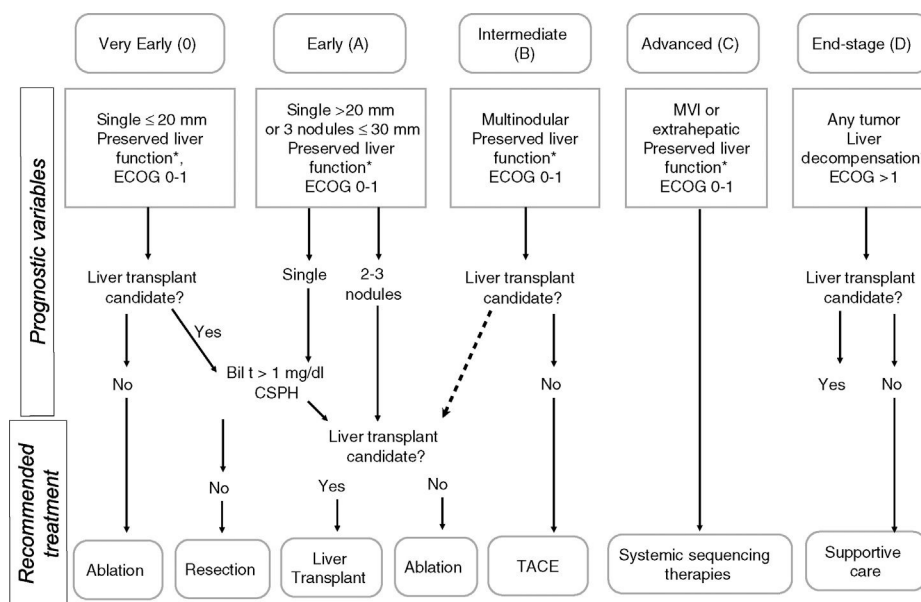


Fig. 2. Staging for hepatocellular carcinoma according to the Barcelona Clinic Liver Cancer (BCLC).

Note: This figure is adopted from its original and latest version from the BCLC. Some changes were done, particularly for liver transplant candidates regarding BCLC-D or BCLC-B (if these patients are selected through composite models or specific UCSF downstaging protocol + AFP <100 ng/ml). Preserved liver is equivalent to Child Pugh A or absence of any of the following decompensation events: jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome, variceal bleeding. ECOG: Eastern Cooperative Oncology Group (performance status).

superiority over RFA is lacking [178–180]. The only RCT comparing the superiority of cryoablation over RFA was negative [178]. Table 2 shows level of recommendations and quality of the evidence.

3.5.2. Liver resection

The selection of appropriate candidates for LR is mandatory. Presence of extrahepatic tumor, main portal trunk invasion or unreserved liver function are absolute contraindications [181–183]. Patients with CSPH have a higher risk of liver decompensation [153,154,184–186], higher postoperative morbidity and lower 5-year overall survival [HR 1.48 (CI 1.11;1.98)] [154,187,188], even if “minor resections” are done [187]. Not clinically evident CSPH (gastroesophageal varices, ascites, portosystemic shunts) should be assessed through manometry [153,184,185,189] or surrogate markers (splenomegaly >120 mm with low platelet count <100,000 mm⁻³) [124,186]. LSM may have a role as a surrogate of CSPH, a threshold of >20 kPa has been proposed [190]. Finally, a minimum remnant liver volume of 40% is important to avoid post-operative liver decompensation and can be estimated through CT volumetric assessment or other metabolic tests [191]. The evidence does not suggest any direction in favor or against any specific modality (open vs. laparoscopic LR) [192,193] but anatomical resections have been associated with lower HCC recurrence rates [194].

In BCLC-0 or A stages, LR was associated with lower 5-year recurrence rates (63.8%) compared to RFA 71.7% or PEI 76.9% [150,197,198] but with longer hospitalization and a higher rate of serious adverse events [199]. Cost-effective analysis and Markov modeling have shown that for single HCC <2 cm, RFA is as comparable as LR in overall survival. For single lesion BCLC-A, LR is more cost-effective and for BCLC-A with 2–3 nodules, both techniques had similar overall survival, RFA was more cost-effective but LR had lower recurrence rate [200]. Finally, multipolar RFA presented similar survival and recurrence rates for single HCC <40 mm compared to LR [201].

Additionally, LR may be performed by expert surgeons in “non-ideal” candidates [182,185,186,189]. However, the quality of the evidence is low. A MELD score less or equal than 9 points may

select candidates for minor resections (less than 3 liver segments) [182,185,186,189]. Other authors have proposed LR among BCLC-B patients but with a significant risk of bias [181–183,202]. Recently, a low to moderate quality meta-analysis compared LR vs. TACE in BCLC-B/C patients [204]. In the only RCT included, median survival was significantly higher for LR (41 months vs. TACE 14 months) [204]. However, unbalanced co-interventions and an indefinite number of TACEs might have led to ischemic injury and liver decompensation [204]. Additionally, LR was not superior to sorafenib in patients with macrovascular invasion [205] (Table 2).

3.5.3. Management of HCC recurrence following ablative therapies and liver resection

HCC recurrence after locoregional therapies or LR ranges from 40% to 70% at 5 years, either intra or extrahepatic [149,206–208]. Pathology variables associated with a higher risk of recurrence are macro or microvascular invasion, satellites or undifferentiated tumors [152,208,209]. The quality of the evidence supporting either one or the other therapeutic modality for HCC recurrence is low. RFA or re-resection [206,210], “salvage” LT [211,212] or preventive LT or “*abb initio*” [152,208] have been proposed. Salvage LT has shown similar survival but lower recurrence rates vs. re-resection [212–214]. In spite of being novel approach, preventive or “*abb initio*” LT needs to be externally validated [152,208]. Several strategies and therapeutic modalities of adjuvant and neo-adjuvant have failed to show any clinical benefit [215], including sorafenib (STORM trial) [216]. Other on-going RCT including pembrolizumab (MK-3475, NCT03867084), nivolumab (CheckMate-9DX, NCT03383458), dendritic cells based therapy [217] and induced natural killer cells [218] have been reported.

3.5.4. Locoregional-endovascular therapies

(a) *Transarterial chemoembolization (TACE)* consists in the instillation through arterial hepatic branches of a chemotherapeutic agent with lipiodol (e.g. doxorubicin or epirubicin, among others) followed by arterial embolization either conventionally (e.g. alcohol or spongostan) or through microspheres or drug-eluting beads (DEB) [220,229]. TACE is the standard

Table 2
Quality of evidence and level of recommendations for HCC locoregional therapies, liver resection and liver transplantation.

Topic	Statement	Grade of Recommendation	Quality of the evidence
RFA, PEI and others	Either liver resection or RFA are recommended for patients with single tumor <2 cm.	Strong	High
	If LR or RFA are not feasible, PEI or MWA (if costs are comparable) are suggested to be second options.	Conditional	Moderate
	Cryoablation is not recommended as first line option.	Strong	Moderate
	SBRT or IRE are not recommended as first line options but are uncertain as second options.	Conditional	Low to very low
Liver resection	LR is recommended for single tumors, irrespective of diameter, absence of CSPH, preserved liver function	Strong	High
	RFA is recommended as an alternative option to LR, specifically for patients with up-to 3 tumors less than 3 cm each in patients with comorbidities.	Strong	High
Liver transplantation	LT is recommended for BCLC-A patients or with decompensated cirrhosis (BCLC-D).	Strong	High
	Composite criteria (either AFP model or Metroticket 2.0) are suggested to optimize LT candidates selection.	Conditional	Moderate
	AFP >1000 ng/ml is recommended as an exclusion independent criteria.	Strong	Moderate
	Bridging therapies in the waitlist period are recommended considering tumor burden, AFP >400 ng/ml and expected waitlist times.	Conditional	Low to moderate
	It is suggested to individualize the benefits and risks of <i>downstaging</i> ; UCSF plus AFP <100 ng/ml is suggested to identify ideal candidates.	Conditional	Low to moderate
Adjuvant systemic therapies	"All-comers" are not recommended for <i>downstaging</i> .	Strong	Low to moderate
	There is uncertain quality of evidence to recommend any particular locoregional modality for bridging or <i>downstaging</i> procedures.	Conditional	Low
	Sorafenib is not recommended for reducing the risk of HCC recurrence after RFA or LR.	Strong	High
Other	There is no sufficient evidence to recommend adjuvant systemic therapies prior or after LT to avoid HCC recurrence.	Conditional	Very Low
	It is suggested to use MELD score <10 to select non-ideal LR candidates (with CSPH).	Conditional	Low to very low
	It is uncertain to suggest or recommend multimodal combination therapies for BCLC-A or B patients.	Conditional	Low to very low
	It is suggested to follow BCLC algorithm for HCC recurrence therapies after RFA or PEI or LR or other locoregional therapies.	Conditional	Low to very low
	There is insufficient evidence to recommend any specific therapy for HCC recurrence after LT.	Conditional	Very low

Abbreviations: BCLC: Barcelona Clinic Liver Cancer; CSPH: clinically significant portal hypertension; IRE: irreversible electroporation; LR: liver resection; LT: liver transplantation; MELD: model for end-stage liver disease; PEI: percutaneous ethanol injection; RFA: radiofrequency ablation; SBRT: stereotaxic body radiation therapy.

treatment for BCLC-B patients [155–157]. Neither chemoinfusion alone, "lipiodolization" nor bland embolization (without chemotherapeutic agent) have shown any survival benefit [155,157,221,222]. Some authors have questioned these results in low quality studies with significant risk of bias [223,224]. Eligible candidates for TACE are those with preserved liver function, with a tumor diameter <10 cm, less than 50% of total liver involvement, without vascular or biliary tumoral or non-tumoral obstruction, without portosystemic shunts, impaired kidney function or other major comorbidities [220]. Main non-tumoral portal trunk obstruction precludes conventional TACE but it may be done with hyperselective TACE or with DEB.

In one RCT, TACE with DEB of 300–500 μm was not superior to conventional TACE (PRECISION V trial) in overall survival and tumor control [220]. Systemic adverse events were lower in Child–Pugh B >7 patients with DEB [220]. Other uncontrolled studies have shown median survival of 47 months with DEB [225]. Nevertheless, there is lack of evidence comparing conventional TACE vs. smaller DEB (75–100 μm).

The most common adverse event is the post-chemoembolization syndrome, occurring in 20% of the patients (pain, fever, increasing liver enzymes). Less frequently observed are those associated with the chemotherapeutic agent such

as alopecia, mucositis, bone marrow suppression or cardiac dysfunction (more frequently observed with conventional TACE) [220].

- (b) *Transarterial Radioembolization* (TARE) consists of the endovascular administration of Yttrium-90 (Y-90) radiospheres selectively within the tumor [226]. In some patients with unresectable large tumors (>7 cm) or with portal vein thrombosis, TACE maybe not feasible or efficient enough. In these cases, TARE may be more radical with less therapeutic sessions. Ideal candidates are unresectable BCLC-A or B, with preserved liver function, total bilirubin <2 mg/dl, absence of extrahepatic metastasis and with up-to 5 HCC liver lesions, a total diameter <20 cm or single lesion <10 cm, with or without portal vein obstruction [226–232]. Before TARE, other procedures such as arterial liver angiography, a Technetium 99 (Tc-99) scan to evaluate intrahepatic-pulmonary shunts (if >15%, TARE is not recommended) or the equivalent to lung exposure of no more than 30 Gy for 1 session or 50 Gy for >1 sessions should be evaluated [226–232].

TARE is not associated with a post-embolization syndrome; the most serious adverse event is the Radioembolization Induced Liver Disease or "REILD"; occurring in less than 10% of the patients, within 4 to 8 weeks after TARE including

Table 3
Quality of the evidence and level of recommendations for HCC endovascular and systemic therapies.

Topic	Statement	Grade of Recommendation	Quality of the evidence
TACE	It is recommended as first line option in BCLC-B patients.	Strong	High
	DEB TACE is not superior to conventional TACE ¹	Strong	High
	DEB TACE is suggested for Child Pugh B <9	Conditional	High
TARE	Insufficient evidence to recommend or suggest TARE over TACE as first option for BCLC-B patients	Conditional	Low to very low
	In some patients with unresectable large tumors, with portal vein obstruction TARE may have a therapeutic role.	Conditional	Low
	It is uncertain to recommend or suggest TARE after TACE failure in BCLC-B.	Conditional	High
	TARE is not recommended for BCLC-B patients with tumor progression or BCLC-C patients (with vascular invasion) over sorafenib.	Strong	High
Systemic therapies with TACE/TARE/other	Sorafenib or other TKI agents in combination with TACE for BCLC-B patients are not recommended to avoid tumor progression.	Strong	High
	There is no recommendation to support the combination of TARE with sorafenib for BCLC-B patients to avoid tumor progression.	Strong	High
	Intra-hepatic arterial chemotherapy in combination with sorafenib is not recommended for BCLC-B or C patients	Strong	High
First line systemic therapy	The combination of atezolizumab plus bevacizumab is recommended as first-line systemic therapy ^{2,3}	Strong	High
	If atezo + beva is not available or approved: sorafenib or lenvatinib are first-line systemic options ⁴	Strong	High
	Nivolumab is not recommended for first-line systemic therapy.	Strong	High
Second line systemic therapy	Regorafenib, cabozantinib and ramucirumab are recommended second-line systemic therapies for post-sorafenib progression.	Strong	High
	Cabozantinib or ramucirumab are recommended for intolerant-sorafenib patients.	Strong	High
	Ramucirumab is only recommended for patients with AFP values ≥ 400 ng/ml.	Strong	High
	Pembrolizumab may be use in patients with AFP values <400 ng/ml, without main portal vein invasion (tolerant or intolerant to sorafenib).	Conditional	High
	Nivolumab may be suggested as second line (tolerant or intolerant to sorafenib).	Conditional	Moderate
Third line systemic therapy	There is lack of robust evidence supporting second line options after lenvatinib but these options may be use as for sorafenib.	Conditional	Very Low
	Cabozantinib is recommended as third line (only with prior sorafenib plus other systemic therapy).	Strong	High
	There is lack of robust evidence supporting any other third line options but some first or second-line agents may be used.	Conditional	Very Low

Notes: 1 – Only one RCT compared conventional TACE vs. DEB using large microspheres; uncertain efficacy regarding tiny microspheres. 2- Waiting for approval. 3-Without main portal trunk invasion or any prior autoimmune disease or uncontrolled arterial hypertension for atezolizumab + bevacizumab. 4- Without main portal trunk invasion or no more than 50% liver involvement or uncontrolled arterial hypertension for lenvatinib.

Abbreviations: BCLC: Barcelona Clinic Liver Cancer; DEB: drug eluting beads; TACE: transarterial chemoembolization; TARE: transarterial radioembolization.

jaundice, ascites and liver decompensation. Radiotoxicity may affect other abdominal organs [226,232].

(c) *Radioembolization vs. TACE.* The evidence comparing these techniques is of low to very low quality [227–232]. Two meta-analyses with high statistical heterogeneity and significant risk of bias have shown that TARE may be associated with better 1-year survival rate [HR 0.74 (CI 0.61–0.90)], similar time to progression (TTP), shorter length of hospitalization and fewer adverse events [234,235]. However, a small pilot randomized, open-label, controlled trial (SIRTACE) showed no significant differences in 1-year overall survival (TARE 46.2% vs. TACE 66.7%), TTP and rate of adverse events [236]. Other small randomized trials showed longer TTP in favor of TARE but without a significant survival benefit [237,238]. There is an on-going phase III RCT (TRACE trial; NCT01381211) (Table 3).

(d) *Radioembolization vs. systemic therapy.* Two phase III trials have compared the superiority of TARE over sorafenib in BCLC-B upon tumor progression or failure following sequential TACE and BCLC-C without extrahepatic disease (SARAH and SIRveNIB) [239,240]. Both showed negative results in terms of

survival with median survival of 8.0 months for TARE and 9.9 months for sorafenib [HR of 1.17 (CI 0.94;1.41)] (SARAH). Median TTP was similar and although there was a lower rate of intrahepatic tumor progression with TARE, a lower and similar disease control rate (DCR) vs. sorafenib was observed in SARAH and SIRveNIB, respectively [239,240]. A similar rate of all adverse events were observed in SARAH; although there was a higher incidence of grade ≥ 3 related adverse events with sorafenib (63% vs. TARE 41%) [239]. There was a higher rate of all adverse events as well as higher rate of serious adverse events with sorafenib in SIRveNIB [240]. Opposite results were observed with quality of life, better in SARAH and similar in SIRveNIB [239,240]. Some differences between studies should be underlined. A larger proportion of BCLC-C patients were included in SARAH and total bilirubin was up-to 3 mg/dl vs. <2 mg/dl in SIRveNIB. In SARAH there were significant cross-overs, un-standardized radiation dose and inexperienced participating centers [239]; whereas there were logistical issues reported in SIRveNIB [240]. In both trials, the median treatment duration with sorafenib was shorter than expected [241,242] (Table 3).

3.5.5. Locoregional-endovascular therapies in combination with systemic treatment

Different combinations of TACE with antiangiogenic drugs have been explored aiming at better TTP or disease-free survival (DFS) and in some of them, overall survival. The rationale for this combination is that higher expression of vascular endothelial growth factor (VEGF) following TACE was associated with worse survival [243].

Studies evaluating sorafenib+TACE with TTP as primary outcome include two non-randomized phase II trials (SOCRATES and START trials) [244,245] and three phase III RCT, the double-blinded SPACE trial [246], HELViCA study [247] and the open-label TACTICS trial [248]. The SOCRATES study enrolled patients with unreserved liver function reporting higher adverse events [244]; whereas the combination was tolerable in patients with preserved liver function (START trial) [245]. Both studies used conventional TACE; DEB was used in another uncontrolled phase II trial [249]. In SPACE and HELViCA trials, the combination of TACE with DEB plus sorafenib did not show better TTP than TACE alone + placebo [247,247]. On the contrary, a longer DFS was observed in the TACTICS trial [median TTP 25.2 months vs. 13.5 months; HR 0.56 (CI 0.38;0.83)] [248]. These opposite results may be due to different eligibility criteria and different definition of tumor progression between trials. However, in both trials the combination showed a longer time to extrahepatic progression. The STAHL trial evaluated overall survival as primary outcome with negative results but it included BCLC-C patients [250].

Other antiangiogenic agents in combination with TACE were negative including brivaniv (BRISK-TA phase III RCT) [251], bevacizumab [252] and axitinib [253]. More recently, intra-arterial chemotherapeutic agents in combination with sorafenib have also failed to show any survival benefit vs. sorafenib alone [254]. In another RCT including BCLC-C patients with main portal trunk invasion, the combination of intra-hepatic arterial infusion of FOLFOX plus sorafenib vs. sorafenib alone showed promising survival but with higher myelotoxicity [255]. Finally, the combination of sorafenib plus TARE did not show any survival benefit (SORAMIC trial) [242,256]. There are on-going trials exploring the TACE plus immunotherapy with nivolumab (IMMUTACE NCT03572582 and NCT03143270) (Table 3).

3.6. Liver transplantation

3.6.1. Transplant eligibility criteria and outcomes following LT

Taking into account that it has the potential to cure not only HCC but also the underlying disease, LT is the HCC treatment with the highest survival probability. As it deals with donor scarcity and social justice, it should only be offered to patients with a minimum 60% 5-year survival rate. Moreover, HCC recurrence, occurring in approximately 10–30% of the cases, is the most frequent cause of death after LT in these patients [257,258]. Thus, to select the best candidates with the lowest risk of HCC recurrence is another main transplant end-point.

Although Milan criteria (single nodule up-to 5 cm or up-to 3 nodules none of them more than 3 cm in diameter) have been the gold standard for transplant eligibility, some issues should be addressed [259,260]. On the one hand, tumor burden based only on number and diameter has a 25% discordance compared to explant pathology analysis [261–263]. On the other hand, other variables are associated with post-LT outcomes [136,264–269]. Different authors have proposed extended criteria beyond Milan including pre-LT AFP values as a biomarker for candidate selection [136,138,266–268] or histological pre-LT evaluation assessing tumor differentiation (Toronto criteria) [269]. Nevertheless, pre-LT histological evaluation is not always feasible [270].

The fact is that when extending criteria from beyond Milan without including AFP as a biomarker, higher HCC recurrence and lower post-LT survival have been reported [136,138,266–268,271]. AFP values are independently associated with post-LT survival and HCC recurrence and correlate with biologically aggressive tumor features at explant pathology [136,138,266–268,271]. Particularly, AFP levels >1000 ng/ml have been proposed as a contraindication for LT [135]. Consequently, composite criteria have been recently proposed. Duvoux et al. included AFP values to number and tumor diameter (French AFP model: range 0 to 9 points with a threshold of up-to 2 points) [136]. This model was externally validated in Latin America and afterwards, in other regions around the world [271–273]. Other composite models included the sum of the largest diameter plus the total number of HCC nodules with the logarithmic transformation of AFP values (the Metroticket 2.0) [138]. Finally, dynamic AFP changes, as well as tumor progression in the waitlist period, should also be considered [274–277] (Table 2).

3.6.2. Locoregional therapies as adjuvant treatment and “downstaging” before LT

“Bridging” or adjuvant locoregional therapies before LT, either TACE or RFA/PEI among others, aim to avoid tumor progression and remain within LT criteria [277–279]. Tumor progression beyond Milan criteria is 7–11% at 6 months and 38% at 12 months of listing [72,265,275,276]. Variables associated with a higher risk of waitlist tumor progression are tumors beyond Milan criteria, AFP >400 ng/ml and unfeasible or unresponsive to “bridging” therapies [275,276]. On the contrary, patients with complete response (CR) following locoregional treatments have lower rates of tumor progression and waitlist *drop-out* when compared to stable disease (SD) or progressive disease (PD) (1% vs. 10% at 12 months and 1% vs. 51% at 24 months) [275,280].

“Downstaging” consists of reduction of tumor burden, either in tumor diameter or number, to values within Milan criteria [276,281–285]. However, there is no consensus on the “upper limits” beyond Milan for *downstaging*. Most popular LT *downstaging* protocol are those proposed by the University of California San Francisco (UCSF) (1 nodule >5 cm but ≤8 cm or 2–3 nodules all ≤5 cm and sum of diameters ≤8 cm or 4–5 lesions all ≤3 cm and sum of diameters ≤8 cm, plus AFP values below 1000 ng/ml) [285,286]. There was a significant statistical heterogeneity in a metaanalysis reporting the effect of “downstaging” upon survival [287]. On the one hand, effective “downstaging” was 48% (CI 39;58%), even lower in those beyond UCSF (“all-comers”) [288]. This latter group was associated with higher drop-out rate, lower probability of tumor reduction and worse outcomes after LT [288]. It seems that there should be a limit in tumor burden for “downstaging”. In this regard, AFP values below 100 ng/ml were recently proposed to select better candidates within the UCSF protocol [289]. Also, a minimum observation period of 3 months to assess stable disease is required [290]. Finally, there is no robust data supporting the superiority of any therapeutic modality [178,287,291] (Table 2).

3.6.3. Systemic treatment as adjuvant therapy before or after LT

There is no robust data in favor or against the use of sorafenib or other multikinase inhibitors, or other chemotherapeutic agents before or after transplantation as adjuvant therapy to reduce the risk of HCC recurrence [247,292–294]. Although immunosuppression with mTOR inhibitors was promising [295–297], there was neither survival nor recurrence benefit in a recent RCT [298].

3.6.4. Surveillance and management of HCC recurrence after LT

The risk of HCC recurrence should be reassessed at explant pathology analysis. Presence of extensive tumor burden (beyond Up-to 7 criteria) [270], microvascular invasion, undifferentiated tumors or absence of complete necrosis are associated with

higher recurrence risk [137,299,300]. Surveillance for HCC recurrence is controversial since it is considered an advanced stage with a high mortality rate independently from its location and there is no robust data to support any particular therapy. Moreover, most recurrences occur during the first 18 months after LT [137,257] and its earlier detection has been associated with worse survival [257,258]. Nevertheless, international consensus recommends surveillance for HCC recurrence with CT or MRI scans plus AFP values with a minimum interval of 6 months up-to the 3rd to 5th years following LT [299]. Locoregional therapies have been reported in retrospective studies for single intra or extrahepatic lesions [258,301], re-transplantation is strongly not recommended and in patients in whom locoregional therapies are not feasible, sequential systemic therapy has prolonged overall survival in retrospective studies [302–306]. No robust data supports any change in the type of immunosuppression [302–306] (Table 2).

3.7. Systemic therapies for advanced HCC

3.7.1. First-line systemic treatment agents

During the last decade, an enormous improvement in the treatment of these patients has been achieved, with unthinkable survival rates years ago. Systemic conventional chemotherapeutic agents such as FOLFOX or GEMOX [307–309] or other agents as tamoxifen [157] have failed to show any survival benefit.

Sorafenib, a tyrosine multikinase inhibitor (TKI) was the first drug to show a survival benefit over placebo in two double-blind, phase III RCT (SHARP and Asia-Pacific) [241,310]. The exact mechanism of action is unknown with anti-angiogenic, hypoxic and antiproliferative effects. Eligibility criteria included preserved liver function, ECOG 0–1 and BCLC-C or BCLC-B under tumor progression [241,310]. Sorafenib (400 mg bid) had a 70% relative risk reduction of death [HR of 0.69 (CI 0.55;0.87)] [241,310] and better TTP. However, radiological CR or PR were infrequently observed with a DCR of 43–53% [241,310]. Other real-world uncontrolled studies have been published so far [311], suggesting that sorafenib may be extended up-to Child–Pugh B7; however, lower survival and higher rate of adverse events with unreserved liver function were reported [312–315].

Since then, other non-inferiority [e.g. sunitinib [316] and brivanib [317] or superiority trials [erlotinib [318], linifanib [319], dovitinib [320]] have failed to show any survival benefit or have shown excessive toxicity vs. sorafenib [bevacizumab + sorafenib [321]. More recently, lenvatinib showed non-inferiority (REFLECT trial) [322] and atezolizumab plus bevacizumab superiority over sorafenib (IMbrave trial, NCT03434379).

The REFLECT phase III, open-label RCT, showed non-inferior survival of lenvatinib (8 mg day if <60 kg or 12 mg day if >60 kg) vs. sorafenib [322]. This TKI blocks VEGF as well as FGF and PDGF pathways. In this trial, eligibility criteria excluded patients with main portal trunk tumor invasion and those with >50% of total liver volume involvement [322,323]. Median survival was 13.6 months with lenvatinib vs. 12.3 months with sorafenib [HR 0.92 (CI 0.79;1.06)] [322]. TTP, as well as higher rates of partial response and objective response rates (ORR) were observed with lenvatinib. Higher rates of severe adverse events were observed in lenvatinib arm (57% vs. 49%), mainly hypertension, hypothyroidism and proteinuria (Table 3). In Argentina, lenvatinib was approved in late 2018.

3.7.2. Immunotherapy alone or in combination for first-line systemic therapy

Immunotherapy for cancer treatment has evolved into a complete novel paradigm. Cancer cells avoid lymphocyte T cell activation and proliferation, highly expressing “programmed cell death ligands” PD-1 ligand 1 and 2 (PD-L1, PD-L2) or “cytotoxic T lymphocyte protein 4” ligands (CTLA-4 and its ligands).

Blockade of these unions through monoclonal antibodies (anti-PD-(L)1 or anti-CTLA-4) unblocks the anti-cancer immune host response (“immune check-point inhibitors”). The first anti-PD1 IgG4 monoclonal antibody was nivolumab. Later on, pembrolizumab (IgG4 anti-PD1), tremelimumab and ipilimumab (IgG1 anti-CTLA-4) and atezolizumab, durvalumab and avelumab (IgG1 anti PD-L1).

Recently, the CheckMate-459 phase III, open-label RCT (NCT02576509) for first-line therapy in patients with advanced HCC naïve of systemic therapy, Child A, ECOG 0–1, BCLC-B or C in the absence of main portal trunk invasion did not show superior survival of nivolumab (240 mg iv every 3 weeks) over sorafenib [median survival nivolumab 16.4 months vs. sorafenib 14.7 months; HR 0.85 (CI 0.72–1.02); $P=0.07$]. There was not a significant difference of DFS, even showing a higher rate of ORR in favor of nivolumab (15% vs. 7% with sorafenib). Nivolumab was associated with a lower rate of grade 3/4 adverse events (22% vs. 49%).

More recently, another phase III, open-label RCT, IMbrave-150 (NCT03434379) showed superiority of atezolizumab 1200 mg iv (anti-PD-L1) plus bevacizumab 15 mg/kg iv every 3 weeks vs. sorafenib [median survival not reach vs. 13.2 months for sorafenib; HR 0.58 (CI 0.42–0.79); $P=0.0006$] [324]. Eligibility criteria included preserved liver function, systemic-naïve advanced HCC, ECOG 0–1 in the absence of main portal trunk invasion. Longer progression free survival (PFS) with a significant higher ORR rate in the combination arm 27% vs. 12% and DCR of 74% vs. 55% ($P<.0001$) were observed. Similar incidence of all grade adverse events and a lower incidence of grades 3/4 related adverse events were observed with the combination arm (36% vs. 46%). The most frequent adverse events were systemic hypertension, diarrhea, proteinuria, hyporexia, elevated liver enzymes and infusion reaction. However, treatment discontinuation was higher in atezolizumab + bevacizumab arm (16% and 10%, respectively) (Table 3).

Other combinations are being explored in phase III trials: pembrolizumab + lenvatinib vs. lenvatinib (LEAP-002, NCT03713593), sorafenib vs. durvalumab (anti PDL-1) vs. durvalumab + tremelimumab (CTLA-4) (HIMALAYA, NCT03298451), cabozantinib with/without atezolizumab vs. sorafenib (COSMIC-312; NCT03755791) and nivolumab + ipilimumab vs. sorafenib or lenvatinib (CheckMate-9DW; NCT04039607).

3.7.3. Second-line systemic treatment agents

Tumor progression under sorafenib is the natural course of the disease in most of the patients and 10–20% of the patients may not tolerate this treatment. Thus, several second-line phase III trials have been explored after sorafenib progression or intolerance. Some agents failed to show any survival benefit vs. placebo including brivanib (BRISK-PS, phase III RCT) [325], axitinib (phase II trial) [326], everolimus (EVOLVE-1, phase III RCT) [327] and tivantinib (METIV, phase III RCT) [328].

The RESORCE trial included patients with advanced HCC, preserved liver function, with tumor progression and tolerant to sorafenib (a minimum dose of 400 mg daily during the last month). Dose was scheduled in 160 mg day in a 4 week-cycle (3 weeks ON-1 week OFF). Median survival was 10.6 months for regorafenib and 7.8 months for placebo [HR of 0.62 (CI 0.50;0.79)]; this survival benefit was observed in all stratified analyses even in patients with worse baseline prognosis (AFP >400 ng/ml or macrovascular invasion) [329]. A benefit on TTP was also observed, with a significant difference in DCR (65% vs. 36%). Adverse events were common for TKIs (fatigue, hyporexia, hypertension, diarrhea and hand-foot skin reaction-HFSR); 46% were grade III and 4% grade IV, with a discontinuation rate of 10% [329]. In Argentina, it was approved during 2018.

The CELESTIAL trial compared cabozantinib 60 mg/day vs. placebo [134] including unresectable BCLC-B or C patients, Child–Pugh A, ECOG 0–1, with previous sorafenib treatment (either tolerant or intolerant), with tumor progression after up-to 2 prior systemic therapies. Median survival was 10.2 months for cabozantinib and 8 months for placebo [HR of 0.76 (CI 0.63;0.92)]; this survival benefit was also observed in all post hoc analyses, even in patients with sorafenib as the only prior systemic therapy [HR 0.74 (IC 0.59–0.92)]. However, the efficacy of cabozantinib in tolerant vs. intolerant to sorafenib is uncertain. TTP was also in favor of cabozantinib with a DCR of 64% vs. 33%. Dose reductions and discontinuations were more common in cabozantinib arm, likewise for adverse events such as HFSR, asthenia and diarrhea [134].

The REACH I failed to show any survival benefit of ramucirumab (8 mg/kg iv every 2 weeks), a monoclonal antibody that blocks VEGF receptors, vs. placebo. However, in a post hoc analysis there was a specific survival benefit among patients with baseline AFP values ≥ 400 ng/ml, a group with an expected lower survival rate [133]. This motivated to performed the REACH II RCT including patients with histologically or cytologically confirmed HCC with AFP ≥ 400 ng/ml, with prior sorafenib therapy – tolerant or intolerant – and tumor progression [330]. Median survival was 8.5 months for ramucirumab and 7.3 months for placebo [HR of 0.71 (CI 0.53;0.95)]. Stratified analyses confirmed the efficacy of ramucirumab in all groups but uncertain in prior-intolerant to sorafenib. TTP was longer and there were higher ORR and DCR rates over placebo (60% vs. 39%). Serious adverse events were similar between arms; ramucirumab presented more frequently hypertension (13%) and hyponatremia (6%) with a discontinuation rate due to adverse events of 11% [330]. Neither cabozantinib nor ramucirumab has been approved for HCC in Argentina (Table 3).

3.7.4. Immunotherapy for second-line systemic therapy

Tremelimumab has been explored in an uncontrolled phase II trial in patients with HCV+; it was well tolerated with no HCV biochemical flares, even with decreasing HCV viral loads [331]. In another phase I/II, uncontrolled trial of nivolumab (CheckMate-040) in Child–Pugh A–B <9 patients under progression with sorafenib (tolerant or intolerant) [332]. There were escalating and expansion cohorts (3 mg/kg iv every 3 weeks). The survival rate at 9 months was 74% (CI 67%;79%) with ORR of 20% and a DCR of 64%. PD-L1 expression on tumor biopsies ($\geq 1\%$ vs. $<1\%$) was not associated with a better survival but higher ORR was observed. Nivolumab showed a very good safety profile; common adverse events were rash, pruritus, diarrhea or colitis and liver or pancreatic enzymes elevation. This granted FDA temporary approval and motivated the CheckMate-459 at frontline (NCT02576509).

More robust data comes from a phase III, double-blind, RCT of pembrolizumab 200 mg iv every 3 weeks vs. placebo (KEYNOTE-240) in patients under progression with sorafenib or intolerant to sorafenib, Child A, ECOG 0–1, BCLC B or C without main portal trunk invasion and AFP levels <400 ng/ml [333]. The trial was negative in terms of survival benefit according to its null hypothesis alpha level; however, median survival was significantly longer for pembrolizumab vs. placebo [13.9 vs. 10.6 months, HR of 0.78 (CI 0.71–0.99); $P=0.024$]. DFS did not reach its primary efficacy endpoint too, although there was a higher ORR in favor of pembrolizumab (18.3% vs. 4.4%; $P=0.00007$), with a longer median duration of response. The incidence of immune-related adverse events (irAEs) was 18.3% with pembrolizumab, 7.2% grade 3/4 and in 3.6% motivated treatment discontinuation. The most frequent adverse events were liver enzymes elevation, fatigue, pruritus, hyporexia and diarrhea. In a stratified analysis, patients with AFP <200 ng/ml or with post-progression (vs. intolerant to sorafenib) or with HBV had the highest benefit of pembrolizumab [333]. In

Argentina, nivolumab and pembrolizumab were approved in late 2019 (Table 3).

3.8. Clinical and radiological assessment after treatments for HCC

The main outcome of the treatment of HCC patients is overall survival. Secondary outcomes should be cancer eradication for curative therapies or delaying tumor progression with palliative therapies [334]. Liver decompensation events are competing events (jaundice, ascites, hepatic encephalopathy) leading to higher mortality and lower survival. These events are considered to be “untreatable progression” [335,336]. On the other hand, TTP or DFS are not surrogate markers of overall survival in patients with HCC; both are lower robust end-points with different risk of bias [291,317].

“Target lesions” are those potentially treatable with at least APHE [337,338]; which should not be confounded with inflammatory signals. In cases of CR for curative therapies, imaging controls should be done every 3 months thereafter. Tumor response evaluation should be assessed with triphasic CT or MRI scans 4–6 weeks following TACE; particularly, with MRI after conventional TACE avoiding confounding effect with lipiodol. TARE response should be assessed not earlier than 8 weeks; with the best response usually occurring even after 6 months. Tumor re-assessment for systemic therapies is done every 8–12 weeks if second or third lines are available. Different imaging criteria to address tumor response have been proposed through the Response Evaluation Criteria for Solid Tumors (RECIST), including different versions (RECIST 1.0, RECIST 1.1), modified RECIST (mRECIST) [337,338]. Other criteria include the EASL or WHO [337,338]. mRECIST and EASL consider residual hyperenhancement diameters [337,338]. For locoregional therapies, mRECIST or EASL are preferable and for systemic therapies, RECIST 1.1 or mRECIST have been validated in RCT [339]. LIRADS tumor response assessment has not been validated in RCT [108,118]. Finally, evaluation after immunotherapy should consider that inflammatory infiltrates may increase tumor diameters at the very beginning (iRECIST).

3.8.1. Clinical management after locoregional endovascular therapies

Although it has been shown that TACE number of sessions is directly proportional to tumor diameter [340] and CR has been associated with better survival [340], it is important to underline the risk of liver decompensation with unnecessary sequential TACEs when no response or tumor progression is observed, due to ischemic injury on the non-tumoral liver. Thus, it may be prudent to perform no more than 2 or 3 TACE sessions to achieve local tumor control and if not achieved, start systemic therapy [337,341]. Although the risk of liver ischemic injury with TARE is much lower, potential REILD should be evaluated.

Some scoring models have been published to identify candidates for sequential re-TACE, including the ART, STATE-ART and HAP scores [342–344]. However, significant risk of selection and information bias precluded these scores to be robust enough. Patients with “untreatable progression” are neither candidates for sequential TACE nor systemic therapy [335,336]. The rate of progression from Child–Pugh A to B or C following TACE was 13.8% and 15.9%, respectively (RELPEC cohort study) [345]. In Argentina, patients with “untreatable progression” following TACE had lower survival compared to those with sequential TACE-systemic therapy [311]. Data from first and second line RCT considered two intrahepatic tumor progression following TACE in BCLC-B as eligible for systemic therapy [241,317,322]. TARE as a rescue therapy following TACE failure was reported in the SARAH and SIRveNIB trials [240,241].

Table 4
Radiological tumor response assessment, management of adverse events and dose scheme for HCC systemic therapies.

Topic	Statement	Grade of Recommendation	Quality of the evidence
Radiological response assessment	mRECIST is recommended for post-locregional therapies tumor reassessment.	Strong	Moderate to high
	RECIST 1.1 or mRECIST are recommended to assess tumor response under systemic treatments.	Strong	High
	There is no robust evidence to support tumor reassessment by LIRADS.	Strong	Low to very low
Stopping rules	Grade 4 adverse events for any therapy.	Strong	High
	Unresolved grade 3 adverse events for any therapy.	Strong	High
	Grades 2 or higher for irAEs ¹	Strong	High
	"Untreatable progression" ² for locoregional and systemic therapies.	Strong	High
Dosing schedules for systemic therapies	Dose is fixed for atezolizumab 1200 mg iv + bevacizumab 15 mg/kg iv; cycles every 21 days may be postpone or interrupted for adverse events.	Strong	High
	Dose scheme reduction for sorafenib is 400 mg bid to 400 mg/day and 400 mg every other day.	Strong	High
	Dose scheme reduction for lenvatinib depends on initial weight but it is 12 mg/day to 8 mg/day, 4 mg/day to 4 mg every other day.	Strong	High
	Dose scheme reduction for regorafenib is 160 mg/day to 120 mg/day and 80 mg/day (ON-OFF cycles).	Strong	High
	Dose scheme reduction for cabozantinib is 60 mg/day to 40 mg/day and 20 mg/day.	Strong	High
	Dose is fixed for ramucirumab 8 mg/kg iv; cycles every 14 days may be postpone or interrupted for adverse events.	Strong	High
	Dose is fixed for pembrolizumab 200 mg iv; cycles every 21 days may be postpone or interrupted for adverse events.	Strong	High
	Dose is fixed for nivolumab 3 mg/kg or up-to 240 mg; cycles every 14 days may be postpone or interrupted for adverse events.	Strong	High

Notes: 1-Specific management for each irAE should be addressed with other practice guidelines. 2- Defined as jaundice, ascites, hepatic encephalopathy and other related complications (hepatorenal syndrome, among others).

Abbreviations: iv: intravenous infusion. irAE: immune-related adverse event.

3.8.2. Clinical management and radiological assessment after systemic therapies

Clinical evaluation and management of patients receiving systemic therapies should include "untreatable progression", PD and tolerability. Any type of PD may not defined prognosis [134,329,330,332]. Whereas vascular invasion, new or growing extrahepatic lesions are prognostic markers, at least two consecutive new intrahepatic or growing intrahepatic lesions may be needed to start a second line [335].

Adverse events following TKIs should be addressed at every clinical visit; the need for dose reduction or treatment discontinuation. Intolerance to sorafenib was differently defined in the RESORCE and KEYNOTE-224 trials [329,333]. Treatment discontinuation rates were 9% with lenvatinib [322], 10% with regorafenib [329], 11% with sorafenib [241,310] and 16% with cabozantinib [134]. This comparison should consider different eligibility criteria and assessment of adverse events [346]. Most common adverse events for TKIs are fatigue, hyporexia, diarrhea, dermatologic events including rash and HFSR, hypertension, hypothyroidism, elevated liver enzymes, elevated total bilirubin and proteinuria [134,241,310,322,329]. Ramucirumab presented hypertension and hyponatremia [330]. Dermatological adverse events during the first 45 days of sorafenib therapy have been associated with better overall survival [314,347]. In general, grades I-II adverse event should prompt specific treatment and may continue with TKI dose until resolution of symptoms; grades III demand TKI reduction or transient interruption until resolution and grades IV definite treatment discontinuation [346]. Schemes of dose reduction according to RCT are shown in Table 4.

Management of irAEs should be addressed following other international guidelines [348]. The irAEs have been reported in 83% of treated patients with less than 10% being grades 3 or 4 [332,333,349,350]. Although well-tolerated, irAEs could be life-threatening and demand a low threshold of suspicion [348]. Every

organ can be involved, with a median occurrence between 3 to 6 months of initiation, earlier for anti-CTLA-4 compared to anti PD-(L)1 [348]. Most frequently involved organs are the skin (rash, pruritus), gastrointestinal (diarrhea or colitis) and the liver (hepatitis) [333]. Most of irAEs respond to steroid treatment and resolve between 6 to 8 weeks; steroid treatment has not been associated with lower efficacy in other tumors. However, steroids should be cautiously used in patients with cirrhosis due to a higher risk of infections or liver decompensation [351]. Recurrence of irAEs has been reported 55% of the cases, associated with time of occurrence with the first event [348]. Viral load for HBV before immunotherapy should be controlled with antivirals below 100 or 500 UI/ml because of the risk of HBV flares [332].

3.9. Special populations

Hepatocellular carcinoma in non-cirrhotic or non-advanced fibrotic patients, mixed hepato-cholangio carcinoma and fibrolamellar HCC are special populations with low quality evidence to support for or go against any specific recommendations and these patients have been excluded from RCT. Although the BCLC could be applied, these patients should be discussed in multidisciplinary boards and LR should be the first-line option.

3.10. Final considerations

With the coming new diagnostic and novel therapies for HCC, these patients will demand multidisciplinary team-working specifically trained on liver-related complications and HCC including hepatologist, gastroenterologists, liver surgeons, oncologists, radiologists, palliativies and pathologists [7]. Hepatologists have had a key role in research in this field [73,91,136,138,155,157,228,241,285,322,328]. Consequently, international associations and guidelines should not only underline

Table 5
Comparison between A.A.E.E.H and other international guidelines.

Topic/Guideline	AAEEH	AASLD [1]	EASL [2]	ALEH [3]	APASL [4]
General organization	Consensus meeting 2015 Key clinical questions. GRADE approach	Ten key clinical questions. GRADE approach Published in 2018	GRADE approach Published in 2018	GRADE approach Published in 2014	Consensus meeting GRADE approach Published in 2017
Epidemiology	Definition of the population at high risk for HCC. Primary, secondary and tertiary prevention detailed. Strongly recommends treatment of liver disease to avoid progression of liver disease. HCV therapy after curative therapies for HCC: benefit vs. recurrence risk to be individualized. Uncertainty for recommending coffee consumption.	Definition of the population at high risk for HCC.	Definition of the population at high risk for HCC. Primary, secondary and tertiary prevention detailed. Strongly recommends treatment of liver disease to avoid progression of liver disease. HCV therapy after curative therapies for HCC: benefit vs. recurrence risk to be individualized. Strongly recommends coffee consumption.	Definition of the population at high risk for HCC. Primary and secondary prevention detailed.	Definition of the population at high risk for HCC. Special focus on HBV HCC. Primary, secondary and tertiary prevention detailed. Universal HBV vaccination in infants, specially HBV-endemic areas. Long-term antiviral HBV therapy as secondary prophylaxis. Recommends achievement of viral eradication for HCV but in high risk patients warrants surveillance. Further studies to assess risk and benefits of DAA after curative therapies for HCC.
Surveillance	Recommends surveillance with US. Suggests surveillance with US with AFP in cases of unknown or inexpert US operators based on 3 AFP cut-off values. Every 6 months.	Suggests surveillance with US with or without AFP Suggest not performing surveillance in Child Pugh C if not listed for LT. Time-frame for surveillance every 4–8 months.	Recommends surveillance with US. Does not recommend biomarkers Recommended in patients with preserved liver function or listed for LT. Every 6 months.	Recommends US. Every 6 to 12 months.	Recommends US with AFP (suggested cut-off 200 ng/ml) or even a lower cut-off after HBV or HCV viral eradication. Suggests simultaneous use of biomarkers: AFP, AFP-L3 and DCP. Every 6 months.
Imaging Diagnosis	Imaging diagnosis strongly recommended either with triphasic CT or MRI. Suggests using LI-RADS in a specific algorithm.	Imaging diagnosis strongly recommended either with triphasic CT or MRI.	Imaging diagnosis strongly recommended either with triphasic CT or MRI or contrast-US. PET-CT not recommended. MRI with hepatobiliary contrast agents included in algorithm but recalling lower specificity.	Imaging diagnosis strongly recommended either with triphasic CT or MRI	Imaging diagnosis strongly recommended either with triphasic CT or MRI or gadoteric acid MRI for non-hypervascular nodules and contrast US.

Table 5 (Continued)

Topic/Guideline	AAEEH	AASLD [1]	EASL [2]	ALEH [3]	APASL [4]
Tumor biopsy	Tumor biopsy for non-cirrhotic and indeterminate nodules. Maybe assessed after gadoxetic acid contrast MRI. Tumor biopsy only in non-cirrhotic patients.	Tumor biopsy conditional. Against routine biopsy of every indeterminate nodule.	Tumor biopsy only in non-cirrhotic patients.	Tumor biopsy in non-cirrhotic patients.	Tumor biopsy for non-cirrhotic and indeterminate nodules after gadoxetic acid contrast MRI.
Staging	BCLC staging. Includes specific key question for LT candidates in BCLC-B and D stages.	BCLC not included. Staging based on TNM.	BCLC staging. “Not optimal surgical candidate” with portal hypertension may be done including extension of hepatectomy and MELD <10.	BCLC staging.	Asia-Pacific treatment algorithm.
Endovascular therapies	Strongly recommends TACE for BCLC-B patients. TACE with DEB not recommended over conventional TACE. Suggests evaluating TARE in patients with unresectable large tumors, with/without portal vein thrombosis (non-tumoral invasion).	Strongly recommends with TACE, TARE or external radiation over BSC for T2 or T3 HCC not candidates for surgery or LT. Does not recommend one form of therapy over another.	Strongly recommends TACE, either conventional or with DEB, over BSC. Does not recommend TARE or other therapy for intermediate HCC.	Strongly recommends TACE over BSC. TACE with DEB although “showing benefits over conventional TACE, not recommended due to higher costs”.	TACE, either conventional or with DEB, over BSC in multinodular, un-resectable and without extrahepatic or vascular disease HCC TARE or SBRT conditional options. Concept or “TACE failure/refractoriness” (2 or more consecutive ineffective responses or 2 or more intrahepatic progressions).
Locoregional therapies	Either RFA or LR for very early HCC. PEI if RFA not feasible. Does not recommend cryoablation. Uncertain recommendation for SBRT or IRE. CSPH and preserved liver function recommended to select candidates for LR.	Suggests resection over RFA: for T1 or T2.	Either RFA or LR for very early HCC Suggests “resection” in non-ideal candidates: MELD <10.	Either RFA or PEI for very early HCC not suitable for surgery.	RFA first line for single <2 cm, Child A or B. RFA as alternative for LR. PEI for cases in which RFA is not feasible in patients with up-to 3 nodules <3 cm each.

Table 5 (Continued)

Topic/Guideline	AAEEH	AASLD [1]	EASL [2]	ALEH [3]	APASL [4]
Liver Transplantation	Suggests using composite criteria for candidate selection. Suggests bridging therapies while on the waitlist period depending on tumor burden, AFP >400 ng/ml and expected time on the waitlist. Suggests <i>downstaging</i> for patients beyond Milan criteria but with AFP <100 ng/ml.	Suggest for T1 HCC listed for LT to undergo observation period. Suggests bridging therapies for T2 while on the waitlist period; without any specific treatment recommendation. Suggests <i>downstaging</i> for patients beyond Milan criteria within T3 stage.	Recommends Milan criteria for appropriate candidate selection but recalls for <i>composite models</i> including biomarkers. Suggests bridging therapies while on the waitlist period; without any specific treatment Weak recommendation for <i>downstaging</i> .	Recommends Milan criteria for appropriate candidate selection. Conditional recommendation for <i>downstaging</i> . Recall for AFP cut-offs for LT selection.	Resectability vs. LT based on Child Pugh and “surgeons evaluation”.
Adjuvance	Against adjuvant therapy after LR or ablation.	Against adjuvant therapy after LR or ablation.	Against adjuvant therapy after LR or ablation.	Not up-dated.	
Systemic treatment	Specific recommendations for available options in first-line (sorafenib, lenvatinib) and second line (regorafenib, pembrolizumab and nivolumab). Not yet approved: atezolizumab + bevacizumab in first-line and cabozantinib in second-line. Against TARE over sorafenib.	Strongly recommends systemic therapy over BSC for Child A or B in advanced HCC patients. No specific recommendation for first or second lines. Not up-dated.	Specific recommendations for first and second lines (sorafenib, regorafenib, cabozantinib). Against TARE over sorafenib Not up-dated.	Only sorafenib. Not up-dated.	Sorafenib for first line therapy. Regorafenib as second line. Not up-dated.
Other remarks	Specific recommendations for adverse events, stopping rules and radiological response assessment. Recalls resection as main therapy in non-cirrhotic patients. Multidisciplinary team working.		Multidisciplinary team working Recalls resection as main therapy in non-cirrhotic patients.	Recalls resection as main therapy in non-cirrhotic patients. LT may be offer in these patients. HCC in pediatric population.	Multidisciplinary team working.

Notes:

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the main role of hepatologists but also the need for multidisciplinary team-working [352–355]. Similarities and differences between this and other guidelines are described on Table 5. Differences between these practice guidelines with the former may be related to feasibility and availability of diagnostic and therapeutic modalities but also to cost-effective, and healthcare system barriers. Cost-effective analysis in countries with limited health resources should be done, as well as local patient's preferences. Approval of some interventions in these countries should be carefully addressed. For this reason, it is important to have local or regional data, analyzing access to health care [358,359]. In this clinical practice guideline, in 7.5% of the total included references, Argentinian colleagues participated as first authors, or as participating co-authors from international observational and RCT. However, the first authorship rate was 4.4%, this is a common problem in Latin America, a region where there is a low rate in the clinical setting [356–358].

On the other hand, genetic regional variations should also be considered [357]. During the coming years, advancement of medical technology, based on novel genetic [357,359], epigenetic researches [360], as well as radiomics and artificial intelligence [361], may help to enhance surveillance, diagnosis and treatment response assessment in the clinical setting of HCC patients. In this regard, clinical practice guidelines should be appropriately updated [357].

Conflict-of-interest

F Piñero has received Advisory Board and speaker honoraria and he is consultant of Bayer Healthcare; has received speaker honoraria from Raffo and research grants from the Argentinean National Institute of Cancer (INC ID-190), Argentinean National Ministry of Science and Technology Development (PICT 2017, FON-CYT) and from the Latin American Liver Research Educational and Awareness Network (LALREAN). G Aballay Soteras has received speaker honoraria and Advisory Board fees and research grants from Bayer Healthcare, MSD; he is consultant for Bayer and has received Advisory Board fees from Roche. S Marciano has received speaker honoraria from Gador, Gilead and Abbvie; has received educational grants from Gilead, Bristol-Myers Squibb, Bayer, Biotoscana and Gador and research grants from Gilead and Bristol-Myers Squibb. M Silva has received speaker honoraria and is a consultant for Abbvie, Gador, Bristol-Myers Squibb, Merck, Bayer and research grants from the Argentinean National Institute of Cancer (INC ID-190), Argentinean National Ministry of Science and Technology Development (PICT 2017, FONCYT). A Ruf has received Advisory Board and speaker honoraria and he is consultant of Bayer Healthcare, Novartis, Gador, Astellas and has received research grants from the Executive Secretariat of the Group of 77 at the United Nations. M Dirchwolf has received Advisory Board and speaker honoraria and he is consultant of Bayer Healthcare and has received a research grant from Novartis. M Tanno, M Tisi Baña, E Fassio, S Mengarelli, S Borzi, N Fernandez, E Ridruejo, V Descalzi, M Anders, G Mazzolini, V Reggiardo, JC Spina, L McCormack, M Maraschio, C Lagues, F Villamil, F Cairo and B Ameigeiras do not have any conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at [doi:10.1016/j.aohep.2020.06.003](https://doi.org/10.1016/j.aohep.2020.06.003).

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