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EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma

European Association for the Study of the Liver*,
European Organisation for Research and Treatment of Cancer

Introduction

EASL–EORTC Clinical Practice Guidelines (CPG) on the management of hepatocellular carcinoma (HCC) define the use of surveillance, diagnosis, and therapeutic strategies recommended for patients with this type of cancer. This is the first European joint effort by the European Association for the Study of the Liver (EASL) and the European Organization for Research and Treatment of Cancer (EORTC) to provide common guidelines for the management of hepatocellular carcinoma. These guidelines update the recommendations reported by the EASL panel of experts in HCC published in 2001 [1]. Several clinical and scientific advances have occurred during the past decade and, thus, a modern version of the document is urgently needed.

The purpose of this document is to assist physicians, patients, health-care providers, and health-policy makers from Europe and worldwide in the decision-making process according to evidence-based data. Users of these guidelines should be aware that the recommendations are intended to guide clinical practice in circumstances where all possible resources and therapies are available. Thus, they should adapt the recommendations to their local regulations and/or team capacities, infrastructure, and cost–benefit strategies. Finally, this document sets out some recommendations that should be instrumental in advancing the research and knowledge of this disease and ultimately contribute to improve patient care.

The EASL–EORTC CPG on the management of hepatocellular carcinoma provide recommendations based on the level of evidence and the strength of the data (the classification of evidence is adapted from National Cancer Institute [2]) (Table 1A) and the strength of recommendations following previously reported systems (GRADE systems) (Table 1B).

Clinical Practice Summary

The clinical practice guidelines below will give advice for up to date management of patients with HCC as well as providing an in-depth review of all the relevant data leading to the conclusions.

Clinical Practice Summary

Surveillance

- Patients at high risk for developing HCC should be entered into surveillance programs. Groups at high risk are depicted in Table 3
  (**evidence 1B/3A; recommendation 1A/B**)
- Surveillance should be performed by experienced personnel in all at-risk populations using abdominal ultrasound every 6 months
  (**evidence 2D; recommendation 1B)**
  Exceptions: A shorter follow-up interval (every 3-4 months) is recommended in the following cases: (1). Where a nodule of less than 1 cm has been detected (see recall policy), (2). In the follow-up strategy after resection or loco-regional therapies
  (**evidence 3D; recommendation 2B)**
- Patients on the waiting list for liver transplantation should be screened for HCC in order to detect and manage tumor progression and to help define priority policies for transplantation
  (**evidence 3D; recommendation 1B**)

Recall policy

- In cirrhotic patients, nodules less than 1 cm in diameter detected by ultrasound should be followed every 4 months the first year and with regular checking every 6 months thereafter
  (**evidence 3D; recommendation 2B**)
- In cirrhotic patients, diagnosis of HCC for nodules of 1-2 cm in diameter should be based on non-invasive criteria or biopsy-proven pathological confirmation. In the latter case, it is recommended that biopsies are assessed by an expert hepatopathologist. A second biopsy is recommended in case of inconclusive findings, or growth or change in enhancement pattern identified during follow-up
  (**evidence 2D; recommendation 1B**)
- In cirrhotic patients, nodules more than 2 cm in diameter can be diagnosed for HCC based on typical features on one imaging technique. In case of uncertainty or atypical radiological findings, diagnosis should be confirmed by biopsy
  (**evidence 2D; recommendation 1A**)

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Abbreviations: HCV, Hepatitis C virus; SNP, Single nucleotide polymorphism; PEG, Polyethylene glycol; HALT-C, Hepatitis C antiviral long-term treatment against cirrhosis; EPIC, Evaluation of PegIntron in control of hepatitis C cirrhosis; CT, Computed tomography; MR, Magnetic resonance; MRI, Magnetic resonance imaging; EpCAM, Epithelial cell adhesion molecule; PPV, Positive predictive value; qRT-PCR, Real-time reverse-transcription polymerase chain reaction; CUPI, Chinese university prognostic index; CLIP, Cancer of the Liver Italian program; SHARP, Sorafenib hepatocellular carcinoma assessment randomised protocol.

These Guidelines were developed by the EASL and the EORTC and are published simultaneously in the *Journal of Hepatology* (volume 56, issue 4) and the *European Journal of Cancer* (volume 48, issue 5).

Clinical Practice Summary

Diagnosis

- Diagnosis of HCC is based on non-invasive criteria or pathology (**evidence 2D; recommendation 1A**)
- Pathological diagnosis of HCC is based on the recommendations of the International Consensus Panel. Immunostaining for GPC3, HSP70, and glutamine synthetase and/or gene expression profiles (*GPC3, LYVE1* and survivin) are recommended to differentiate high grade dysplastic nodules from early HCC (**evidence 2D; recommendation 2B**)
  Additional staining can be considered to detect progenitor cell features (K19 and EpCAM) or assess neovascularisation (CD34)
- Non-invasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI. Diagnosis should be based on the identification of the typical hallmark of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases). While one imaging technique is required for nodules beyond 1 cm in diameter (**evidence 2D; recommendation 2B**), a more conservative approach with 2 techniques is recommended in suboptimal settings. The role of contrast-enhanced ultrasound (CEUS) and angiography is controversial. PET-scan is not accurate for early diagnosis

Staging systems

- Staging systems in HCC should define outcome prediction and treatment assignment. They should facilitate exchange of information, prognosis prediction and trial design. Due to the nature of HCC, the main prognostic variables are tumor stage, liver function and performance status
- The BCLC staging system is recommended for prognostic prediction and treatment allocation (**evidence 2A; recommendation 1B**)
  This staging system can be applied to most HCC patients, as long as specific considerations for special subpopulations (liver transplantation) are incorporated
- Other staging systems applied alone or in combination with BCLC are not recommended in clinical practice
- Molecular classification of HCC based on gene signatures or molecular abnormalities is not ready for clinical application (**evidence 2A; recommendation 1B**)

Treatment

- Treatment allocation is based on the BCLC allocation system

Resection

- Resection is the first-line treatment option for patients with solitary tumors and very well-preserved liver function, defined as normal bilirubin with either hepatic venous pressure gradient ≤10 mmHg or platelet count ≥100,000
  (evidence 2A; recommendation 1B)
  Anatomical resections are recommended (**evidence 3A; recommendation 2C**)
- Additional indications for patients with multifocal tumors meeting Milan criteria (≤3 nodules ≤3 cm) or with mild portal hypertension not suitable for liver transplantation require prospective comparisons with loco-regional treatments (**evidence 3A; recommendation 2C**)
- Peri-operative mortality of liver resection in cirrhotic patients is expected to be 2-3%
- Neo-adjuvant or adjuvant therapies have not proven to improve outcome of patients treated with resection (or local ablation) (**evidence 1D; recommendation 2C**)
- Tumor recurrence represents the major complication of resection and the pattern of recurrence influences subsequent therapy allocation and outcome. In case of recurrence, the patient will be re-assessed by BCLC staging, and re-treated accordingly

Liver Transplantation

- Liver transplantation is considered to be the first-line treatment option for patients with single tumors less than 5 cm or ≤3 nodules ≤3 cm (Milan criteria) not suitable for resection (**evidence 2A; recommendation 1A**)
- Peri-operative mortality and one-year mortality are expected to be approximately 3% and ≤10%, respectively
- Extension of tumor limit criteria for liver transplantation for HCC has not been established. Modest expansion of Milan criteria applying the “up-to-seven” in patients without microvascular invasion achieves competitive outcomes, and thus this indication requires prospective validation (**evidence 2B; recommendation 2B**)
- Neo-adjuvant treatment can be considered for loco-regional therapies if the waiting list exceeds 6 months due to good cost-effectiveness data and tumor response rates, even though impact on long-term outcome is uncertain (**evidence 2D; recommendation 2B**)
- Down-staging policies for HCCs exceeding conventional criteria cannot be recommended and should be explored in the context of prospective studies aimed at survival and disease progression end-points (**evidence 2D; recommendation 2C**)
  Assessment of downstaging should follow modified RECIST criteria
- Living donor liver transplantation is an alternative option in patients with a waiting list exceeding 6-7 months, and offers a suitable setting to explore extended indications within research programs (**evidence 2A; recommendation 2B**)

Local ablation

- Local ablation with radiofrequency or percutaneous ethanol injection is considered the standard of care for patients with BCLC 0-A tumors not suitable for surgery (**evidence 2A; recommendation 1B**)
  Other ablative therapies, such as microwave or cryoablation, are still under investigation
- Radiofrequency ablation is recommended in most instances as the main ablative therapy in tumors less than 5 cm due to a significantly better control of the disease (**evidence 1iD; recommendation 1A**)
  Ethanol injection is recommended in cases where radiofrequency ablation is not technically feasible (around 10-15%)
- In tumors <2 cm, BCLC 0, both techniques achieve complete responses in more than 90% of cases with good long-term outcome. Whether they can be considered as competitive alternatives to resection is uncertain (**evidence 1iA; recommendation 1C**)

Chemoembolization and transcatheter therapies

- Chemoembolization is recommended for patients with BCLC stage B, multinodular asymptomatic tumors without vascular invasion or extra-hepatic spread (**evidence 1iiA; recommendation 1A**)
  The use of drug-eluting beads has shown similar response rates than gelfoam-lipiodol particles associated with less systemic adverse events (**evidence 1D; recommendation 2B**)
  Chemoembolization is discouraged in patients with decompensated liver disease, advanced liver dysfunction, macroscopic invasion or extrahepatic spread (**evidence 1iiA; recommendation 1B**)
  Bland embolization is not recommended
- Internal radiation with ^{131}I or ^{90}Y glass beads has shown promising anti-tumoral results with a safe profile, but cannot be recommended as standard therapy. Further research trials are needed to establish a competitive efficacy role in this population (**evidence 2A; recommendation 2B**)
- Selective intra-arterial chemotherapy or lipiodolization are not recommended for the management of HCC (**evidence 2A; recommendation 2B**)
- External three-dimensional conformal radiotherapy is under investigation, and there is no evidence to support this therapeutic approach in the management of HCC (**evidence 3A; recommendation 2C**)

Clinical Practice Summary

Systemic therapies

- Sorafenib is the standard systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh A class) and with advanced tumors (BCLC C) or those tumors progressing upon loco-regional therapies (**evidence 1iA; recommendation 1A**)
- There are no clinical or molecular biomarkers available to identify the best responders to sorafenib (**evidence 1A; recommendation 2A**)
- Systemic chemotherapy, tamoxifen, immunotherapy, anti-androgen, and herbal drugs are not recommended for the clinical management of HCC patients (**evidence 1-2A; recommendation 1A/B**)
- There is no available second-line treatment for patients with intolerance or failure to sorafenib. Best supportive care or the inclusion of patients in clinical trials is recommended in this setting (**recommendation 2B**)
- In specific circumstances, radiotherapy can be used to alleviate pain in patients with bone metastasis (**evidence 3A; recommendation 2C**)
- Patients at BCLC D stage should receive palliative support including management of pain, nutrition and psychological support. In general, they should not be considered for participating in clinical trials (**recommendation 2B**)

Table 1A. Levels of evidence according to study design and end-points National Cancer Institute: PDQ Levels of Evidence for Adult and Pediatric Cancer Treatment Studies. Bethesda **[2]**[¶].

Strength of evidence according to study design:
Level 1: Randomized controlled clinical trials or meta-analyses of randomized studies* (i) Double-blinded (ii) Non-blinded treatment delivery
Level 2: Non-randomized controlled clinical trials**
Level 3: Case series*** (i) Population-based, consecutive series (ii) Consecutive cases (not population-based) (iii) Non-consecutive cases
Strength of evidence according to end-points:
A. Total mortality (or overall survival from a defined time)
B. Cause-specific mortality (or cause-specific mortality from a defined time)
C. Carefully assessed quality of life
D. Indirect surrogates# (i) Event-free survival (ii) Disease-free survival (iii) Progression-free survival (iv) Tumor response rate

[¶]National Cancer Institute: PDQ® Levels of Evidence for Adult and Paediatric Cancer Treatment Studies. Bethesda, MD: National Cancer Institute. Date last modified 26/August/2010. Available at: http://cancer.gov/cancertopics/pdq/levels-evidence-adult-treatment/HealthProfessional. Accessed <March 1st, 2011>.
*The randomized, double-blinded controlled clinical trial (1i) is the gold standard of study design. Meta-analyses of randomized studies are placed in the same category of strength of evidence as are randomized studies.
**This category includes trials in which treatment allocation was made by birth date, chart number (so-called quasi randomized studies) or subset analyses of randomized studies (or randomized phase II studies).
***All other prospective (cohort studies) or retrospective studies (case–control studies, case series).
#These end-points may be subjected to investigator interpretation. More importantly, they may, but do not automatically, translate into direct patient benefit such as survival or quality of life. Nevertheless, it is rational in many circumstances to use a treatment that improves these surrogate end-points while awaiting a more definitive end-point to support its use.

Epidemiology, risk factors, and prevention

- The incidence of HCC is increasing in Europe and worldwide.
- Vaccination against hepatitis B is recommended to all newborns and high risk groups **(evidence: 2D; recommendation 1A)**
- Governmental health agencies should recommend policies for preventing HCV/HBV transmissions, encourage life styles preventing obesity and alcohol abuse **(evidence 3A; recommendation 1A)** and controlling metabolic conditions, such as diabetes **(evidence 3; recommendation 2B)**
- In patients with chronic hepatitis, antiviral therapies leading to maintained HBV suppression in chronic hepatitis B and sustained viral response in hepatitis C are recommended since they have been shown to prevent progression to cirrhosis, and hence HCC development **(evidence 1A; recommendation 1A)**. The application of antiviral therapies should follow the EASL guidelines for management of chronic hepatitis B and C infection
- Once cirrhosis is established, the benefits of anti-viral therapy in preventing HCC development are not robustly demonstrated **(evidence 1D; recommendation 2B)**

Epidemiology

The burden of cancer is increasing worldwide. Each year there are 10.9 million new cases of cancer and 6.7 million cancer-related deaths. The most commonly diagnosed cancers are lung, breast, and colorectal while the most common causes of cancer death are lung, stomach, and liver [3,4]. Liver cancer is the sixth most common cancer (749,000 new cases), the third cause of cancer-related death (692,000 cases), and accounts for 7% of all cancers [4]. HCC represents more than 90% of primary liver cancers and is a major global health problem.

The incidence of HCC increases progressively with advancing age in all populations, reaching a peak at 70 years [5]. In Chinese and in black African populations, the mean age of patients with the tumor is appreciably younger. This is in sharp contrast to Japan, where the incidence of HCC is highest in the cohort of men aged 70–79 years [6]. HCC has a strong male preponderance with a male to female ratio estimated to be 2.4 [4].

The pattern of HCC occurrence has a clear geographical distribution, with the highest incidence rates in East Asia, sub-Saharan Africa, and Melanesia, where around 85% of cases occur [3,4]. In developed regions, the incidence is low with the exception of Southern Europe where the incidence in men (10.5 age-standardized

Table 1B. Grading evidence and recommendations (adapted from GRADE system).

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	C
Grading recommendation	**Notes**	**Symbol**
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty: higher cost or resource consumption	2

Nation	M	F
Albania	5.8	2.9
Austria	9.3	2.9
Belgium	3.3	1.5
Bosnia-Erzegovina	4.3	1.5
Bulgaria	5.6	2.2
Croatia	7.7	2.4
Czech Republic	5.9	2.4
Denmark	4.0	1.3
Estonia	3.5	1.5
Finland	5.8	2.4
France	10.5	2.2
Germany	6.2	2.2
Great Britain	3.8	1.7
Greece	5.2	2.0
Netherland	2.0	0.8
Hungary	7.5	2.0
Ireland	3.4	1.5
Italy	13.4	4.4
Latvia	4.6	1.8
Lithuania	4.1	1.4
Luxembourg	9.8	3.8
Macedonia	5.3	2.3
Moldova	14.2	4.6
Montenegro	5.3	2.5
Norway	2.2	1.0
Poland	3.1	1.5
Portugal	3.5	1.2
Romania	8.1	3.0
Russia	4.4	1.9
Serbia	4.8	2.6
Slovenia	5.4	1.8
Spain	9.6	2.5
Sweden	3.2	1.4
Switzerland	7.8	2.3
Ukraine	3.2	1.6

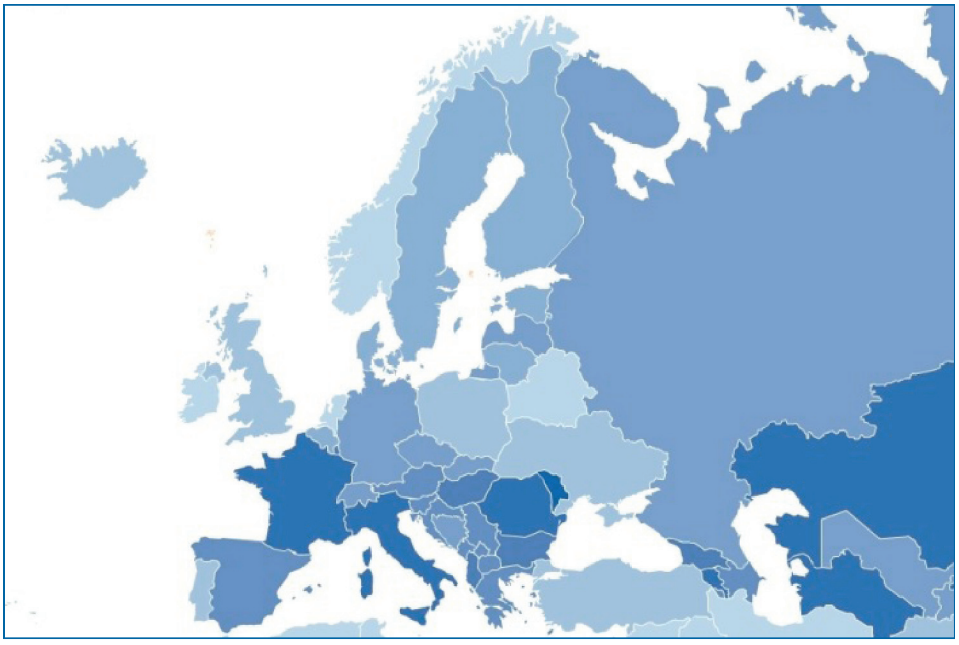

Fig. 1. Incidence rates of primary liver cancer according to geographical distribution in Europe. Age-adjusted incidence rates per 100,000 of liver cancer in Europe in 2008. The color intensity is proportional to the magnitude of incidence. M, males; F, females. (Data from: Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr.)

incidence rates per 100,000) is significantly higher than in other developed regions [7] (Fig. 1).

There is a growing incidence of HCC worldwide. Overall, the incidence and mortality rates were of 65,000 and 60,240 cases in Europe and 21,000 and 18,400 cases in the United States in 2008, respectively. It is estimated that by 2020 the number of cases will reach 78,000 and 27,000, respectively [4]. People infected with HCV in Europe during the period 1940–60 and in the United States of America (USA) one decade later led to the current increase of HCC incidence. In Europe, the incidence and mortality rates reported are heterogeneous. HCC mortality during the last decades increased in males in most of the countries (i.e. Austria, Denmark, Germany, Greece, Ireland, Portugal, Norway, Spain, Switzerland, and United Kingdom), but decreased in others (Finland, France, Italy, Netherlands, and Sweden) [7]. In the United States, the rate of HCC deaths appears to have increased by about 40% over the period 1990–2004, whereas the overall rate of cancer deaths has declined by about 18% during this same period [8]. Besides the emergence of liver disease due to hepatitis C, this growth in incidence may be also due to an increase in HBV-related HCC, particularly among immigrants from endemic countries. Conversely, in Japan, a country where the impact of HCV-related HCC was first noticed after World War II, there has been an apparent decline in the incidence of this neoplasm for the first time since 1990 [6]. Finally, the impact of universal infant vaccination against HBV has decreased the rate of HBV-related HCC in endemic countries. So far, this has been observed among children in Taiwan, but it is expected to become more apparent as these vaccinated children grow into adults [9].

Etiology and risk factors

Approximately 90% of HCCs are associated with a known underlying risk factor (Table 2). The most frequent factors include chronic viral hepatitis (types B and C), alcohol intake and aflatoxin exposure. In Africa and East Asia, the largest attributable fraction is due to hepatitis B (60%) whereas in the developed Western world, only 20% of cases can be attributed to HBV infection, while chronic hepatitis C appears to be the major risk factor [3]. Worldwide, approximately 54% of cases can be attributed to HBV infection (which affects 400 million people globally) while 31% can be attributed to HCV infection (which affects 170 million people), leaving approximately 15% associated with other causes.

Cirrhosis is an important risk factor for HCC, and may be caused by chronic viral hepatitis, alcohol, inherited metabolic diseases such as hemochromatosis or alpha-1-antitrypsin deficiency, and non-alcoholic fatty liver disease. All etiologic forms of cirrhosis may be complicated by tumor formation, but the risk is higher in patients with hepatitis infection. Overall, one-third of cirrhotic patients will develop HCC during their lifetime [10]. Long-term follow-up studies have demonstrated that approximately 1–8% per year of patients with cirrhosis develop HCC (e.g. 2% in HBV-infected cirrhotic patients and 3–8% in HCV-infected cirrhotic patients) [11]. In general, features of liver disease severity (low platelet count of less than 100×10^3, presence of esophageal varices), in addition to older age and male gender, correlate with HCC development among patients with cirrhosis [12]. Recent studies have shown that liver cancer incidence increases in parallel to portal pressure as directly measured [13] or in parallel to the degree of liver stiffness as measured by transient elastography [14,15].

Several studies have identified HBV-related factors as key predictors of HCC development in patients with chronic hepatitis B infection [16]. Hepatitis B virus e antigen (HBeAg) seropositivity [17], high viral load [18], and genotype C [19] are independent predictors of HCC development. In addition, hepatitis B viral load correlates with the risk of progression to cirrhosis [20]. Similarly, in a recent meta-analysis, HCV genotype 1b is claimed to increase the risk of HCC development [21].

Dietary exposure to aflatoxin B1, derived from the fungi *Aspergillus flavus* and *A. parasiticus*, is an important co-factor for HCC development in some parts of Africa and Asia. These molds are ubiquitous in nature and contaminate a number of staple foodstuffs in tropical and subtropical regions. Epidemiologic studies have shown a strong correlation between the dietary intake of aflatoxin B1, TP53 mutations and incidence of HCC, specifically in HBV-infected individuals [22]. Regarding other risk factors, patients with hemochromatosis develop HCC in up to 45% of cases [23], most often with a background of cirrhosis, and HCC is well documented as a complication of cirrhosis associated with alpha-1-antitrypsin deficiency [24]. HCC develops occasionally in patients with Wilson's disease, but only in the presence of cirrhosis [25].

Obesity, diabetes and fatty liver disease have come to be recognized as a cause of HCC [26,27], although the mechanisms by which these overlapping conditions contribute to cancer development remain elusive. Cirrhosis due to non-alcoholic steatohepatitis may give rise to HCC but it appears that these factors may also be additive to chronic viral hepatitis [27]. Epidemiologic evidence of a link between cigarette smoking and the occurrence of HCC was traditionally conflicting [26], but recent evidence support that smoking is a clear co-factor [28]. Heavy smokers have a higher risk than non-smokers. In the general population, the incidence of HCC is increased among patients with HIV infection compared to controls, and HIV appears to be an additive co-factor, exacerbating the risk of HCC in patients with chronic viral hepatitis [29].

Table 2. Geographical distribution of main risk factors for HCC worldwide.*

Geographic area	AAIR	Risk factors		Alcohol	Others
	M/F	HCV (%)	HBV (%)	(%)	(%)
Europe	6.7/2.3	60-70	10-15	20	10
Southern	10.5/3.3				
Northern	4.1/1.8				
North America	6.8/2.3	50-60	20	20	10 (NASH)
Asia and Africa		20	70	10	10 (Aflatoxin)
Asia	21.6/8.2				
China	23/9.6				
Japan	20.5/7.8	70	10-20	10	10
Africa	1.6/5.3				
WORLD	16/6	31	54	15	

*Updated from Llovet *et al.* [99], according to IARC data [4]. AAIR, age-adjusted incidence rate.

Identification of mutations in germline DNA that define patients at high risk of developing cancer has become a challenge for surveillance programs and chemopreventive strategies. This is the case of mutations in *BRCA1* or *BRCA2* and increased risk of breast or ovarian cancer [30] or in genes involved in DNA mismatch repair and hereditary colon cancer [31]. In HCC, a recent case–control study found a significant association between an epidermal growth factor (EGF) gene polymorphism and the risk of HCC [32], while another study suggests genetic predisposition of SNPs at loci involved in immune response [33]. These findings require validation by independent investigators.

Prevention

Primary prevention of HCC can be achieved with universal vaccination against HBV infection [9]. Vaccination against hepatitis B is recommended to all newborns and high risk groups, following the recommendations of the World Health Organization [34]. Since perinatal or early postnatal transmission is an important cause of chronic HBV infections globally, the first dose of hepatitis B vaccine should be given as soon as possible after birth, even in low-endemicity countries (those with prevalence of HBsAg carriers <2%). Vaccination is also recommended in age-specific cohorts (young adolescents) and people with risk factors for acquiring HBV infection (i.e. health workers, travellers to areas where HBV-infection is prevalent, injecting drug users, and people with multiple sex partners).

Antiviral treatment for patients with chronic hepatitis B and C infection should follow the recommendations from existing EASL guidelines [35,36]. Interferon, lamivudine, adefovir, entecavir, telbivudine and tenofovir are now available for HBV treatment, but long-term follow-up data assessing their effect in secondary prevention are only available with interferon and lamivudine. Observational studies assessing the effect of interferon showed a potential effect in reduction of HCC incidence [37], but this was not confirmed by Asian case-controlled studies [38]. Similarly, a randomized controlled trial (RCT) assessing the effect of lamivudine showed a significant reduction in HCC incidence. Nonetheless, there are some concerns regarding the effects obtained in this study as prevention of HCC occurrence was not the primary end-point of the study, and because the marginal effect obtained disappeared once adjusted for co-variables [39]. As a result, it appears prudent to conclude that surveillance for HCC should be maintained in those patients who already qualified before starting the treatment.

In hepatitis C viral infection, the results of a meta-analysis of retrospective studies suggest that the risk of HCC is reduced among patients with HCV who achieve a sustained virological response (SVR) with antiviral therapy with interferon–ribavirin [40]. Once cirrhosis is established, there is no conclusive evidence that anti-viral therapy can prevent or delay the occurrence of HCC [41,42]. Maintenance therapy with PEG–interferon in cirrhotic patients has not significantly decreased the incidence of HCC according to the HALT-C [43,44] and EPIC studies [45]. Additional studies are required to test the potential preventive effect of combination with new protease inhibitors (boceprevir, telaprevir) in cirrhotic patients.

Surveillance

- Implementation of surveillance programs to identify at-risk candidate populations and identification of biomarkers for early HCC detection are a major public health goal to decrease HCC-related deaths **(evidence 1D; recommendation 1B)** Government health policy and research agencies should address these needs
- Patients at high risk for developing HCC should be entered into surveillance programs. Groups at high risk are depicted in Table 3 **(evidence 1B/3A; recommendation 1A/B)**
- Surveillance should be performed by experienced personnel in all at-risk populations using abdominal ultrasound every 6 months **(evidence 2D; recommendation 1B)**

  Exceptions: A shorter follow-up interval (every 3-4 months) is recommended in the following cases: 1. Where a nodule of less than 1 cm has been detected (see recall policy), 2. In the follow-up strategy after resection or loco-regional therapies (**evidence 3D; recommendation 2B)**
- Accurate tumor biomarkers for early detection need to be developed. Data available with tested biomarkers (i.e. AFP, AFP-L3 and DCP) show that these tests are suboptimal for routine clinical practice **(evidence 2D; recommendation 2B)**
- Patients on the waiting list for liver transplantation should be screened for HCC in order to detect and manage tumor progression and to help define priority policies for transplantation **(evidence 3D; recommendation 1B)**

Surveillance consists of the periodic application of a diagnostic test to subjects at risk for developing a given disease. Its usefulness and applicability are influenced by several factors, such as the incidence of the surveyed disease in the target population, the availability of efficient diagnostic test(s) at bearable costs and their acceptability by the target population, and the availability of treatments and their effectiveness [46]. The aim of surveillance is to obtain a reduction in disease-related mortality. This is usually achieved through an early diagnosis (stage migration) that, in turn, enhances the applicability and cost–effectiveness of curative therapies. Stage migration, however, cannot serve as a surrogate for the main end-point, which is patient survival.

HCC is a condition which lends itself to surveillance as at-risk individuals can readily be identified because of the presence of underlying viral hepatitis or other liver diseases. In fact, in the Western world, HCC arises in a cirrhotic background in up to 90% of cases [47], and cirrhosis itself is a progressive disease that affects patient survival. The presence of cirrhosis then influences the chances for anti-tumoral treatment and affects their results, thus rendering early diagnosis of HCC even more crucial. Moreover, many available treatments can have an adverse impact on cirrho-

sis, and the exact cause of death, which could be either the underlying disease or HCC, cannot be clearly defined in some instances. For this reason, a reduction in overall mortality represents a more appropriate end-point to assess the efficacy of surveillance.

Target populations

Cirrhotic patients

Decision analysis and cost–effectiveness models suggest that an intervention is considered cost-effective if it provides gains of life expectancy of at least 3 months with a cost lower than approximately US$ 50,000 per year of life saved [48]. Cost–effectiveness studies indicate that an incidence of 1.5%/year or greater would warrant surveillance of HCC in cirrhotic patients [49], irrespective of its etiology [10,17,50,51]. It may also be possible to identify cirrhotic patients at low risk of developing HCC [52–54] and hence exclude them from surveillance, thereby saving costs although this approach is not proven yet. Conversely, the presence of advanced cirrhosis (Child–Pugh class C) prevents potentially curative therapies from being employed, and thus surveillance is not cost-effective in these patients [1,55]. As an exception, patients on the waiting list for liver transplantation, regardless of the liver functional status, should be screened for HCC in order to detect tumors exceeding conventional criteria and to help define priority policies for transplantation. Finally, although it seems intuitive that surveillance might not be cost-effective above a certain age cut-off, the lack of data prevents the adoption of any specific recommendation.

Non-cirrhotic subjects

Patients with chronic HBV infection are at risk of HCC development even in the absence of cirrhosis. In these cases, the recommended cut-off of annual incidence above which surveillance should be recommended cannot be applied. The cut-off of annual incidence in these patients is ill-defined, albeit expert opinion indicates that it would be warranted if HCC incidence is at least 0.2%/year [56,57]. Thus, cost–benefit modeling is needed in this scenario. The incidence of HCC in adult Asian or African active HBV carriers or with a family history of HCC exceeds this value, whereas HCC incidence ranges from 0.1% to 0.4%/year in Western patients with chronic HBV infection [58,59]. Viral load also appears to increase the risk of developing HCC. In Asian patients, serum HBV-DNA above 10,000 copies/ml was associated with an annual risk above 0.2%/year [18].

Unfortunately, there is scanty and sometimes contradictory information on the incidence of HCC in patients with chronic hepatitis C without cirrhosis. Data from Japan would suggest that patients with mild fibrosis have a yearly HCC incidence of 0.5% [51]. A recent study from the United States has pointed out that HCC does occur in patients with chronic hepatitis C and bridging fibrosis in the absence of cirrhosis (Metavir F3) [12]. The fact that the transition from advanced fibrosis and cirrhosis cannot be accurately defined led the EASL guidelines to recommend surveillance also for patients with bridging fibrosis [1]. This panel also endorses such a policy. In this respect, transient elastography appears to be a promising tool able to stratify patients at different HCC risks [14,60].

Information about the incidence of HCC in patients with non-viral chronic liver disease without cirrhosis, such as non-alcoholic and alcoholic steatohepatitis, autoimmune liver disease, genetic hemochromatosis, α_1-antitripsin deficiency, and Wilson disease is limited [23–25,61]. However, available evidence suggests that HCC usually arises in these contexts once cirrhosis is established [1]. Certainly, patients with metabolic syndrome or non-alcoholic steatohepatitis leading to cirrhosis should undergo surveillance [62], whereas the risk of HCC development is not established in non-cirrhotic individuals.

Treated viral chronic hepatitis

Recent advances in therapy have led to relatively high rates of viral clearance or suppression among those patients being treated for chronic hepatitis B or C. Successful treatment, leading to sustained virological response in chronic hepatitis C, and HBeAg seroconversion or sustained HBV-DNA suppression in chronic hepatitis B, decreases, but does not eliminate the risk of HCC [63–66]. Surveillance should be offered to treated patients with chronic hepatitis B who remain at risk of HCC development due to baseline factors, or to those with HCV-induced advanced fibrosis or cirrhosis, even after achieving sustained virological response.

Table 3. Recommendations for HCC surveillance: categories of adult patients in whom surveillance is recommended.

1.	Cirrhotic patients, Child-Pugh stage A and B*
2.	Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation**
3.	Non-cirrhotic HBV carriers with active hepatitis or family history of HCC***
4.	Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3****

*Evidence 3A; strength B1;

**evidence 3D; strength B1;

***evidence 1B; strength A1 for Asian patients; evidence 3D; strength C1 for Western patients;

****evidence 3D; strength B1 for Asian patients; evidence 3D; strength B2 for Western patients.

Surveillance tests

Tests that can be used in HCC surveillance include serological and imaging examinations. The imaging test most widely used for surveillance is ultrasonography (US). US has an acceptable diagnostic accuracy when used as a surveillance test (sensitivity ranging from 58% to 89%; specificity greater than 90%) [67,68]. A recent meta-analysis including 19 studies has showed that US surveillance detected the majority of HCC tumors before they presented clinically, with a pooled sensitivity of 94%. However, US was less effective for detecting early-stage HCC, with a sensitivity of only 63% [69]. In contrast, in a recent Japanese cohort including 1432 patients, careful US surveillance performed by highly skilled operators resulted in an average size of the detected tumors of 1.6 ± 0.6 cm, with less than 2% of the cases exceeding 3 cm [70].

The widespread popularity of US also relies on the absence of risks, non-invasiveness, good acceptance by patients and relatively moderate cost. Nonetheless, US detection of HCC on a cirrhotic background is a challenging issue. Liver cirrhosis is

characterized by fibrous septa and regenerative nodules. These features produce a coarse pattern on US, which may impair identification of small tumors. Because of these limitations, the performance of US in early detection of HCC is highly dependent on the expertise of the operator and the quality of the equipment. Thus, special training for ultrasonographers is recommended. The recent introduction of US contrast agents has not proven to increase the ability of US to detect small HCC tumors [71].

There are no data to support the use of multidetector CT or dynamic MR imaging for surveillance. Practical experience suggests that the rate of false-positive results that will trigger further investigation is very high and non-cost-effective. These circumstances are overcome in the setting of the waiting list for liver transplantation where CT scan or MRI are alternatives to US. These techniques should be also considered when obesity, intestinal gas, and chest wall deformity prevent an adequate US assessment. Even in these circumstances, radiation risk due to repeated exposure to CT scan and high cost of MR make debatable their use in long-term surveillance.

Serological tests that have been investigated or are under investigation for early diagnosis of HCC include alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP) – also known as prothrombin induced by Vitamin K Absence II (PIVKA II) – the ratio of glycosylated AFP (L3 fraction) to total AFP, alpha-fucosidase, and glypican 3 [12,72]. AFP is the most widely tested biomarker in HCC. It is known that persistently elevated AFP levels are a risk factor for HCC development and can be used to help define at-risk populations [73]. Of note is that AFP has been mostly tested in the diagnostic mode rather than for surveillance. This is relevant, since its performance as a diagnostic test cannot be extrapolated to the surveillance setting. As a serological test for surveillance, AFP has a suboptimal performance. One randomized study [74] and one population-based observational study [75] reached opposite results. The latter study provides rationale for testing AFP in special populations or health care environments when US is not readily available [75]. However, when combined with US, AFP levels are only able to provide additional detection in 6–8% of cases not previously identified by US. Reasons for the suboptimal performance of AFP as a serological test in the surveillance mode are twofold. Firstly, fluctuating levels of AFP in patients with cirrhosis might reflect flares of HBV or HCV infection, exacerbation of underlying liver disease or HCC development [76]. Secondly, only a small proportion of tumors at an early stage (10–20%) present with abnormal AFP serum levels, a fact that has been recently correlated with a molecular subclass of aggressive HCCs (S2 class, EpCAM positive) [77–79]. When used as a diagnostic test, AFP levels at a value of 20 ng/ml show good sensitivity but low specificity, whereas at higher cut-offs of 200 ng/ml the sensitivity drops to 22% with high specificity [80].

All other serum markers have usually been evaluated, alone or in combination, in a diagnostic rather than surveillance setting. Moreover, their diagnostic performance has often been assessed at an HCC prevalence remarkably higher than that expected in the context of surveillance [81]. In the latter setting, DCP, measured with a first generation assay, did not offer substantial advantages with respect to AFP [82]. In addition, DCP levels have been associated to portal vein invasion and advanced tumoral stage, a fact that prevents the usage of this marker for early detection [82]. A similar situation occurs with AFP-L3 fraction levels [83]. At present, none of these tests can be recommended to survey patients at risk of developing HCC. Several markers, such as fucosylated proteins, are currently under investigation [84].

In conclusion, US can be seen as the most appropriate test to perform surveillance. The combination with AFP is not recommended, as the 6–8% gain in the detection rate does not counterbalance the increase in false positive results, ultimately leading to an about 80% increase in the cost of each small HCC diagnosed [69,85].

Surveillance efficacy

Two randomized controlled trials have been published on HCC surveillance. In one population-based study cluster randomization (randomizing entire villages) was performed comparing surveillance (US and AFP measurements every 6 months) versus no surveillance in a population of Chinese patients with chronic hepatitis B infection, regardless of the presence of cirrhosis [86]. Despite suboptimal adherence to the surveillance program (55%), HCC-related mortality was reduced by 37% in the surveillance arm as a result of increased applicability of resection in detected cases. The other AFP-based surveillance study carried out in Qidong (China) in high-risk individuals (males, HBsAg+) did not identify differences in overall survival [74].

Other types of evidence include population and non-population-based cohorts and cost–effectiveness analysis, which mostly reinforce the benefits of regular US schemes [55,69,87–93]. However, these studies are heterogeneous as far as stage and etiology of liver disease, and surveillance protocols. Moreover, almost all suffer from methodological biases such as lead-time bias (apparent improvement of survival due to an anticipated diagnosis) and length time bias (over-representation of slower-growing tumors). While the latter is unavoidable in this type of study, lead-time bias can be minimized using correction formulas. When this was done, the advantage of surveillance remained [94].

Surveillance interval

The ideal interval of surveillance for HCC should be dictated by two main features: rate of tumor growth up to the limit of its detectability, and tumor incidence in the target population. Based on available knowledge on mean HCC volume doubling time [87–89]; a 6-month interval represents a reasonable choice. Considering, though, that inter-patient variability is so huge, a shorter 3-month interval has been proposed by Japanese guidelines [90,95]. However, the unique randomized study comparing 3 versus 6-month based programs failed to detect any differences [91]. On the other hand, cohort comparisons of 6 versus 12-month schemes provide similar results [52,92], while retrospective studies identified better performance of the 6-month interval in terms of stage migration (small HCC amenable for curative treatments) [96] and survival [97]. Meta-analysis of prospective studies has shown that the pooled sensitivity of US-based surveillance decreases from 70% with the 6-month program to 50% with the annual program [69].

Finally, cost–effectiveness studies have shown that semi-annual US-based surveillance improves quality-adjusted life expectancy at a reasonable cost [98]. In light of available knowledge, a 6-month scheduled surveillance appears the preferable choice. Further trials in this setting would be difficult to implement.

Recall policy

- In cirrhotic patients, nodules less than 1 cm in diameter detected by ultrasound should be followed every 4 months the first year and with regular checking every 6 months thereafter
(evidence 3D; recommendation 2B)

- In cirrhotic patients, diagnosis of HCC for nodules of 1-2 cm in diameter should be based on non-invasive criteria or biopsy-proven pathological confirmation. In the latter case, it is recommended that biopsies are assessed by an expert hepatopathologist. A second biopsy is recommended in case of inconclusive findings, or growth or change in enhancement pattern identified during follow-up
(evidence 2D; recommendation 1B)

- In cirrhotic patients, nodules more than 2 cm in diameter can be diagnosed for HCC based on typical features on one imaging technique. In case of uncertainty or atypical radiological findings, diagnosis should be confirmed by biopsy
(evidence 2D; recommendation 1A)

Recall policy is crucial for the success of surveillance procedures. It consists of a defined algorithm to be followed when surveillance tests show an abnormal result. This definition must take into account the ideal target of surveillance, i.e. the identification of HCC at a very early stage (2 cm or less), when radical treatments can be applied with the highest probability of long-term cure [99]. In case of HCC, abnormal US results are either a newly detected focal lesion or a known hepatic lesion that enlarges and/or changes its echo pattern [100].

Pathology studies show that the majority of nodules smaller than 1 cm, that can be detected in a cirrhotic liver, are not HCCs [101]. Thus, a tight follow-up is recommended in these cases (Fig. 2). An accepted rule is to consider any nodule larger than about 1 cm as an abnormal screening result warranting further investigation [56]. These new nodules should trigger the recall strategy for diagnosis with non-invasive or invasive (biopsy) criteria, as described in the section of diagnosis. If a diagnosis cannot be reached with non-invasive criteria due to atypical radiological appearance, then biopsy is recommended. If even biopsy provides inconclusive results, then a tight follow-up every 4 months is recommended. A second biopsy can be considered in case of growth or change in the enhancement pattern. Upon detection of a suspicious nodule, the recommended policy is to evaluate the patient in a referral center with appropriate human and technical resources [56].

Diagnosis

Nowadays, early HCC diagnosis is feasible in 30–60% of cases in developed countries and this enables the application of curative treatments. In fact, while tumors less than 2 cm in diameter represented <5% of the cases in the early nineties in Europe, currently they represent up to 30% of cases in Japan. This trend is expected to continue growing in parallel to the wider implementation of surveillance policies in developed countries [102]. However, detection of these minute nodules of ~2 cm poses a diagnostic challenge as they are difficult to characterize by radiological or pathological examination [103–105].

- Diagnosis of HCC is based on non-invasive criteria or pathology
(evidence 2D; recommendation 1A)

- Pathological diagnosis of HCC is based on the recommendations of the International Consensus Panel. Immunostaining for GPC3, HSP70, and glutamine synthetase and/or gene expression profiles (*GPC3*, *LYVE1* and survivin) are recommended to differentiate high grade dysplastic nodules from early HCC
(evidence 2D; recommendation 2B)
Additional staining can be considered to detect progenitor cell features (K19 and EpCAM) or assess neovascularisation (CD34)

- Non-invasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI. Diagnosis should be based on the identification of the typical hallmark of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases). While one imaging technique is required for nodules beyond 1 cm in diameter **(evidence 2D; recommendation 2B),** a more conservative approach with 2 techniques is recommended in suboptimal settings.
The role of contrast-enhanced ultrasound (CEUS) and angiography is controversial. PET-scan is not accurate for early diagnosis

Proper definition of nodules as pre-neoplastic lesions or early HCC has critical implications. Dysplastic lesions should be followed by regular imaging studies, since at least one-third of them develop a malignant phenotype [106,107]. Conversely, early tumors are treated with potentially curative procedures – albeit expensive – such as resection, transplantation and percutaneous ablation. Thus, there is an urgent need to identify better tools to characterize these lesions. Otherwise, the cost–effectiveness of the recall policies applied within surveillance programs will be significantly undermined.

Non-invasive diagnosis

Accurate diagnosis of small liver nodules is of paramount importance. Until 2000, diagnosis was based on biopsy. This approach had some limitations related to feasibility due to location and risk of complications, such as bleeding or needle-track seeding [108]. In addition, achieving accuracy in differentiating between high-grade dysplastic nodules and early HCCs was complex, since stromal invasion, the most relevant criteria, is difficult to recognize even for an expert pathologist [105]. In 2001, a panel of experts on HCC convened in Barcelona by EASL reported for the first time non-invasive criteria for HCC based on a combination of imaging and laboratory findings [1]. In principle, a unique dynamic radiological behavior (contrast up-take in the arterial phase by CT, MRI, angiography or US) represented the backbone of radiological diagnosis of early HCC. In cirrhotic patients with nodules >2 cm, coinci-

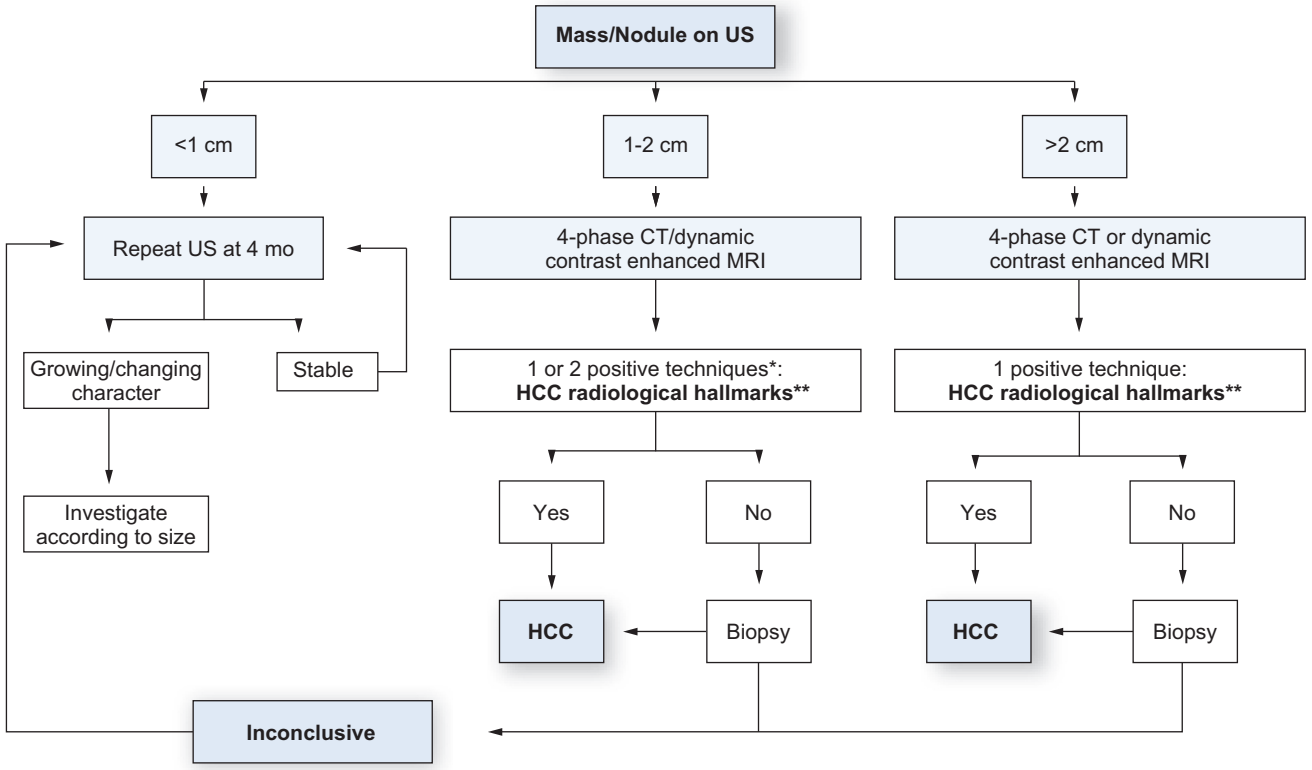

Fig. 2. Diagnostic algorithm and recall policy. *One imaging technique only recommended in centers of excellence with high-end radiological equipment. **HCC radiological hallmark: arterial hypervascularity and venous/late phase washout.

dental findings by two imaging techniques were considered diagnostic, or alternatively, one imaging technique along with AFP levels above 400 ng/ml. In all other circumstances biopsy was mandatory. In 2005, the EASL panel of experts and the American Association for the Study of Liver Diseases (AASLD) guidelines adopted a new *HCC radiological hallmark*, i.e. contrast uptake in the arterial phase and washout in the venous/late phase [109]. Non-invasive diagnosis was established by one imaging technique in nodules above 2 cm showing the HCC radiological hallmark and two coincidental techniques with nodules of 1–2 cm in diameter (CT, MRI and US-contrast). AFP levels were dropped from the diagnostic scheme [109]. Recent updated AASLD guidelines have proposed that one imaging technique (CT or MRI) showing the *HCC radiological hallmark* suffices for diagnosing tumors of 1–2 cm in diameter [56].

In order to update the EASL guidelines for non-invasive diagnostic criteria of HCC, two questions are posed. First, what data provides reliable non-invasive diagnostic accuracy for nodules of 1–2 cm in diameter taking into account that the recommendations apply to a wide range of expert physicians and radiologists. And second, what imaging techniques can be used. Regarding the first issue, two prospective studies have shown that using 2 imaging techniques is an approach with high PPV and specificity [104,109]. In one study including 89 consecutive cases of nodules between 0.5 and 2 cm detected within surveillance programs in cirrhotic patients showed that non-invasive criteria are accurate for the diagnosis of HCC, with a specificity of 100% [104]. Unfortunately, such an absolute specificity had the downside of a low sensitivity of 30%, meaning that two-thirds of nodules required pathological confirmation. The other study suggested that the use of a sequential algorithm would maintain an absolute specificity but increase the sensitivity, with significant savings in terms of liver biopsy procedures for nodules of 1–2 cm [110]. A retrospective study reporting diagnostic accuracies of MRI in large series of transplanted patients showed an overall false positive rate exceeding 10% when using one imaging technique [111]. Finally, a recent prospective study, testing the accuracy of imaging techniques in nodules between 1 and 2 cm detected by ultrasound, showed false positive diagnosis – mostly due to high grade dysplastic nodules – above 10% with either 1 or 2 imaging techniques, with a specificity of 81% and 85%, respectively [112]. Hence, the non-invasive diagnosis of 1–2 cm lesions remains a challenging issue, with no unequivocal data in prospective validation studies. While the panel considers incorporating the 1 technique rule in order to have a consistent approach in the field, a more cautious application of this rule is recommended in suboptimal settings, where the technology at disposal or the local skills are not at the high-end level. In these circumstances, we recommended to use two coincidental techniques, since the negative consequences of high rates of false-positive diagnosis offset the benefit. Additional prospective studies to confirm the accuracy of this approach are recommended in order to support a more strong recommendation at the 1A level.

Regarding which imaging techniques should be used, it has to be pointed out the fact that the *HCC radiological hallmark* is based on the tumor vascular dynamic performance. This limits the usage of US-contrast – since US microbubbles are confined to the intravascular space – as opposed to iodinated contrast-CT or gadolinium-based MR imaging, in which standard contrast agents are rapidly cleared from the blood pool into the extracellular space. A recent study showed that lesions other than HCC, i.e. cholangiocarcinoma,

displayed homogeneous contrast uptake at US-contrast followed by washout, i.e. the vascular pattern assumed to represent the *hallmark of* HCC [113]. Thus, latest generation CT and/or MRI following reported protocols are recommended for non-invasive diagnosis of HCC [114]. On the other hand, recent advances in the use of perfusion CT or MRI with liver-specific contrast agents have not so far provided solid data to support their use as alternate criteria.

It is important to point out that the *HCC radiological hallmark* only occurs in a small proportion of patients with tiny tumors (1–2 cm) [103], and thus biopsy or tissue biomarkers will be required in most instances. Delaying diagnosis beyond 2 cm leads to increased levels of treatment failure or recurrence, since it is known that satellites and microscopic vascular invasion rise exponentially beyond this size cut-off [101]. Therefore, it is crucial to provide reliable tools for a final diagnosis before the 2 cm cut-off.

Pathological diagnosis

Pathological diagnosis of HCC is based on the definitions of the International Consensus Group for Hepatocellular Neoplasia [115] and is recommended for all nodules occurring in non-cirrhotic livers, and for those cases with inconclusive or atypical imaging appearance in cirrhotic livers. Sensitivity of liver biopsy depends upon location, size and expertise, and might range between 70% and 90% for all tumor sizes. Pathological diagnosis is particularly complex for nodules between 1 and 2 cm [105]. Morphological criteria alone still pose problems for the differential diagnosis of high-grade dysplastic nodules versus early HCC, especially because the *pathological hallmark of HCC*, stromal invasion, can be absent or difficult to identify in biopsy specimens [105]. In a prospective study, first biopsy was reported positive in ~60% of cases for tumors less than 2 cm [104]. Thus, a positive tumor biopsy is clinically useful to rule in a diagnosis of HCC, but a negative biopsy does not rule out malignancy. The risk of tumor seeding after liver biopsy is 2.7% with a median time interval between biopsy and seeding of 17 months [116].

Tissue markers might provide a more across-the-board standardized diagnosis of these tumors. Distinct technologies such as genome-wide DNA microarray, qRT-PCR, proteomic and inmunostaining studies have been used in an attempt to identify markers of early diagnosis of HCC. Few studies, however, include a thorough analysis of several markers in a training-validation scheme and with a sufficient number of samples [78]. A study conducted in 128 human samples described a 13-gene signature able to identify HCC lesions with high diagnostic accuracy [117]. Similarly, a three-gene signature (the genes that encode GPC3, LYVE1, and survivin) has been proposed as an accurate molecular tool (>80% accuracy) to discriminate between dysplastic nodules and small HCCs (<2 cm) [118]. The performance of this signature was externally validated in a different set of samples [118,119].

The diagnostic performance of some markers of early HCC identified by genomic studies has been prospectively assessed by immunohistochemistry, a low-cost technique. By examining the tissue, the pathologist can select a representative tumor sample without necrosis or inflammation and define the cell type expressing protein markers and the specific pattern. A promising marker is GPC3, which shows a sensitivity of 68–72% with a specificity superior to 92% [120,121]. Similarly, combinations of different protein markers – HSP70, GPC3, and GS – in 105 hepatocellular nodules performed acceptably (sensitivity and specificity of 72% and 100%, respectively) [120], and were afterwards validated in two larger series [122,123]. The International Consensus Group of Hepatocellular Neoplasia has adopted the recommendation to define a pathological diagnosis of HCC if at least two of these markers are positive [115]. Additional staining can be considered to assess neovascularisation (CD34) or potential progenitor cell origin (Keratin 19, EpCAM) [101,105,124]. In particular, keratin 19 (K19), a progenitor cell/biliary marker, at a cut-off of 5% of positive tumor cells with immunohistochemistry, has been shown to correlate with poorest outcome [105,124,125]. Moreover, K19 recognizes biliary features in mixed forms of HCC/cholangiocarcinoma, which are not always detected on hematoxylin–eosin stain.

Assessment of disease extension

Assessment of tumor extension is critical for defining staging and treatment strategy. Several studies with pathological correlation have shown that dynamic contrast-enhanced MRI and 4-phase multidetector CT are the most effective imaging techniques for detecting tumors smaller than 2 cm. However, underestimation of 25–30% is expected even with the best state-of-the-art technology [126,127]. Pre-specified protocols should define the amount and rate of contrast given, the precise individualized timing of the image acquisition and image reconstruction with minimum slice thickness. Lipiodol contrast staining should not be used. Contrast-enhanced ultrasound is unable to compete with CT and MRI in terms of accuracy for detection of lesions. Bone scintigraphy can be used for evaluating bone metastases. PET-based imaging is not accurate to stage early tumors. Pre-operative staging prior to liver transplantation should include abdominal dynamic CT or MRI, chest CT and bone scintigraphy.

Staging systems

- Staging systems in HCC should define outcome prediction and treatment assignment. They should facilitate exchange of information, prognosis prediction and trial design. Due to the nature of HCC, the main prognostic variables are tumor stage, liver function and performance status
- The BCLC staging system is recommended for prognostic prediction and treatment allocation **(evidence 2A; recommendation 1B)**. This staging system can be applied to most HCC patients, as long as specific considerations for special subpopulations (liver transplantation) are incorporated
- Refinement of BCLC class C by clinical or biomarker tools should further facilitate understanding of outcome data and trial stratification
- Other staging systems applied alone or in combination with BCLC are not recommended in clinical practice
- Molecular classification of HCC based on gene signatures or molecular abnormalities is not ready for clinical application **(evidence 2A; recommendation 1B)**

Cancer classification is intended to establish prognosis and enable the selection of the adequate treatment for the best candidates. In addition, it helps researchers to exchange information and design clinical trials with comparable criteria. In patients with HCC, unlike most solid tumors, the coexistence of two life-threatening conditions such as cancer and cirrhosis complicates prognostic assessments [99,128]. Thus, staging systems for this cancer should be designed with data coming from two sources. First, prognostic variables obtained from studies describing the natural history of cancer and cirrhosis. Second, treatment-dependent variables obtained from evidence-based studies providing the rationale for assigning a given therapy to patients in a given subclass.

Based on data reporting the natural history of the disease, the main clinical prognostic factors in HCC patients are related to tumor status (defined by number and size of nodules, presence of vascular invasion, extrahepatic spread), liver function (defined by Child–Pugh's class, bilirubin, albumin, portal hypertension, ascites) and general health status (defined by ECOG classification and presence of symptoms) [129–133]. Etiology has not been identified as an independent prognostic factor.

Tissue and serum biomarkers predicting prognosis have been less explored in HCC patients. Strict rules for incorporating prognostic or predictive markers into clinical practice have been published [134]. According to these rules, acceptable biomarkers should be obtained from randomized investigations, as is the case with KRAS status and response to cetuximab in colon cancer. Only in particularly compelling circumstances can prognostic or predictive markers tested in cohort studies be adopted in clinical practice. The panel recommends to incorporate biomarkers for the management of HCC when the following requirements are met: (1) demonstrate prognostic prediction in properly powered randomized studies or in training and validation sets from cohort studies; (2) demonstrate independent prognostic value in mutivariate analysis, including known clinico-pathological predictive variables; and (3) confirmation of results using the same technology in an external cohort reported by independent investigators. None of the biomarkers tested so far fulfil these criteria in HCC, but four just require external validation by independent groups: gene signatures or biomarkers from the tumor (EpCAM signature, G3-proliferation subclass, and miR-26a) [77,135,136] and adjacent tissue (poor-survival signature) [137]. Regarding serum markers, AFP levels, VEGF and Ang2 have been shown to have independent prognostic value in large cohorts of untreated advanced tumors [138]. The prognostic relevance of high AFP levels has been scarcely reported in controlled investigations [139], but has been shown to predict risk of drop-out in patients on the waiting list for liver transplantation (cut-off of 200 ng/ml, or by increases of >15 ng/ml) [140,141], response to local ablation [142], response to loco-regional therapies [143] and in the outcome of advanced tumors (cut-off of 200 ng/ml [138]; 400 ng/ml [130,144]). The heterogeneity of the above studies prevents the formulation of a clear recommendation, but it is advised to test levels >200 and/or >400 ng/ml as prognostic factors of poor outcome in research investigations.

Several staging systems have been proposed to provide a clinical classification of HCC. In oncology, the standard classification of cancer is based on the TNM staging. In HCC, the 7th TNM edition in accordance with the AJCC [145], which was obtained from the analysis of a series of patients undergoing resection, has several limitations [146]. First, pathological information is required to assess microvascular invasion, which is only available in patients treated by surgery (~20%). In addition, it does not capture information regarding liver functional status or health status. One-dimensional systems, such as the Okuda staging and the Child–Pugh classification, albeit popular, serve purposes distinct to class prediction in HCC patients. Among more comprehensive staging systems, five have been broadly tested, three European (the French classification [147], the Cancer of the Liver Italian Program (CLIP) classification [130], and the Barcelona-Clínic Liver Cancer (BCLC) staging system [148,149]) and two Asian (the Chinese University Prognostic Index (CUPI score) [150] and the Japan Integrated Staging (JIS), which was recently refined including biomarkers (AFP, DCP AFP-L-3) (bm-JIS) [151]). The CUPI and CLIP scores largely subclassify patients at advanced stages, with a small number of effectively treated patients. Overall, few of the most used systems or scores have been externally validated (BCLC, CUPI, CLIP, and bm-JIS), only two include the three types of prognostic variables (BCLC, CUPI) and only one assigns treatment allocation to specific prognostic subclasses (BCLC).

The current EASL–EORTC GP guidelines endorse the Barcelona-Clínic Liver Cancer (BCLC) classification for several reasons [148,149]. It includes prognostic variables related to tumor status, liver function and health performance status along with treatment-dependant variables obtained from cohort studies and randomized trials. It has been externally validated in different clinical settings [152–154]. This is an evolving system that links tumor stage with treatment strategy in a dynamic manner enabling the incorporation of novel advancements in the understanding of the prognosis or management of HCC. In this regard, the seminal classification reported in 1999 [148] was updated with the incorporation of stage 0 (very early HCC) and chemoembolization for intermediate HCC in 2003 [99], and further modified in 2008 to incorporate sorafenib as first-line treatment option in advanced tumors [149]. As discussed below, further refinements in class stratification (for instance to incorporate biomarkers) or treatment allocation resulting from positive high-end trials are expected in the following years. The BCLC classification was first endorsed by the EASL [1], and thereafter by the AASLD guidelines for the management of HCC [56].

BCLC classification: outcome prediction and treatment allocation

The Barcelona-Clínic Liver Cancer (BCLC) classification divides HCC patients in 5 stages (0, A, B, C and D) according to pre-established prognostic variables, and allocates therapies according to treatment-related status (Fig. 3). Thus, it provides information on both prognostic prediction and treatment allocation. Prognosis prediction is defined by variables related to tumor status (size, number, vascular invasion, N1, M1), liver function (Child–Pugh's) and health status (ECOG). Treatment allocation incorporates treatment dependant variables, which have been shown to influence therapeutic outcome, such as bilirubin, portal hypertension or presence of symptoms-ECOG.

Early stages

Very early HCC (BCLC stage 0) is defined as the presence of a single tumor <2 cm in diameter without vascular invasion/satellites in patients with good health status (ECOG-0) and well-preserved liver function (Child–Pugh A class). Nowadays, 5–10% of patients in the West are diagnosed at this stage while in Japan the figure is almost 30% due to the widespread implementation of surveillance programs [155]. From pathological studies, though, two

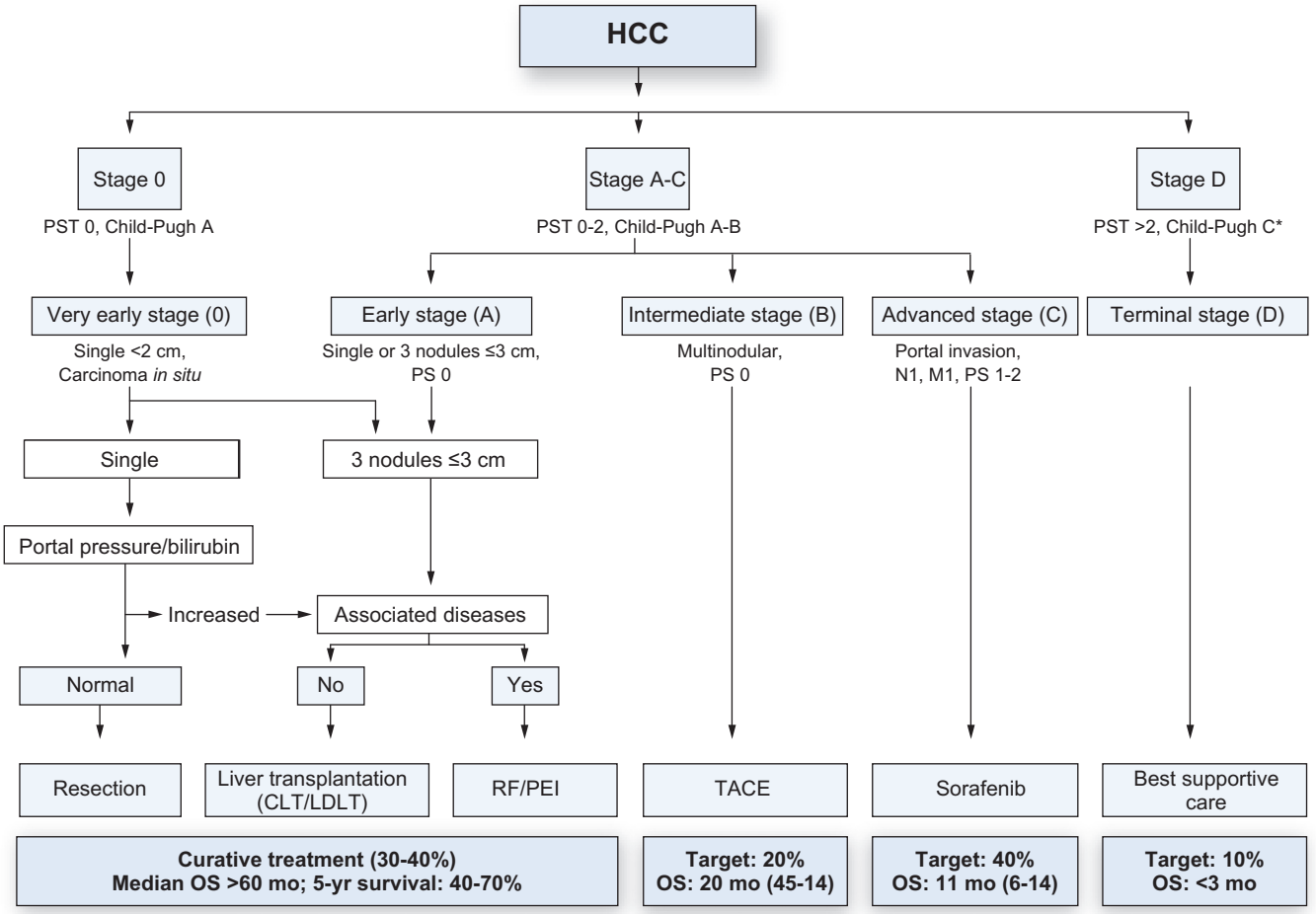

Fig. 3. Updated BCLC staging system and treatment strategy, 2011.

subclasses of tumors have been defined: vaguely nodular type – size around 12 mm without local invasiveness – and the distinctly nodular type – mean size 16 mm which might show local invasiveness. Vaguely nodular types are very well-differentiated HCCs that contain bile ducts and portal veins, have ill-defined nodular appearance and, by definition, do not have invaded structures. Distinctly nodular type show local metastases surrounding the nodule in 10% of cases, and microscopic portal invasion in up to 25% [101,105]. Therefore, some tumors smaller than 2 cm are prone to locally disseminate, but others behave as *carcinoma in situ* and those are defined as Stage 0. Recent data have shown a 5-year survival in 80–90% of patients with resection and liver transplantation and in 70% with local ablation [156–159]. Whether patients at very early stage can be offered local ablation as a first line treatment option is a topic of controversy. No RCT addressing this issue have been reported so far and comparison of cohort studies suffers from selection bias.

Early HCC (BCLC stage A) is defined in patients presenting single tumors >2 cm or 3 nodules <3 cm of diameter, ECOG-0 and Child–Pugh class A or B. Median survival of patients with early HCC reaches 50–70% at 5 years after resection, liver transplantation or local ablation in selected candidates [102,160]. The natural outcome of these cases is ill-defined due the scarcity of reported data, but it is estimated to be a median survival of around 36 months. An improvement in survival is universal when applying the so-called treatment-dependent variables in the selection of candidates.

Tumor status is defined by size of the main nodule and multicentricity (single 2–5 cm, 3 nodules $\leqslant$3 cm), each of these categories showing significantly different outcomes. As discussed below, single tumors beyond 5 cm are still considered for surgical resection as first option, because if modern MRI is applied in pre-operative staging, the fact that solitary large tumors remain single and with no macrovascular involvement – which might be common in HBV-related HCC – reflects a more benign biological behavior.

Variables related to liver function are relevant for candidates to resection. Absence of clinically relevant portal hypertension and normal bilirubin are key predictors of survival in patients with single tumors undergoing resection [161]. Similarly, Child–Pugh class A is the strongest prognostic variable in patients undergoing local ablation, along with tumor size and response to treatment [162]. Since liver transplantation may potentially cure both the tumor and the underlying liver disease, variables mostly related with HCC have been clearly established as prognostic factors (single tumors $\leqslant$5 cm or 3 nodules $\leqslant$3 cm), defining the so-called Milan criteria.

Intermediate-advanced HCC

Prognosis of HCC was assumed to be poor for *unresectable* cases, with a median survival of less than 1 year. Analysis of heterogeneous outcomes within 25 RCT (2 year survival 8–50%) [131,133,139,163]

leads to the identification of at least three subgroups of patients with *unresectable* HCC: the intermediate, advanced and end-stage classes, according to the BCLC classification.

Intermediate HCC (BCLC stage B): Untreated patients at an intermediate stage – BCLC B class (multinodular asymptomatic tumors without an invasive pattern) present a median survival of 16 months [139,164], or 49% at 2 year [133]. Chemoembolization extends the survival of these patients to a median of up to 19–20 months according to RCT and meta-analysis of pooled data [139]. Nonetheless, outcome prediction is heterogeneous for BCLC B subclass patients, and has been reported to range from around 36–45 months [165–167] for the best responders to chemoembolization in recent series, to 11 months for the worst scenario of untreated candidates (placebo arm of the SHARP trial-BCLC B patients) [168]. A recent meta-analysis of RCT assessing outcome of patients in the control arm suggests that ascites – which contraindicates TACE treatment – is the worst prognostic factor for this subclass [133].

Advanced HCC (BCLC stage C): Patients with cancer related-symptoms (symptomatic tumors, ECOG 1–2), macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases) bear a dismal prognosis, with expected median survival times of 6 months [131,164], or 25% at 1 year [133]. Nonetheless, it is obvious that this outcome varies according to the liver functional status and other variables. For instance, patients with preserved liver function (Child–Pugh's A class) have a median survival of 7 months [168], while those with severe liver impairment (Child–Pugh's B class) present 5 months of median life expectancy. In 2006, there was no FDA-approved first line treatment for patients with advanced HCC. This scenario has changed as a result of the data reported showing survival benefits from patients receiving sorafenib – a multi tyrosine kinase inhibitor – in advanced cases [168]. The results of this RCT represent a breakthrough in the management of HCC, as it is discussed in the molecular targeted therapies section of this document. Overall median survival in the sorafenib arm was 10.7 months, ranging from 14.7 months in BCLC B and 9.5 months in BCLC C patients.

End-stage HCC: Patients with end-stage disease are characterized by presenting with tumors leading to a very poor Performance Status (ECOG 3–4), which reflects a severe tumor-related disability. Their median survival is 3–4 months [148] or 11% at 1-year [133]. Similarly, Child–Pugh C patients with tumors beyond the transplantation threshold also have a very poor prognosis.

Concept of treatment stage migration

A proportion of patients in each stage do not fulfil all the criteria for the treatment allocation. In those cases, it is advised to offer the patient the next most suitable option within the same stage or the next prognostic stage. For instance, patients at BCLC A failing local ablation should be offered chemoembolization. Similarly, patients at BCLC B stage non-responding to chemoembolization – at least two cycles of treatment – should be offered sorafenib, as reported in the SHARP trial [168,169].

Refinement of BCLC classification

Some studies challenged the capacity of BCLC to properly provide a fine stratification of patients for trial design. These studies mostly included patients at BCLC C stage of the disease [170]. The panel of experts acknowledges that the range of survival reported for patients at BCLC B (from 45 months to 11 months) and C (from 11 months to 5 months) deserves to be addressed. Further stratification of patients within each class according to liver function (Child–Pugh A versus B, or ascites), prognostic molecular biomarkers or prognostic variables (ECOG, cancer invasiveness) should be explored.

Molecular classification of HCC

Molecular classification of cancer should aid in understanding the biological subclasses and drivers of the disease and optimize benefits from molecular therapies and enrich trial populations. Few molecular classifications have been proposed in cancer. One such is the case of breast cancer, where Her2/nu status discriminates subgroups of patients with different outcome and treatment response to trastuzumab [171]. Similarly, EGFR mutational status in non-small cell lung cancer identifies a subgroup of responders to tyrosine kinase inhibitors [172]. More recently, the fact that a subgroup of patients with melanoma and BRAF mutations respond to specific B-RAF inhibitors has defined a new paradigm and subclass in the management of this cancer [173].

In HCC, no molecular subclass has been reported as responding to specific targeted therapy. Nonetheless, clear advancements in the understanding of the pathogenesis and molecular subclasses of the disease occurred during the last decade. From the biological standpoint, different tumoral classes have been characterized including a Wnt subclass, a proliferation class (with two subclasses: S1-TGF-beta and S2-EpCAM positive) and an inflammation class [77,137,174,175]. Samples obtained from different parts of a given neoplastic nodule showed identical class stratification in 95% of cases [136]. Equally relevant, gene profiling of adjacent non-tumoral tissue defines two subgroups of patients with good and poor outcome [137]. Thus, a portrait of the *field effect* is currently available, although further studies are required to confirm the prognostic significance of these subclasses, and whether specific drivers within them can provide the rationale for a more stratified medicine.

Treatment

- Treatment allocation is based on the BCLC allocation system, and the levels of evidence of treatments according to strength and magnitude of benefit are summarized in Fig. 4

In oncology, the benefits of treatments should be assessed through randomized controlled trials and meta-analysis. Other sources of evidence, such as non-randomized clinical trials or observational studies are considered less robust. Few medical interventions have been thoroughly tested in HCC, in contrast with other cancers with a high prevalence worldwide, such as lung, breast, colorectal and stomach cancer. As a result, the strength of evidence for most interventions in HCC is far behind the most prevalent cancers worldwide. The level of evidence for efficacy according to trial design and end-points for all available treatments in HCC and the strength of recommendations according to GRADE are summarized in Fig. 4.

In principle, recommendations in terms of selection for different treatment strategies are based on evidence-based data in circumstances where all potential efficacious interventions are available.

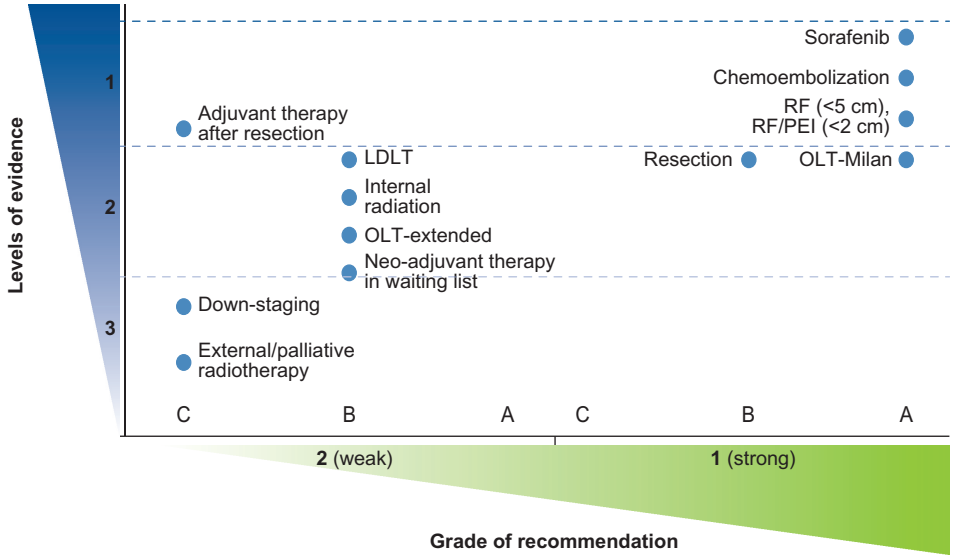

Fig. 4. Representation of EASL–EORTC recommendations for treatment according to levels of evidence (NCI classification [2]) and strength of recommendation (GRADE system). RF, radiofrequency ablation; PEI, percutaneous ethanol injection; OLT, orthotopic liver transplantation; LDLT, living donor liver transplantation.

Multidisciplinary HCC teams including hepatologists, surgeons, oncologists, radiologists, interventional radiologists, pathologists and translational researchers are encouraged to apply these guidelines. Strategic recommendations should be adapted to local regulations and/or team capacities and cost–benefit strategies.

Resection

- Resection is the first-line treatment option for patients with solitary tumors and very well-preserved liver function, defined as normal bilirubin with either hepatic venous pressure gradient ≤10 mmHg or platelet count ≥100,000
  (evidence 2A; recommendation 1B)
  Anatomical resections are recommended
  (evidence 3A; recommendation 2C)
- Additional indications for patients with multifocal tumors meeting Milan criteria (≤3 nodules ≤3 cm) or with mild portal hypertension not suitable for liver transplantation require prospective comparisons with loco-regional treatments
  (evidence 3A; recommendation 2C)
- Peri-operative mortality of liver resection in cirrhotic patients is expected to be 2-3%
- Neo-adjuvant or adjuvant therapies have not proven to improve outcome of patients treated with resection (or local ablation)
  (evidence 1D; recommendation 2C)
- Tumor recurrence represents the major complication of resection and the pattern of recurrence influences subsequent therapy allocation and outcome. In case of recurrence, the patient will be re-assessed by BCLC staging, and re-treated accordingly

Surgery is the mainstay of HCC treatment. Resection and transplantation achieve the best outcomes in well-selected candidates (5-year survival of 60–80%), and compete as the first option in patients with early tumors on an intention-to-treat perspective [176,177]. Hepatic resection is the treatment of choice for HCC in non-cirrhotic patients (5% of cases in the West, 40% in Asia) [178,179], where major resections can be performed with low rates of life-threatening complications and acceptable outcome (5-year survival: 30–50%).

Modern standards of HCC resection in cirrhotic patients are defined by the panel as follows: expected 5-year survival rates of 60%, with a peri-operative mortality of 2–3% and blood transfusion requirements of less than 10% [102,157,180–182]. In fact, peri-operative mortality has decreased from 15% in the 1980s to 3–5% in the majority of referral units. Some centers have reported zero peri-operative mortality [176,183]. Blood loss is significantly associated with patient outcome and may be controlled both by selecting patients with preserved liver functional reserve and by applying intermittent inflow occlusion during the hepatic parenchymal transection. Nowadays the selection of candidates for resection has been refined, and both the surgical technique – pre-resection imaging planning, ultrasonic dissector, intermittent Pringle maneuvre, low central venous pressure maintenance, etc. – and immediate post-operative management have been optimized. These strategies have led to a decrease in blood transfusion from 80% to 90% to less than 10% in two decades [183]. In addition, the implementation of anatomic resections according to Couinaud has ensured a surgical approach based on sound oncologic principles, although associated with modest decrease in early recurrence [184]. Anatomic resections aiming at 2 cm margins provide better survival outcome than narrow resection margins <1 cm [185] and are recommended only in case that the maintenance of appropriate function to the remnant liver volume is ensured. Retrospective studies linking anatomic resections and better outcome should be interpreted with caution, due to the propensity of performing wider interventions in patients with well-preserved liver function. Thus, caution should be exercised as the surgical effort is aimed at preservation of adequate hepatic

reserve through tailoring of the procedures to individual patients and tumor characteristics – i.e. body size, central versus peripheral location of tumor nodule and solitary large HCC (versus infiltrating tumor types).

Selection of the ideal candidates involves an adequate assessment of the liver functional reserve and tumor extension. The refinement of assessment of liver function has moved from the gross determination of Child–Pugh class to a more sophisticated measurement of indocyanine green retention rate at 15 min (ICG15) [186] or hepatic venous pressure gradient (HVPG) $\geqslant$10 mmHg as a direct measurement of relevant portal hypertension [187]. This concept of portal hypertension as prognostic factor in patients undergoing resection has recently been validated in Asia [182]. Surrogate measures of portal hypertension include two variables: platelet count below 100,000/mm^3 associated with splenomegaly, being the spleen size the less among clinical parameters associated with portal hypertension [188]. Platelet count has been recently confirmed as independent predictor of survival in resected HCC cases [189]. In line with these considerations, although the extensive assessment of each component of portal hypertension (HVPG, esophageal varices, splenomegaly and platelet count) is recommended before surgery, platelet count remains the most accessible parameter of portal hypertension available. In practice, selection of patients with HVPG <10 mmHg or absence of surrogates of portal hypertension (esophageal varices, or splenomegaly with platelet count <100.000/mm^3) lead to a resectability rate of less than 10% [99]. Expansion of these restrictive criteria by applying MELD score of $\leqslant$10 needs to be prospectively validated with a survival end-point [189].

Some groups apply pre-operative portal vein embolization (PVE) of the branches supplying the portion of the liver to be resected in order to increase the residual liver volume if a major resection is envisioned [183,190]. This approach is associated with a complication rate of 10–20% and occurrence of severe portal hypertension in 1% of cirrhotic patients [191]. However, the effectiveness of PVE in the frame of HCC in cirrhosis has not yet been properly tested in large controlled studies. Finally, an increasing number of data are collected on laparoscopic video-assisted hepatic resection, as an alternative non-invasive approach aimed at preventing liver deterioration compared to open approaches. The positive results reported for specific tumor locations in cohort series [192] need prospective comparison with traditional laparotomic resection before any change in current practice is made.

In patients properly selected according to liver functional status, the main predictors of survival are tumor size, tumor number presence of microsatellites and vascular invasion [176]. Tumor extension should be assessed by latest generation CT scan or MRI. Intraoperative ultrasonography (IOUS) enables the detection of nodules between 0.5 and 1 cm and is considered the standard of care for discarding the presence of additional nodules and to guide anatomical resections [193]. The Japanese Nationwide Survey has shown that a cut-off below 2 cm is an independent predictor of survival in a series of thousands of patients [194]. Five year survival rates for patients with HCC $\leqslant$2 cm was of 66%, compared with 52% for tumors 2–5 cm and 37% for tumors >5 cm. Multinodularity also predicts survival, with 5-year survival rates after resection of single tumors of 57% and 26% for three or more nodules, respectively. Recently, some referral centers reported 5-year survival rates above 50% in patients undergoing resection for multiple tumors fulfiling Milan criteria (up to 3 nodules $\leqslant$3 cm) not suitable for transplantation [180–182]. The positive results reported need further comparison of resection with loco-regional therapies prior to being adopted by these guidelines.

Vascular invasion is a known predictor of recurrence and survival, directly associated with histological differentiation, degree and size of the main nodule. Characteristically, microscopic vascular invasion involves 20% of tumors of 2 cm in diameter, 30–60% of cases in nodules 2–5 cm and up to 60–90% in nodules above 5 cm in size [176]. A more accurate observation of microvascular invasion has led to the identification of invasion of a muscular wall vessel or of more than 1 cm beyond the tumor edge as the 2 worst risk factors for prognosis [157]. Outcome of patients with single resected tumors varied from median survival ~87 months for patients with no vascular invasion, 38–71 months for those with microvascular invasion with 0–1 risk factors, and 8–12 months for those with microvascular invasion and 2 risk factors or macrovascular invasion. This classification requires external validation [157].

Adjuvant treatments to prevent recurrence

Tumor recurrence complicates 70% of cases at 5 years, reflecting either intrahepatic metastases (true recurrences) or the development of *de novo* tumors [161,157,180–182,195,196]. These entities can be differentiated by means of comparative genomic hybridization, integration pattern of hepatitis B virus, DNA fingerprinting using loss of heterozygosity assays, or DNA microarray studies [197]. No clinical definition of both entities has been established, but the cut-off of 2 years has been adopted to grossly classify early and late recurrences [149,198].

Several strategies to prevent and treat recurrence have been tested in the setting of randomized studies. Almost all published RCT have been conducted in Asia. Interferon is the most frequently evaluated drug so far. Different meta-analyses have evaluated the effect of adjuvant interferon treatment [199–201]. In one analysis including 13 studies (9 small RCT) there was a significant improvement in recurrence-free survival with interferon (estimated 3-year RFS of 54% versus 30% of placebo) [200]. Similar results were reported in other studies, in which different patient populations were studied. In the first Western RCT assessing interferon-alpha in 150 patients, negative results were obtained, but a positive trend in preventing *de novo* late recurrences was identified, providing the rationale for assessing this strategy in future research [181]. Considering the available information, the panel does not recommend adjuvant interferon due to the lack of significant patient numbers and partially conflicting data. Interestingly, recently miR-26 was identified as a potential marker predicting response to adjuvant interferon therapy [135]. Future studies in the adjuvant setting should include this type of molecular marker to more precisely categorize patients responding to adjuvant therapy.

Other strategies tested include chemotherapy, chemoembolization, internal radiation, immune therapies and retinoids. Adjuvant chemoembolization and chemotherapy do not bring any benefit in terms of prevention of relapse [202]. Internal radiation with ^{131}I-labeled lipiodol showed a positive effect in a small trial and cohort study [203,204]. Adoptive immunotherapy with activated lymphocytes with interleukin-2 reduced first recurrence in a trial with 150 patients (3-year recurrence: 33% versus 48% in the control group) [205]. A similar beneficial effect, described with retinoids and vitamin K2 preventing *de*

novo tumors, has not been recently confirmed in the setting of two large RCT studies [206–208]. Overall, according to a recent Cochrane systematic review, 12 RCTs were identified with less than 1000 patients randomized leading to an unclear body of evidence for efficacy of any of the adjuvant and neo-adjuvant protocols reviewed [209]. Thus, none of these strategies are recommended in clinical practice.

Larger trials with a lower risk of systematic error will have to be conducted according to previously reported guidelines [149]. The primary end-point of the studies should be time to recurrence or overall survival. Due to the lack of proven effective treatments, it is justified to randomize patients to an untreated control arm. Selection of patients should be based on the BCLC staging system, and stratification prior to randomization should be done according to tumor size, number of nodules/satellites, and vascular invasion. Due to the nature of these investigations, multi-institutional studies are required. The positive results reported with sorafenib for advanced HCC warrant an international study in the adjuvant setting with this multikinase inhibitor.

Liver transplantation

- Liver transplantation is considered to be the first-line treatment option for patients with single tumors less than 5 cm or ≤3 nodules ≤3 cm (Milan criteria) not suitable for resection
  (evidence 2A; recommendation 1A)
- Peri-operative mortality and one-year mortality are expected to be approximately 3% and ≤10%, respectively
- Extension of tumor limit criteria for liver transplantation for HCC has not been established. Modest expansion of Milan criteria applying the "up-to-seven" in patients without microvascular invasion achieves competitive outcomes, and thus this indication requires prospective validation
  (evidence 2B; recommendation 2B)
- Neo-adjuvant treatment can be considered for loco-regional therapies if the waiting list exceeds 6 months due to good cost-effectiveness data and tumor response rates, even though impact on long-term outcome is uncertain
  (evidence 2D; recommendation 2B)
- Down-staging policies for HCCs exceeding conventional criteria cannot be recommended and should be explored in the context of prospective studies aimed at survival and disease progression end-points
  (evidence 2D; recommendation 2C)
  Assessment of downstaging should follow modified RECIST criteria
- Living donor liver transplantation is an alternative option in patients with a waiting list exceeding 6-7 months, and offers a suitable setting to explore extended indications within research programs
  (evidence 2A; recommendation 2B)

Liver transplantation is the first treatment choice for patients with small multinodular tumors (⩽3 nodules ⩽3 cm) or those with single tumors ⩽5 cm and advanced liver dysfunction. Theoretically, transplantation may simultaneously cure the tumor and the underlying cirrhosis. The broad selection criteria applied two decades ago led to poor results in terms of recurrence (32–54% at 5 years) and survival (5-year survival <40%), but allowed the identification of the best candidates for this procedure [210,211]. Following this concept, some pioneering groups selecting "optimal candidates" reported 70% 5-year survival with a recurrence rate below 15% [161,212–215]. In a landmark manuscript the so-called Milan criteria were established for patients with a single HCC ⩽5 cm or up to three nodules ⩽3 cm [212]. Following these criteria and according to modern standards, peri-operative mortality, 1 and 5-year mortality are expected to be 3%, ⩽10%, and ⩽30%, respectively. Data on 10-year survival is scarce, and the panel endorses the practice of reporting these figures for surgical interventions following the intention-to-treat principle, in order to better discriminate differences in outcome between resection and transplantation not apparent at the conventional 5-year cut-off.

A recent systematic review including 90 studies, comprising a total of 17,780 patients over 15 years, identified the Milan criteria as an independent prognostic factor for outcome after liver transplantation [177]. Overall 5-year survival of patients within the Milan criteria (65–78%) was similar compared with non-HCC indications according to European (ELTR) and American registries (OPTN) (65–87%) [177,216,217]. ELTR reports 10-year survival rates of around 50% in more than 12,000 cases performed [216]. As a consequence of their success, the Milan criteria have been integrated in the BCLC staging system [148,149] and in the UNOS pre-transplant staging for organ allocation in the US [218], and remain the benchmark for any other prognostic criteria proposed for expanding the indication to liver transplantation in cirrhotic patients with HCC [219].

The major drawback of liver transplantation as a treatment of HCC is the scarcity of donors. Increases in waiting time have led to 20% of transplant candidates dropping out of the lists before receiving the procedure, thus jeopardizing the outcome if analyzed according to intention-to-treat [161,220]. Four concepts have been addressed by the panel in the context of transplantation for patients with HCC: (1) priority and delisting policies; (2) neoadjuvant treatments in the waiting list; (3) extension of criteria and downstaging for transplantation; and (4) living donor liver transplantation. The recently reported International Consensus Conference on Liver Transplantation has been instrumental in complementing the current guidelines [219].

Priority and delisting policies

UNOS developed a priority system to manage waiting lists for transplantation based on the MELD score [218], which was originally generated to predict 3-month survival in patients with End-Stage Liver Disease [221]. Since MELD is unable to predict the drop-out rate of patients with HCC, several priority scores have been assigned to these patients ranging from 24 (single <2 cm) and 29 points (single 2–5 cm or 3 nodules each <3 cm) in early proposals to none and 22 points respectively in the current era. The main difficulty for establishing priority policies is to define the at-risk patients for drop-out, which in some studies are identified as those patients with multinodular tumors, neoadjuvant treatment failures or those with baseline serum AFP levels

>200 ng/ml or steady increase of >15 ng/ml/month [140]. At the opposite end of the spectrum, some patients with UNOS-T1 tumor (single <2 cm) may benefit from alternative non-transplant treatments and avoid futile transplantation, at least until recurrence occurs [222].

Strategies advocating "salvage transplantation" approaches in low-risk populations should be investigated in prospective studies focused on intention-to-treat analysis and survival benefit, as they also depend on waiting time and local scenarios of donor availability. Similarly, patients undergoing resection with pathological high risk of recurrence have been proposed to be enlisted for liver transplantation [223]. Since waiting times vary significantly worldwide, it is recommended that policymakers modulate priority policies along with these variables.

There is even less information available about policies of delisting. The current panel recommends putting on hold those patients whose HCC progressed beyond Milan while on the waiting list and explore neo-adjuvant therapies for them. The panel recommends delisting those patients developing macrovascular invasion or extrahepatic spread.

Neo-adjuvant treatments in the waiting list

Adjuvant therapies for patients within the Milan criteria while on the waiting list are used in most centers to prevent tumor progression. Robust data from RCT are lacking and thus, the potential benefits advocated for local ablation or chemoembolization are derived from observational studies and cost–effectiveness analyses. The main studies assessing neo-adjuvant treatments are case series, case–control studies and cohort studies showing that RFA achieves the higher rates of complete necrosis (12–55%) [224,225] compared with TACE (22–29%) [226–228].

The impact of these treatments on drop-out rate, recurrence and survival is only estimated from non-randomized studies. From initial studies reporting drop-out rates, an actuarial probability of 15–30% at 1 year was established [161,220]. Among the case series and cohort studies reported, some investigations suggest a favorable impact of treatment in decreasing the dropout rate to levels ranging from 0% to 25% [222,224]. Similarly, since treatments on the waiting list have been studied in an uncontrolled fashion, their effects on survival after LT are difficult to assess. Since the publication of the seminal study [226], case–control studies including index treated cases and matched controls indicate similar survival rates as untreated individuals [227,228]. Markov-based cost–effectiveness analysis, on the contrary, pointed to benefits for neo-adjuvant treatments when waiting times exceed 6 months [229]. The use of sorafenib for the treatment of UNOS-T2 patients in the waiting list is not recommended according to the small pilot studies and cost–effectiveness studies published so far [230,231]. The real effect of loco-regional or molecular therapies on patient outcomes and on global gains of life expectancy from a societal perspective is uncertain. Therefore, considering the strength of evidence available, it is recommended to treat patients waiting for transplant with local ablation, and as a second choice with chemoembolization when waiting times are estimated to exceed 6 months.

Extension of indications and downstaging for liver transplantation

Analysis of the expansion of criteria beyond Milan and downstaging to Milan has been extensively explored. In summary, the main concept is that to establish a new policy allowing expansion of criteria for transplantation, it is essential to develop robust data for the specific category of patients included in the proposed expansion. Novel criteria might have a major impact on all transplant programs and the data needed to support any change should be impeccable. In addition, the impact of the expansion on the non-HCC patients waiting for liver transplantation should be taken into account.

The current understanding is that expansion to UCSF criteria (single nodule $\leqslant$6.5 cm or 2–3 nodules $\leqslant$4.5 cm and total tumor diameter $\leqslant$8 cm) – which involves around 5–10% of all enlisted patients [220,232] – has already been challenged from the pathological point of view by the up-to-seven criteria (i.e. those HCCs having the number 7 as the sum of the size of the largest tumor and the number of tumors) [233] This pathology-based proposal has been recently validated in an independent series [234]. The major concerns about the expansion proposals are the lack of specific data on overall survival and drop-out rate on the waiting list for the patients outside the current criteria but fulfiling the expanded criteria. Other recent studies challenging the Milan criteria have proposed different algorithms to optimize patient selection. Nonetheless, 5-year outcome prediction could vary from 70% to 40% according to the presence of microvascular invasion. Thus, preoperative markers of vascular invasion would be required prior to adopting these criteria. In a meta-analysis to evaluate tumor size and nodules, a cut-off of sum of diameters above 10 cm was considered to increase fourfold the risk of death [235], while a combination of tumor volume and AFP levels was considered the best strategy in other studies [140,141]. Molecular markers, such as allelic imbalance reflecting chromosomal instability, have also been shown to predict recurrence after transplantation [236]. Considering the strength of the evidence, it is recommended not to allow the extension of the criteria for transplant eligibility, except in the context of research protocols.

Regarding downstaging, there is not a single RCT, large case–control study or large well-designed cohort study available on patients treated consistently and properly followed. Small prospective studies suggest that downstaging to Milan criteria from patients with liver-only disease treated by radiofrequency or chemoembolization achieves 5-year survival outcomes similar to those within Milan [237,238]. It is unclear whether downstaging therapies yield measurable anti-cancer effects or only provide a time frame in which to evaluate the natural history of HCC, with the ultimate risk of transforming pre-transplant drop-outs into post-transplant recurrences [239,240]. There is no clear upper limit for eligibility of downstaging [240].

Considering the current data, downstaging of patients beyond Milan criteria cannot be adopted as a tool to refine patient selection and further research is required. This research should be based on the principle that 5-year survival outcomes of patients undergoing transplantation after successful downstaging should be similar to those of patients transplanted following Milan criteria [219]. The panel considers, though, that a special policy should be adopted for patients already on the waiting list for liver transplantation with tumors progressing beyond Milan and liver-only disease. In this special circumstance, as stated above, it is recommended to place the candidate on hold until downstaging by local ablation or chemoembolization is achieved and maintained for a period of at least 3 months.

Clinical Practice Guidelines

Living donor liver transplantation

Living donor liver transplantation (LDLT) using the right hepatic lobe of a healthy donor has emerged as an alternative to deceased liver transplantation [241,242]. In 2000, there was great enthusiasm for LDLT, and it was estimated that it would represent a significant proportion of the patients transplanted with HCC [243]. Unfortunately, the associated risks of death (estimated in 0.3%) and life-threatening complications (~2%) for the healthy donor have diminished the interest of the transplant community [244–246]. Currently, LDLT comprises less than 5% of adult liver transplants, significantly less than in kidney transplantation where living donors represent 40% of all cases performed [246]. The risks and benefits of LDLT should take into account both donor and recipient, a concept known as *double equipoise* [219,247,248]. Due to the complexity of the procedure, LDLT must be restricted to centers of excellence in hepatic surgery and transplantation.

Outcome results with LDLT compared with deceased LT have been controversial. Although some studies suggested that LDLT was associated with higher risk of recurrence, these data have not been confirmed [249,250]. Cost–effectiveness studies suggested that LDLT can be offered to patients with HCC if the waiting list exceeds 7 months [248], a policy adopted by the panel. Some authors recommend a period of observation prior transplant of 3 months, in order to avoid transplanting potentially aggressive tumors, a proposition that needs to be confirmed in further investigations [250,251]. LDLT has been proposed as an ideal setting to explore extended indications for HCC, considering the lack of graft allocation and priority policies [252]. Therefore, the panel does not recommend this procedure for any extended indication, except in the context of research studies.

Local ablation

- Local ablation with radiofrequency or percutaneous ethanol injection is considered the standard of care for patients with BCLC 0-A tumors not suitable for surgery **(evidence 2A; recommendation 1B)**
  Other ablative therapies, such as microwave or cryoablation, are still under investigation
- Radiofrequency ablation is recommended in most instances as the main ablative therapy in tumors less than 5 cm due to a significantly better control of the disease **(evidence 1iD; recommendation 1A)**
  Ethanol injection is recommended in cases where radiofrequency ablation is not technically feasible (around 10-15%)
- In tumors <2 cm, BCLC 0, both techniques achieve complete responses in more than 90% of cases with good long-term outcome. Whether they can be considered as competitive alternatives to resection is uncertain **(evidence 1iA; recommendation 1C)**

Local ablation is considered the first line treatment option for patients at early stages not suitable for surgical therapies. Over the past 25 years, several methods for chemical or thermal tumor destruction have been developed and clinically tested [253]. The seminal technique used is percutaneous ethanol injection (PEI), which induces coagulative necrosis of the lesion as a result of cellular dehydration, protein denaturation, and chemical occlusion of small tumor vessels. Subsequently, thermal ablative therapies emerged, and are classified as either hyperthermic treatments (heating of tissue at 60–100 °C) – including radiofrequency ablation (RFA), microwave ablation, and laser ablation – or cryoablation (freezing of tissue at −20 °C and −60 °C). Most procedures are performed using a percutaneous approach, although in some instances ablation with laparoscopy is recommended. PEI is a well-established technique for the treatment of nodular-type HCC that achieves complete necrosis in 90% of tumors <2 cm, 70% in those of 2–3 cm and 50% in those between 3 and 5 cm [162,253,254]. It has been speculated that ethanol diffusion is blocked either by the intratumoral fibrotic septa and/or the tumor capsule. This undermines the curative capacity of this technique, particularly in tumors larger than 2 cm. The recent introduction of a specific device for single-session PEI, a multipronged needle with three retractable prongs, has resulted in a rate of sustained complete response of 80–90% in tumors smaller than 4 cm [255]. In patients with Child–Pugh A cirrhosis and early-stage tumors, treatment with PEI has been shown to result in 5-year survival rates of 47–53% [256,257]. The major limitation of PEI is the high local recurrence rate, which may reach 43% in lesions exceeding 3 cm [258]. Another chemical ablation technique, percutaneous acetic acid injection (PAI), has not offered substantial advantages to PEI [259].

RFA has been the most widely assessed alternative to PEI for local ablation of HCC. The energy generated by RF ablation induces coagulative necrosis of the tumor producing a *safety ring* in the peritumoral tissue, which might eliminate small-undetected satellites. Consistent with previous studies, RF requires fewer treatment sessions to achieve comparable anti-tumoral effects. Five randomized controlled trials have compared RFA versus PEI for the treatment of early-stage HCC. These investigations consistently showed that RFA has a higher anticancer effect than PEI, leading to a better local control of the disease (2 year local recurrence rate: 2–18% versus 11–45%) [260–264]. The assessment of the impact of RFA on survival has been more controversial. Survival advantages favouring RF versus PEI were identified in the Japanese study including 232 patients [261], but no differences in survival were reported in the two European RCT [263,264]. Two additional RCT from the same group reported survival advantages in the subgroup analysis of tumors larger than 2 cm favouring RF compared with either PEI or PAI [260,262]. In patients with early-stage HCC treated with percutaneous ablation, long-term survival is influenced by multiple different interventions, given that a high percentage of patients will develop recurrent intrahepatic HCC nodules within 5 years of the initial treatment and will receive additional therapies. Nevertheless, three independent meta-analyses including all RCT, have confirmed that treatment with RFA offers a survival benefit as compared with PEI in tumors larger than 2 cm [265–267]. The main drawback of RF is its higher rates of major complications (4%; 95% CI, 1.8–6.4%) compared to PEI (2.7%; 95% CI, 0.4–5.1%) [267,268].

Considering the reported data, the best results obtained in series of HCC patients treated by RFA provide 5-year survival rates of 40–70% [269,270], and even beyond in highly selected candidates [142]. The best outcomes have been reported in Child–Pugh A patients with small single tumors, commonly less than 2 cm in diameter [159,162]. Independent predictors of survival are initial complete response, Child–Pugh score, number or size of nodules, and base-line alpha-fetoprotein levels. Thus, Child–Pugh A patients with non-surgical small tumors – that are expected to achieve complete responses – are the ideal candidates to RFA. Around 10–15% of tumors with difficult-to-treat locations can be approached by PEI [271]. Treatment of patients with larger tumors (3–5 cm), multiple tumors (3 nodules <3 cm) and advanced liver failure (Child–Pugh B) along with combination of both techniques could be reasonable on an individual basis. Although these treatments provide good results, they are unable to achieve response rates and outcomes comparable to surgical treatments, even when applied as the first option [194].

An open question is whether RFA can compete with surgical resection as a first-line treatment for patients with small, solitary HCC. Two RCT have been reported with opposite results [272,273]. While the first one did not identify outcome differences, the second trial suggested a survival advantage for surgical resection. Uncontrolled investigations have reported similar results for resection and RFA in BCLC 0 patients [159]. Further trials should overcome methodological issues which prevent the drawing of robust conclusions from the current studies. In addition, while complete removal of neoplastic tissue (R0) is common after surgical resection, some indications highlight the need to proceed with caution after analyzing the pathological specimens of tumors ablated with RFA. Complete tumor necrosis of less than 50% has been reported in tumors >3 cm because of the heat loss due to perfusion-mediated tissue cooling within the area ablated [274]. In addition, HCC tumors in a subcapsular location or adjacent to the gallbladder have a higher risk of incomplete ablation [275] or major complications [268,276,277]. Thus, at this point there are no data to support RFA as a replacement of resection as the first-line treatment for patients with early HCC (BCLC A) stage.

Treatments under investigation

Microwave ablation, laser ablation and cryoablation have been proposed for local ablation in HCC. Microwave ablation has an important advantage compared to RFA, which is that treatment efficacy is less affected by vessels located in the proximity of the tumor. Initial studies were limited by inducing a small volume of coagulation [278], and led to suboptimal performances when compared with RFA in the sole reported RCT [279]. Newer devices remain to be tested. Regarding laser ablation, no RCT has been published so far. In a recent multicenter retrospective analysis including 432 nonsurgical patients with early-stage HCC, 5-year overall survival was 34% (41% in Child–Pugh class A patients) [280]. Cryoablation had limited application in HCC, and no RCT have been reported [281]. The complication rate is not negligible, particularly because of the risk for "*cryoshock*", a life threatening condition resulting in multiorgan failure, severe coagulopathy and disseminated intravascular coagulation following cryoablation.

Non-Chemical Non-Thermal Ablation Techniques are currently undergoing clinical investigation. Irreversible electroporation is currently in clinical evaluation, after pre-clinical positive approach [282]. HIFU is a novel ablative approach reported in cohorts of patients with small tumors, but no randomized studies are available [283]. Light-activated drug therapy uses light-emitting diodes to activate talaporfin sodium in HCC after intravenously administration. Phase 3 studies with this therapy are ongoing [284].

Chemoembolization and transcatheter therapies

- Chemoembolization is recommended for patients with BCLC stage B, multinodular asymptomatic tumors without vascular invasion or extra hepatic spread **(evidence 1iiA; recommendation 1A)**
  The use of drug-eluting beads has shown similar response rates than gelfoam-lipiodol particles associated with less systemic adverse events **(evidence 1D; recommendation 2B)**
  Chemoembolization is discouraged in patients with decompensated liver disease, advanced liver dysfunction, macroscopic invasion or extrahepatic spread **(evidence 1iiA; recommendation 1B)**
  Bland embolization is not recommended
- Internal radiation with ^{131}I or ^{90}Y glass beads has shown promising anti-tumoral results with a safe profile, but cannot be recommended as standard therapy. Further research trials are needed to establish a competitive efficacy role in this population **(evidence 2A; recommendation 2B)**
- Selective intra-arterial chemotherapy or lipiodolization are not recommended for the management of HCC **(evidence 2A; recommendation 2B)**
- External three-dimensional conformal radiotherapy is under investigation, and there is no evidence to support this therapeutic approach in the management of HCC **(evidence 3A; recommendation 2C)**

Chemoembolization

Chemoembolization (TACE) is the most widely used primary treatment for unresectable HCC [160,165,194], and the recommended first line-therapy for patients at intermediate stage of the disease [56,139,149]. HCC exhibits intense neo-angiogenic activity during its progression. 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. TACE should be distinguished from chemo-lipiodolization – delivery of an emulsion of chemotherapy mixed with lipiodol –, bland transcatheter embolization (TAE), where no chemotherapeutic agent is delivered, and intra-arterial chemotherapy, where no embolization is performed. Details on the distinct types and definitions of

image-guided transcatheter embolization have been reviewed elsewhere [285,286].

Conventional chemoembolization (TACE)

This procedure combines transcatheter delivery of chemotherapy emulsioned with lipiodol followed by vascular stagnation achieved with embolic agents. Chemoembolization achieves partial responses in 15–55% of patients, and significantly delays tumor progression and macrovascular invasion. The survival benefit of TAE or chemoembolization has been the subject of a few RCT, which provided contradictory results [287–293]. Survival benefits were obtained in two studies [292,293], one of which identified treatment response as an independent predictor of survival [293]. Meta-analysis of these seven RCT, including a total of 516 patients, showed a beneficial survival effect of embolization/chemoembolization in comparison to the control group [139]. Sensitivity analysis showed a significant benefit of chemoembolization with cisplatin or doxorubicin in four studies, but none with embolization alone in three studies [139]. Overall, the median survival for intermediate HCC cases is expected to be around 16 months, whereas after chemoembolization the median survival is about 20 months. As a result of these investigations, TACE has been established as the standard of care for patients who meet the criteria for the intermediate-stage of the BCLC staging system, i.e. those with multinodular HCC, absence of cancer-related symptoms and no evidence of vascular invasion or extrahepatic spread. Recently, a meta-analysis by Cochrane investigators has challenged the efficacy of TACE [294]. Several biases contained in this approach, including the use of trials with inappropriate control arms or target populations leading to poor outcomes, diminish any impact of this investigation. The benefits of combining TACE with local ablation procedures or systemic therapies are under investigation.

The benefits of chemoembolization should not be offset by treatment-induced liver failure. Treatment-related deaths are expected in less than 2% of cases if proper selection of candidates is in place. The best candidates are patients with preserved liver function and asymptomatic multinodular tumors without vascular invasion or extrahepatic spread [285,293]. Macroscopic vascular invasion of any type and extrahepatic spread are major contraindications for chemoembolization. One positive trial showed no benefit in the subgroup analysis restricted to patients presenting with portal vein invasion [292]. Liver functional reserve is also a critical component for a careful selection. Patients should present relatively well-preserved liver function (mostly Child–Pugh A or B7 without ascites), while those with liver decompensation or more advanced liver failure should be excluded since the ischemic insult can lead to severe adverse events [289]. Absolute and relative contraindications for chemoembolization have been reviewed elsewhere [169]. There is no good evidence for which is the best chemotherapeutical agent and the optimal re-treatment strategy, even though it is recommended to apply the procedures 3–4 times per year and to use doxorubicin or cisplatin as the standard chemotherapy. More intense regimes, i.e. TACE every 2 months, might induce liver failure in an unacceptable proportion of patients [289]. Superselective chemoembolization is recommended to minimize the ischemic insult to non-tumoral tissue.

Chemoembolization with Drug-Eluting Beads (TACE-DEB)

Strategies to improve anti-tumoral activity and clinical benefits with chemoembolization have been launched. The ideal TACE scheme should allow maximum and sustained intratumoral concentration of the chemotherapeutic agent with minimal systemic exposure, along with calibrated tumor vessel obstruction. Embolic microspheres have the ability to sequester chemotherapeutic agents and release them in a controlled mode over a 1-week period. This strategy has been shown to increase the local concentration of the drug with negligible systemic toxicity [166]. A randomized phase II study comparing TACE and TACE-DEB reported a significant reduction in liver toxicity and drug-related adverse events for the latter arm, associated with a non-significant trend of better antitumoral effect [295].

Radioembolization and external radiation

Radioembolization is defined as the infusion of radioactive substances such as Iodine-131 (^{131}I)-labeled lipiodol [296] or microspheres containing Yttrium-90 (^{90}Y) [297–299] or similar agents into the hepatic artery. Given the hypervascularity of HCC, intra-arterially-injected microspheres will be preferentially delivered to the tumor-bearing area and selectively emit high-energy, low-penetration radiation to the tumor. A seminal RCT comparing chemoembolization versus internal radiation with ^{131}I has not been followed by additional investigations [296]. Currently, the most popular radioembolization technique uses microspheres coated with ^{90}Y, a ß-emitting isotope. This treatment requires a third level specialized center with sophisticated equipment and trained interventional radiologists. Severe lung shunting and intestinal radiation should be prevented prior to the procedure. Due to the minimally embolic effect of ^{90}Y microspheres, treatment can be safely used in patients with portal vein thrombosis [298].

Cohort studies reporting long-term outcomes showed a median survival time of 17.2 months for patients at intermediate stages [297] and 12 months for patients at advanced stages and portal vein invasion [298–300]. Objective response rates range from 35% to 50% [297–299]. Around 20% of patients present liver-related toxicity and 3% treatment-related death [297]. Despite the amount of data reported, there are no RCT testing the efficacy of ^{90}Y radioembolization compared with chemoembolization or sorafenib in patients at intermediate or advanced stage, respectively. Further research trials are needed to establish a competitive efficacy role in these populations.

Other loco-regional treatments

The use of conventional external-beam radiation therapy in HCC treatment has been limited by the low radiation tolerance of the cirrhotic liver, which often resulted in radiation-induced liver disease, previously known as radiation-induced hepatitis [301]. The benefits of external three-dimensional conformal radiotherapy have only been tested in uncontrolled investigations [302]. There is no scientific evidence to recommend these therapies as primary treatments of HCC and further research testing modern approaches is encouraged.

Systemic therapies

- Sorafenib is the standard systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh A class) and with advanced tumors (BCLC C) or those tumors progressing upon loco-regional therapies
(evidence 1iA; recommendation 1A)
- There are no clinical or molecular biomarkers available to identify the best responders to sorafenib
(evidence 1A; recommendation 2A)
- Systemic chemotherapy, tamoxifen, immunotherapy, anti-androgen, and herbal drugs are not recommended for the clinical management of HCC patients
(evidence 1-2A; recommendation 1A/B)
- There is no available second-line treatment for patients with intolerance or failure to sorafenib. Best supportive care or the inclusion of patients in clinical trials is recommended in this setting
(recommendation 2B)
- In specific circumstances, radiotherapy can be used to alleviate pain in patients with bone metastasis
(evidence 3A; recommendation 2C)
- Patients at BCLC D stage should receive palliative support including management of pain, nutrition and psychological support. In general, they should not be considered for participating in clinical trials
(recommendation 2B)

Molecular pathogenesis and targets for therapies

Molecular targeted therapies have changed the landscape of cancer management. Around 20 molecular targeted therapies have been approved during recent years for patients with breast, colorectal, non-small cell lung, renal cancer and HCC, among other malignancies [164,303]. Recently a multikinase inhibitor, sorafenib, has shown survival benefits in patients with advanced HCC [168]. This advancement represents a breakthrough in the treatment of this complex disease, and proves that molecular therapies can be effective in this cancer. A better understanding of the molecular hepatocarcinogenesis is critical for identifying novel targets and oncogenic addition loops [304–306]. No pathognomonic molecular mechanism or single dominant pathway exists in hepatocarcinogenesis and this explains why a single-targeted agent will not achieve sustained complete response in HCC. Consequently, it is conceivable to inhibit signals at different levels of one of the main pathways, or to inhibit two or three different pathways at the same time.

Hepatocarcinogenesis is a complex multistep process where multiple signaling cascades are altered leading to a heterogeneous biological portrait of the disease [304–306]. Although no oncogenic addition loop defining growth dependence for any subclass of HCC has been defined, several signaling pathways have been implicated in tumor progression and dissemination:

(1) *Vascular growth factor (VEGF) signaling* is the cornerstone of angiogenesis in HCC, and high level amplifications have been identified [175,307]. VEGFR signaling can be targeted either by the monoclonal antibody bevacizumab directed against VEGF, or by inhibiting the intracellular tyrosine kinase by small molecules such as sorafenib, sunitinib, brivanib, linifanib, vatalinib, cediranib, and others. Other activated angiogenic pathways are Ang2 and FGF signaling.
(2) *Epidermal growth factor (EGF) signaling* is frequently overexpressed in HCC [308]. EGFR can be targeted either by the monoclonal antibody cetuximab or by small molecules that inhibit the intracellular tyrosine kinase such as erlotinib, gefitinib, or lapatinib.
(3) *Ras MAPK signaling* has been shown to be activated in half of early and almost all advanced HCCs [305,309]. Activation of this pathway is dependant upon overexpression of ligands and hypermethylation of promoters of tumor suppressors inducing transcription of genes of the AP-1 family, such as *c-Fos* and *c-Jun* involved in proliferation and differentiation [310]. Mutations of *K-Ras* are infrequent in HCC (<5%). No selective Ras/ERK/MAPK inhibitor has been approved, but sorafenib and regorafenib have shown partial cascade blockage [311].
(4) *The PI3K/PTEN/Akt/mTOR pathway.* This pathway controls cell proliferation, cell cycle and apoptosis, and is activated by various RTKs such as EGFR or IGFR and by inactivation of the tumor suppressor PTEN. It is activated in 40–50% of HCCs [312,313]. Several compounds inhibiting mTOR (rapamycin, temsirolimus and everolimus) are tested in phase II and III studies.
(5) *HGF/c-MET pathway.* Dysregulation of the c-MET receptor and its ligand HGF, critical for hepatocyte regeneration after liver injury, is a common event in HCC [314]. However, their role in targeted therapy needs further investigation.
(6) *Insulin-like growth factor receptor (IGFR) signaling.* IGF-1R and IGF-II expression is increased in HCC, whereas IGFR-II is downregulated in a subgroup of HCCs [315,316]. Several IGF-1R inhibitors are now under early clinical investigation in HCC.
(7) *Wnt/ß-Catenin pathway* is crucial for hepatocarcinogenesis [304–306,317–319]. Around one third of HCCs have activation of the Wnt signaling pathway (particularly HCV-related HCCs), as a result of activating mutations in the transcription factor ß-catenin [175,317,318], overexpression of Frizzled receptors or inactivation of E-cadherin or members of the degradation complex (GSK3B, AXIN, adenomatosis polyposis coli (APC)) [319]. New compounds to block this so-called undrugable pathway are under early clinical investigation.

Additional pathways and their role in targeted therapy such as the extrinsic/intrinsic apoptotic pathway, Hedgehog signaling, JAK/STAT signaling, TGF-ß signaling, Notch pathway, ubiquitin–proteasome pathway, nuclear factor-κB signaling, cell cycle control, and the role of the tumor microenvironment have to be further defined. Similarly, the potential role of recently described oncoMIRs relevant to hepatocarcinogenesis as molec-

ular targets should be confirmed by clinical investigations [135,320].

Molecular targeted therapies

Hepatocellular carcinoma is recognized as among the most chemo-resistant tumor types, and until 2007 no systemic drug was recommended for patients with advanced tumors, an unparalleled situation in oncology. Sorafenib emerged as the first effective systemic treatment in HCC after 30 years of research, and is currently the standard-of-care for patients with advanced tumors [168]. After this study, around 56 molecular agents are being tested in phase II and phase III clinical trials [321] (Table 4), the final results of which might lead to updated treatment recommendations. A summary of the evidence-based data is set out below. The panel recommends that drug development of novel molecules in HCC should be based on the identification of oncogenic biomarkers to guide a more personalized and stratified therapy.

Sorafenib

Sorafenib, an oral multi-tyrosine kinase inhibitor, was the first and remains the only drug that has demonstrated survival benefits in patients with advanced HCC. Following an initial phase II study showing a signal of efficacy [322], a large double-blinded placebo controlled phase III investigation was conducted, leading to positive survival results [168]. In this trial, the benefit of sorafenib was to increase the median overall survival from 7.9 months in the placebo group to 10.7 months in the sorafenib group (HR = 0.69; 95% CI, 0.55–0.87; $p = 0.00058$), which represents a 31% decrease in the relative risk of death. In addition, sorafenib showed a significant benefit in terms of time to progression (TTP) assessed by independent radiological review with a median TTP of 5.5 months for sorafenib and 2.8 months for placebo. The magnitude of survival benefit was similar to that demonstrated in a parallel phase III trial conducted in the Asian-Pacific population, in which hepatitis B was the main cause of HCC [323]. In this later trial, the median overall survival was 6.5 months in the sorafenib group versus 4.2 months in the placebo group (HR = 0.68; 95% CI, 0.50–0.93; $p = 0.014$). The worse outcome of patients included in this trial, regardless of treatment allocation, compared with the SHARP investigation, is due to the fact that the patients had more advanced diseases (ECOG 1–2 or metastatic disease). From these trials, sorafenib emerged as well tolerated; the most common grade 3 drug-related adverse events observed in these studies included diarrhea and hand-foot skin reaction, which occurred in 8–9%, and 8–16% of patients, respectively. Drug discontinuation due to adverse events was 15% in the sorafenib arm and 7% in the placebo arm. Drug-related adverse events were considered manageable, and no death related with toxicity was described. As a result, sorafenib received the European Medicines Agency (EMEA) authorization in October 2007 and was approved by the USA United Food and Drug Administration (FDA) in November 2007.

The panel of experts recommends using sorafenib as the standard systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child–Pugh A class) and with advanced tumors – BCLC C – or those tumors progressing on loco-regional therapies (concept of treatment migration). No clear recommendation can be made in Child–Pugh B patients, although cohort studies have reported a similar safety profile in patients of this class with no decompensation [324,325]. It is recommended to maintain sorafenib at least until progression, and beyond that point second-line studies can be considered. Sorafenib is currently being tested in the adjuvant setting after resection or complete local ablation for early stages, in combination with chemoembolization for intermediate stages [326], in combination with erlotinib or systemic doxorubicin in advanced stages and as first-line treatment in Child–Pugh B patients. Preliminary data from a randomized phase II study suggest a potential additive effect in combination with doxorubicin, although a significant increase in cardiotoxicity was reported [327].

Table 4. Ongoing randomized phase II–III trials aimed to change the standard of care in HCC management during the period 2012–13.

Indication	Randomized studies
Adjuvant	1. Sorafenib *vs.* placebo
Intermediate HCC	1. Chemoembolization ± sorafenib
	2. Chemoembolization ± brivanib
	3. Chemoembolization ± everolimus
Advanced HCC	
First line	1. Sorafenib ± erlotinib
	2. Sorafenib *vs.* brivanib
	3. Sorafenib *vs.* sunitinib*
	4. Sorafenib *vs.* linifanib**
	5. Sorafenib ± Yttrium-90
	6. Sorafenib ± doxorubicin
Second line	1. Brivanib *vs.* placebo**
	2. Everolimus *vs.* placebo
	3. Ramucirumab *vs.* placebo

*Halted 2010 for futility/toxicity.
**See addendum at the end of the Guidelines.

Other targeted molecules under clinical development

Growth factors and proliferative pathway inhibitors.

mTOR inhibitors. Rapamycin (sirolimus) and its analogs (temsirolimus and everolimus) are agents blocking the mTOR signaling cascade and have been tested in preclinical and early clinical investigations [328]. Everolimus, an mTOR blocker approved for kidney cancer therapy, is being tested in phase III for a second-line indication.

EGFR inhibitors. Five EGFR inhibitors have been tested: erlotinib, gefitinib, cetuximab, lapatinib and vandetanib. Erlotinib showed activity in a phase II study with mixed HCC populations with median survival of 13 months [329], and is currently being tested in combination with sorafenib in phase III. The other drugs either have not shown meaningful signals of efficacy in phase II, such as gefitinib and lapatinib [330], or are still in early stages of investigation.

Anti-angiogenic agents. Sunitinib. Sunitinib is an oral multi-tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma, gastrointestinal stromal tumors and pancreatic neuroendocrine tumors. Three reported phase II studies have shown potential signals of activity, but with conflictive adverse events and treatment-related deaths due to severe liver dysfunction in 5–10% of patients [331–333]. A recent multicenter, open-label sorafenib-controlled randomized phase III trial was prematurely

discontinued for safety issues and futility reasons [334]. This drug is presently not recommended for treatment of HCC.

Brivanib alaninate. Brivanib, an oral VEGFR and FGFR tyrosine kinase inhibitor, was evaluated in two phase II studies in first and second-line patients with an advanced tumor. The median overall survival was 10 months in the first-line treated group and 9.8 months in the second-line treated group, with manageable adverse events [335]. Brivanib is currently tested in three phases III trials in HCC patients: in first-line blinded to sorafenib, in second-line blinded to placebo and in combination with chemoembolization.

Bevacizumab. Bevacizumab, a recombinant, humanized monoclonal antibody directed against VEGF, has emerged as an important therapeutic agent in several malignancies and has been approved in the treatment of colorectal cancer, non-small-cell lung cancer and breast carcinoma. Bevacizumab has been evaluated as single agent [336], or in combination with erlotinib [337] or chemotherapy [338]. As a standalone agent, it showed objective responses of 10% with median time to progression of 6.5 months [336]. Combination treatment of bevacizumab with EGFR targeting agents reported a median survival of 15 months for mixed HCC patient populations [337]. Combinations of bevacizumab with chemotherapy, such as gemcitabine and oxaliplatin or capecitabine-based regimes, obtain objective responses of 10–20% with median survivals of 9–10 months [338]. No phase III investigations with this agent are ongoing.

Linifanib, an oral tyrosine kinase inhibitor targeting VEGF and PDGF, and ramucirumab, a monoclonal antibody against VEGFR2 [339] are currently being tested in phase III studies in first-line and second-line indication, respectively. Other new anti-angiogenic agents, such as vatalanib, axitinib and cediranib are at very early stages of investigation. Other molecules such as c-MET inhibitors, MEK inhibitors, TGF-beta and JAK2 inhibitors are being tested in early clinical investigations [321].

Other systemic therapies

Several systemic therapies, including chemotherapy, hormonal compounds, immunotherapy and others showed inconclusive or negative results. These agents are not currently recommended for management of HCC.

Chemotherapy

The problem of using chemotherapy in HCC stems from the coexistence of two diseases. Cirrhosis can perturb the metabolism of chemotherapeutic drugs and enhance their toxicity. In addition, some chemotherapy-related complications, such as systemic infections, are particularly severe in inmmunocompromised patients, like cirrhotics. On the other hand, HCC has been shown to be chemoresistant to the most common chemotherapies, which as single agents have reported modest anti-tumoral response [139,340–342]. Systemic doxorubicin has been evaluated in more than 1000 patients in clinical trials with an objective response rate of around 10%. In a 446-patient trial, nolatrexed, an inhibitor of thymidylate synthase, was compared to systemic doxorubicin with negative results (median survival 5 months versus 7.5 months, respectively) and response rates for the doxorubicin arm of 4%. Other systemic therapies such as gemcitabine, oxaliplatin, cisplatin and capecitabine used as single agents or in combinations have reported heterogeneous responses ranging from 0% to 18% in uncontrolled investigations [340].

Systemic chemotherapy using combinations of two or more agents has been tested in recent RCT. A large RCT which compared combination chemotherapy (Cisplatin/Interferon α2b/Doxorubicin/Fluorouracil-PIAF regime) versus doxorubicin chemotherapy showed objective response rates of 20.9% and 10.5%, respectively [342]. The median survival of the PIAF and doxorubicin groups was 8.67 months and 6.83 months, respectively, without differences between groups. PIAF was associated with a significantly higher rate of myelotoxicity compared with doxorubicin. Treatment-related mortality was 9% in the PIAF regimen arm as a result of HBV reactivation and liver failure. A second RCT conducted in Asia compared the efficacy of the Folfox regimen combining 5-fluorouracil, folinic acid and oxaliplatin against doxorubicin alone. This study included 371 patients with Child–Pugh A/B advanced non-operable or metastatic HCC (BCLC B/C). There was a non-significant trend favoring the Folfox group (median survival 6.4 mo versus 4.9 mo; $p = 0.07$) associated to a better time to progression (2.9 mo versus 1.7 mo) [343]. Chemotherapy for HCC in non-cirrhotic patients is an underexplored area [344]. Thus, considering the available evidence, systemic chemotherapy is not recommended for the treatment of HCC, nor as a control regime for any trial due to the well-known toxic effects. Phase III investigations combining chemotherapy and sorafenib are ongoing.

Hormonal compounds

Hormonal compounds have not shown survival benefits in HCC. A meta-analysis of seven RCT comparing tamoxifen versus conservative management, comprising 898 patients, showed neither anti-tumoral effects nor survival benefits for tamoxifen [139]. Two large RCT were reported afterwards assessing tamoxifen [345,346] with negative results in terms of survival. Thus, this treatment is discouraged in advanced HCC. Antiandrogen therapy is not recommended [347].

Immunotherapy

HCC is a typical inflammation associated cancer. A number of different studies have demonstrated a correlation between immune responses to tumors and patient outcome [348]. Immune-based therapy phase I–II trials have been performed at centers with the appropriate expertise but results have not been confirmed by independent investigators [349]. The concept of immunotherapy requires further investigations from phase II and III studies.

Other treatments

A large RCT compared seocalcitol – a vitamin D like antiproliferative molecule – versus placebo in 746 patients and showed no differences in overall survival (9.6 months seocalcitol versus 9.2 months placebo) [350]. Finally, negative results were also reported with a tubulin inhibitor (T-67) in a large multicenter RCT [351].

Clinical Practice Guidelines

Trial design

1. The panel endorses the trial design and selection of end-points for clinical trials in HCC proposed in previous JNCI guidelines (Fig. 5) and lists the high-end trials currently ongoing which, in case of demonstrating clinically relevant superiority *vs.* the standard of care, might change the current guidelines (Table 4)

2. Assessment of response:

   - Assessment of response in HCC should be based on the modification of the RECIST criteria (mRECIST; Table 5) **(recommendation 2B)**
     Use of changes in serum levels of biomarkers for assessment of response (i.e. AFP levels) is under investigation

   - Dynamic CT or MRI are recommended tools to assess response one month after resection, loco-regional or systemic therapies **(recommendation 1A)**
     Follow-up strategies for detection of recurrence include one imaging technique every 3 months during the first year, and every six months thereafter to complete at least two years. Afterwards, regular ultrasound is recommended every 6 months. Assessment of time to progression is recommended with CT and/or MRI every 6-8 weeks

The increasing number of ongoing clinical trials in HCC has created the need for a common frame to test novel drugs accepted by all disciplines. As a consequence, new guidelines on the design of clinical trials and end-points in HCC have been reported by a multidisciplinary panel of experts [149]. These statements will evolve as new evidence becomes available, including more precise information on the natural history of HCC, new drugs or predictive biomarkers. The panel endorses the trial design and selection of end-points for clinical trials in HCC proposed in previous Journal National Cancer Institute guidelines [149]. In addition, the panel wants to emphasize that the integrity of research is absolutely vital for the advancement of evidence-based medicine. If a study proposing a major change in clinical practice is accepted yet its findings are fraudulent, as recently occurred in HCC with a study that required retraction [352], the threat to patient safety and management could be enormous.

The main recommendations for trial design are summarized below:

(1) *End-points.* Survival and time to recurrence were proposed as primary end-points for phase III studies assessing primary and adjuvant therapies, respectively. Composite end-points such as disease free survival (DFS) or progression free survival (PFS) are suboptimal in HCC research, and should be included as secondary end-points. Randomized phase II studies were considered pivotal prior to conducting phase III trials in HCC. These studies classically consider response rate as the gold-standard for efficacy, but time to progression was recommended as the primary end-point when testing molecular targeted therapies [149]. The panel considers that further data is needed to establish response rate as per mRECIST as surrogate of survival. Quality of life assessment in HCC research suffers from the lack of a reliable, standardized and adequately validated questionnaire, and thus, it is currently recommended as ancillary information.

(2) Trial design is summarized in Fig. 5. Selection of patients should be based on BCLC staging and Child–Pugh A class, in order to minimize the competitive risk of death associated with liver failure. The control arm for clinical

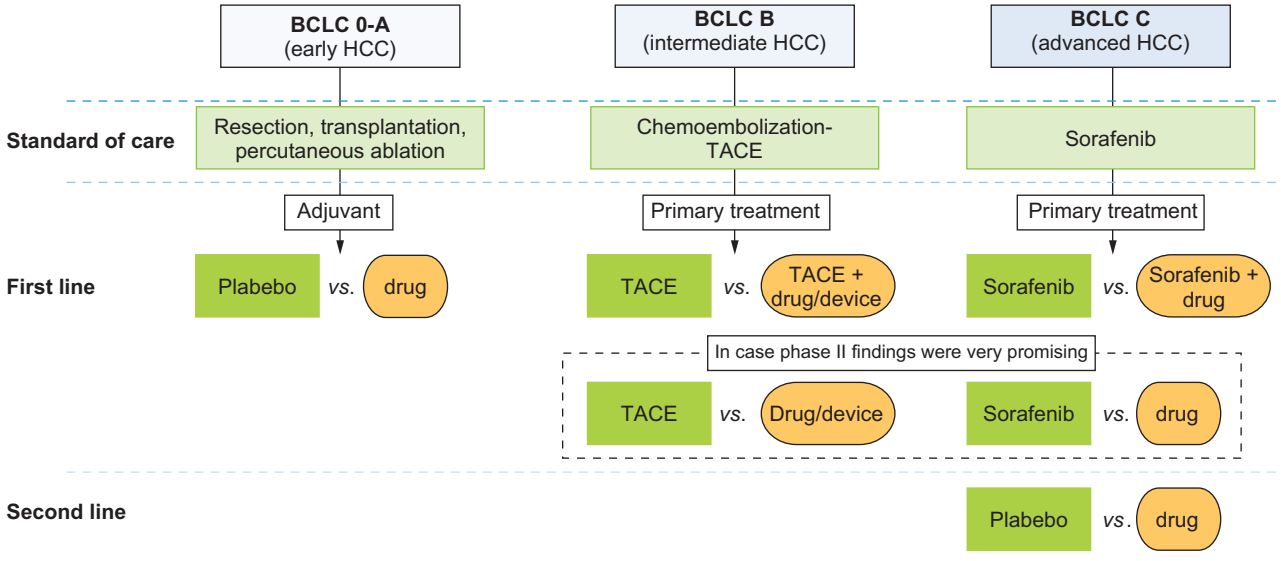

Fig. 5. Summary of trial design strategies and control groups. Adapted from Llovet *et al.* [164].

Table 5. Assessment of response comparing RECIST and mRECIST.*

Target lesions		
Response category	RECIST	mRECIST
CR	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD	Any cases that do not qualify for either PR or PD	Any cases that do not qualify for either PR or PD
PD	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started
Non-target lesions		
Response category	RECIST	mRECIST
CR	Disappearance of all non-target lesions	Disappearance of any intratumoral arterial enhancement in all non-target lesions
IR/SD	Persistence of one or more non-target lesions	Persistence of intratumoral arterial enhancement in one or more non-target lesions
PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
mRECIST recommendations		
Pleural effusion and ascites	Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.	
Porta hepatis lymph node	Lymph nodes detected at the porta hepatis can be considered malignant if the lymph node short axis is at least 2 cm.	
Portal vein thrombosis	Malignant portal vein thrombosis should be considered as a non-measurable lesion and thus included in the non-target lesion group.	
New lesion	A new lesion can be classified as HCC if its longest diameter is at least 1 cm and the enhancement pattern is typical for HCC. A lesion with atypical radiological pattern can be diagnosed as HCC by evidence of at least 1 cm interval growth.	

RECIST, Response Evaluation Criteria In Solid Tumors; mRECIST, modified Response Evaluation Criteria In Solid Tumors; CR, complete response; PR, partial response; IR, incomplete response; SD, stable disease; PD, progressive disease.
*Adapted from Llovet *et al.* [149] and Lencioni and Llovet [100].

trials should be the standard of care, meaning chemoembolization for intermediate HCCs and sorafenib for advanced cases. Therefore, for the assessment of first-line systemic treatments for advanced HCC a design adding a new agent to sorafenib versus sorafenib alone is recommended. Comparison of single agents head-to-head with the standard of care therapy might jeopardize the recruitment of patients for ethical reasons, unless the novel agent showed very promising efficacy in early phase II studies. For second-line treatments, the new agent should be randomized against placebo/best supportive care, and the selection criteria should include patients with contraindications or failures to sorafenib. Randomized studies testing molecular targeted therapies should optimally include biomarker analysis (tissue and/or serum samples) to enable the identification of molecular markers of response and for pharmacokinetic purposes, as reported in other cancers.

(3) *Assessment of tumor response.* The main end-point in cancer research is overall survival. Nonetheless, tumor response and time to progression have been considered pivotal for surrogate assessment of efficacy. In oncology, tumor response was initially measured according to the World Health Organization (WHO) criteria [353], and afterwards according to the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines [354,355]. These criteria were designed primarily for evaluation of cytotoxic agents. They do not address measures of antitumor activity other than tumor shrinkage. As acknowledged in the original RECIST publication, assessments based solely on changes in tumor size can be misleading when applied to other anticancer drugs, such as molecular targeted therapies, or other therapeutic interventions [354]. EASL and AASLD guidelines adopted a modified version of a WHO criterion in which the evaluation of the treatment response accounted for the induction of

intra-tumoral necrotic areas in estimating the decrease in tumor load, and not just a reduction in overall tumor size [1,56].

Results from a number of previous clinical studies in HCC have demonstrated that RECIST criteria do not mirror the extent of tumor necrosis induced by interventional therapies or new molecular targeting drugs [168,356]. Viable tumor formation needs to be assessed using CT or MRI studies and viable tumor should be defined as uptake of contrast agent in the arterial phase of dynamic imaging studies. Consequently, a modification of the RECIST criteria was first proposed by a panel of experts [149], and further expanded [100]. This proposal is based on the fact that diameter of the target lesions with viable tumor should guide all measurements. In addition, specific modifications of the original criteria regarding assessment of vascular invasion, lymph nodes, ascites, pleural effusion and news lesions have been summarized in Table 5. Objective response rates using mRECIST have been reported of 57% in patients treated with chemoembolization [357], ^{90}Y [358], ~20% with sorafenib [359,360] and 15–25% using brivanib [335]. The panel of experts recommends to assess tumor response according to mRECIST criteria, and to test whether these criteria have better performance than conventional RECIST, and correlate with pathological studies and outcome prediction (Table 6).

Table 6. Unmet needs in HCC research.

1. Clinical development of drugs
Targeting pathways with few candidates in the pipeline such as Wnt/β-catenin, Hedgehog/Gli, Notch and ERK pathway
Improve models for pre-clinical testing of novel drugs
2. Identification and validation of biomarkers
Prognostic biomarkers: independent validation of prognosis at all stages of the disease from serum (AFP, Ang2, VEGF) and tissue (gene signatures *EpCAM*, G3-proliferation, poor survival signature; miR26)
Predictive biomarkers: response to specific systemic targeted therapies
Surrogates of microvascular invasion
3. Properly designed and powered clinical trials for:
• Adjuvant therapy after curative treatments
• Therapies to prevent drop-outs in the waiting list and downstaging strategies
• Combinations of local with systemic therapies
• Combinations of systemic targeted therapies
• Second-line therapies
• Radioembolization
4. Systematic inclusion of cost-benefit analyses in clinical trials
5. Search for tools to assess quality of life in clinical trials

Final considerations

1. The panel considers that collection of tissue and serum samples in research studies is highly desirable and recommended. Such biobanking should permit the achievement of two clinical goals:
   - **Refinement of prognostication and BCLC staging system.** Molecular data such as gene signatures (poor survival, *EpCAM*) or biomarkers (AFP, VEGF, Ang2 and miR26) have been shown to have independent prognostic significance and are likely to be incorporated into staging systems after external independent validation
   - **Moving towards personalized/stratified medicine.** Molecular therapies blocking angiogenesis (VEGF, PDGF, Ang2, FGF) or proliferation cascades disrupted in HCC (EGFR, Ras, Akt, mTOR, IGF-1R, MET) are tested in advanced clinical trials. Discovery of biomarkers can be instrumental for trial enrichment and identification of treatment responders, and, therefore, constitutes a major short term goal
2. The panel has listed and categorized here the main unmet needs in the field of HCC research in a categorized manner (see Table 6). It is strongly recommended that physicians, investigators, health policy agencies, pharmaceutical industry and care providers devote future resources as a priority to:
   - Evaluating adjuvant therapies after resection/local ablation
   - Exploring downstaging strategies to rescue patients with HCCs beyond conventional Milan criteria
   - Evaluating the benefits of combining molecular therapies with local ablation and loco-regional treatments
   - Building the backbone package treatment for advanced tumors and second-line therapies
   - Including cost-benefit approaches in research studies with collection of health economic analysis such as incremental cost effectiveness ratio in order to facilitate clinical decision-making
   - Providing adequate quality of life assessment tools. The panel considers quality of life as a relevant end-point for research studies, and thus, refinement of instruments for such assessment in HCC patients is needed
3. Translating efficacy into effectiveness: Despite effective surveillance and treatment strategies are available in HCC, the proportions of patients receiving these interventions are suboptimal [47]. Measures to increase access to surveillance, early diagnosis and effective treatment should be implemented in order to increase the effectiveness

Addendum

During the editing process of the guidelines additional information on two phase 3 RCT mentioned in Table 4 was reported.

1. The study comparing brivanib *vs.* placebo in patients with advanced HCC failing or intolerant to sorafenib was reported not meeting the primary end-point survival. http://www.businesswire.com/portal/site/home/email/alert (Jan 2012).
2. The study comparing linifanib *vs.* sorafenib in first-line was halted by the DSMC at the interim analysis. Abbott's LiGHT (Linifanib Study M10-963) Early Study Closure).

Disclosures

These guidelines reflect the state of knowledge, current at the time of publication, on effective and appropriate care, as well as clinical consensus judgments when knowledge is lacking. The inevitable changes in the state of scientific information and technology mandate that periodic review, updating, and revisions will be needed. These guidelines do not apply to all patients, and each must be adapted and tailored to each individual patient. Proper use, adaptation modifications or decisions to disregard these or other guidelines, in whole or in part, are entirely the responsibility of the clinician who uses the guidelines. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, organizations or imply endorsement by any European or USA Government.

Conflict of interest

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