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EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma☆

European Association for the Study of the Liver*

Summary

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally. Hepatocellular carcinoma represents about 90% of primary liver cancers and constitutes a major global health problem. The following Clinical Practice Guidelines will give up-to-date advice for the clinical management of patients with hepatocellular carcinoma, as well as providing an in-depth review of all the relevant data leading to the conclusions herein.

Introduction

In 2012, the previous guidelines for the management of hepatocellular carcinoma (HCC) were published as a result of a joint effort by the European Association for the Study of the Liver (EASL) and the European Organisation for Research and Treatment of Cancer (EORTC).[1] Since then several clinical and scientific advances have been achieved. Thus, an updated version of the document is needed.

Objectives of the guideline

These EASL Clinical Practice Guidelines (CPGs) are the current update to the previous EASL-EORTC CPGs.[1] These EASL CPGs define the use of surveillance, diagnosis and therapeutic strategies recommended for patients with HCC.

The purpose of this document is to assist physicians, patients, healthcare providers and health-policy makers from Europe and worldwide in the decision making process, based on the currently available evidence. 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 to advancing the research and knowledge of this disease, and ultimately contributing to improved patient care.

Methodology

Composition of the guidelines group

The guideline development group (GDG) of this guideline project is composed of international experts in the field of HCC, comprising the areas of hepatology (PRG, AF, JL, FP), surgery (VM), radiology (VV), oncology (JLR) and pathology (PS). Initially, the EASL governing board nominated a chair (PRG) and a governing board member (AF) to propose a panel of experts and finally nominated the above GDG, Additionally, a guideline methodologist was appointed to support the GDG (MF).

Funding and management of conflict of interests

This guideline project has kindly been supported by EASL. The financial support did not influence the development of this guideline. Key questions to be answered and outcomes were chosen in accordance with the consensus of the expert panel. Recommendations were reached by consensus of the expert panel and based on clinical expertise and existing evidence. A declaration of conflicts of interest was required to participate in the guideline development. The ethical committee of EASL assessed the individual interests and decided that there were no substantial conflicts of interest.

Generation of recommendations

In a first step the panel identified, prioritised and selected relevant topics and agreed on key questions to be answered. These questions were clustered and distributed according to the defined working groups, which are reflected in the different chapters.

According to the key questions, a literature search was performed. The studies identified and included were assessed and assigned to categories related to study design and strength of evidence according to endpoints. Based on this evidence, the drafts for recommendation and chapters were created.

Consent was provided for all recommendations during the consensus conference, moderated by Markus Follmann, MD MPH MSc, a certified moderator for the German Association of Scientific Medical Societies (AWMF). Formal consensus

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methodology (nominal group technique) was used to agree upon the recommendations. All expert panel members participated in person and were entitled to vote on the recommendations. The consensus conference was performed as a personal meeting over two days (in June and September 2017). When evaluating the evidence, the balance of benefits and harms, and the quality of the evidence were taken into consideration. Expert opinion and experience was included, particularly, if the body of evidence was insufficient and if further aspects such as time and costs, additional side effects, quality of life, resource use, *etc.* had to be considered.

To simplify the identification of consented recommendations, all consented recommendations are highlighted throughout the guidelines documents (Tables). In order to avoid ambiguity, a standardised language was used to classify the direction and strength of each recommendation.

These EASL CPGs on the management of HCC provides recommendations (strong or weak) based on the level of evidence (low, moderate, high) according to a simplified adaptation of the GRADE system[2] (Table 1).

Peer review

The final version of these CPGs was subject to peer review.

Update process

Because of the increasing number of publications, guidelines need to be continually updated to reflect the recent state of evidence. After 2023, these guidelines will expire. Should important changes occur in the meantime, such as newly available interventions, new important evidence or withdrawal of drug licensing, the information contained in the guidelines will be outdated earlier. In these cases, an update issue of the guidelines is needed earlier. EASL (cpg@easloffice.eu) will decide if an earlier initiation of an update is required.

Table 1. Level of Evidence and Grade of Recommendations (adapted from GRADE system).

Level of evidence*		Confidence in the evidence
High	Data derived from meta-analyses or systematic reviews or from (multiple) randomized trials with high quality.	Further research is unlikely to change our confidence in the estimate of benefit and risk.
Moderate	Data derived from a single RCT or multiple non-randomized studies.	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
Low	Small studies, retrospective observational studies, registries.	Any estimate of effect is uncertain.
Recommendations†		
Grade		**Wording associated with the grade of recommendation**
strong		"must", "should", or "EASL recommends"
weak		"can", "may", or "EASL suggests"

*Level was graded down if there is a poor quality, strong bias or inconsistency between studies; Level was graded up if there is a large effect size.
†Recommendations were reached by consensus of the panel and included the quality of evidence, presumed patient important outcomes and costs.

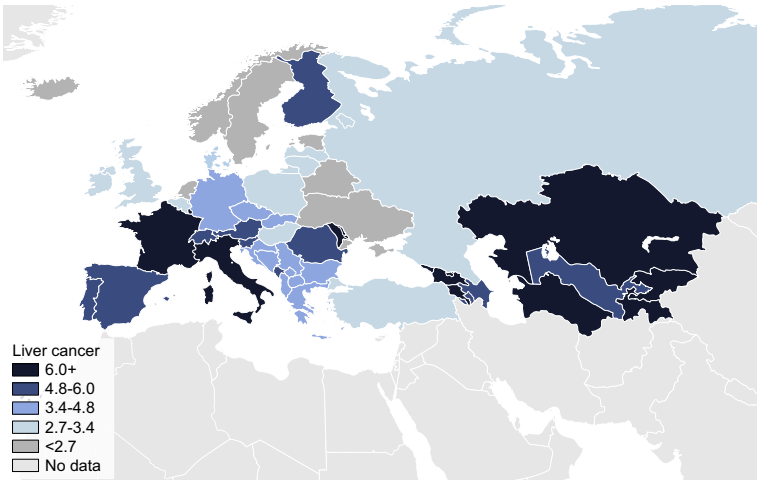
Epidemiology, risk factors and prevention

Recommendations

- The incidence of HCC is increasing both in Europe and worldwide; it is amongst the leading causes of cancer death globally (**evidence high**).
- Vaccination against hepatitis B reduces the risk of HCC and is recommended for all new-borns and high-risk groups (**evidence high; recommendation strong**).
- Governmental health agencies should implement policies to prevent HCV/HBV transmission, counteract chronic alcohol abuse, and encourage life styles that prevent obesity and metabolic syndrome (**evidence moderate; recommendation strong**).
- In general, chronic liver disease should be treated to avoid progression of liver disease (**evidence high; recommendation strong**).
- 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 HCC development (**evidence high; recommendation strong**).
- Once cirrhosis is established, antiviral therapy is beneficial in preventing cirrhosis progression and decompensation. Furthermore, successful antiviral therapy reduces but does not eliminate the risk of HCC development (**evidence moderate**). Antiviral therapies should follow the EASL guidelines for management of chronic hepatitis B and C infection.
- Patients with HCV-associated cirrhosis and HCC treated with curative intent, maintain a high rate of HCC recurrence even after subsequent DAA therapy resulting in sustained viral response. It is presently unclear whether this represents the inherent risk of HCC development in advanced cirrhosis, or if DAA therapy increases recurrence rates. Thus, further research is encouraged. Currently, close surveillance is advised in these patients. The benefit of viral cure must be weighed against a potentially higher recurrence risk (**evidence low; recommendation strong**).
- Coffee consumption has been shown to decrease the risk of HCC in patients with chronic liver disease. In these patients, coffee consumption should be encouraged (**evidence moderate; recommendation strong**).

Epidemiology

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally, with 854,000 new cases and 810,000 deaths per year, accounting for 7% of all cancers.[3] Hepatocellular carcinoma (HCC) represents about 90% of primary liver cancers and constitutes a major global health problem. The incidence of HCC increases progressively with advancing age in all populations, reaching a peak at 70 years.[4,5] In Chinese and black African populations the mean



Population numbers

Italy	10,733	The Netherlands	475
Germany	9,202	Croatia	466
France (metropolitan)	8,332	Republic of Moldova	448
Russian Federation	6,812	Slovakia	398
Spain	5,522	Belarus	327
United Kingdom	4,186	Bosnia Herzegovina	314
Romania	2,214	Denmark	311
Poland	1,998	Ireland	239
Ukraine	1,567	Slovenia	216
Greece	1,054	Norway	190
Portugal	1,004	Lithuania	175
Austria	955	Albania	171
Czech Republic	919	Latvia	154
Switzerland	811	FYR Macedonia	135
Serbia	799	Luxembourg	68
Belgium	645	Estonia	64
Bulgaria	640	Cyprus	56
Hungary	630	Montenegro	51
Finland	620	Malta	19
Sweden	490	Iceland	10

Fig. 1. Incidence rates of primary liver cancer according to geographical distribution in Europe. Total numbers per country and age-adjusted incidence rates per 100,000 of liver cancer in Europe in 2012. The colour intensity is proportional to the magnitude of incidence. Available from: http://globocan.iarc.fr. Data refer to all primary liver cancers (hepatocellular carcinoma, intrahepatic cholangiocarcinoma and liver cancer of mixed differentiation). Source: GLOBOCAN 2012, IARC -29.11.2017

age of patients with the tumour is appreciably younger. This is in sharp contrast to Japan, where the incidence of HCC is highest in the cohort of men aged 70 to 79 years.[6,7] HCC has a strong male preponderance, with a male to female ratio estimated to be 2–2.5:1.[8]

The pattern of HCC occurrence shows a significant geographical imbalance, with the highest incidence rates in East Asia (more than 50% of the cases occurring in China) and sub-Saharan Africa, together accounting for about 85% of all cases.[8] In Europe, the incidence is lower with the exception of Southern Europe, where the incidence in men (10.5 age-standardised incidence rates per 100,000) is significantly higher[9] (Fig. 1).

HCC incidence has been growing on a global scale. Between 1990 and 2015 newly diagnosed HCC cases increased by 75%, mainly due to changing age structures and population growth. Age-standardised incidence rates have increased in many high socio-demographic index countries like the USA, Canada, Australia, New Zealand and most European countries; conversely, some countries with high incidence rates like China and Eastern Sub-Saharan Africa have experienced a decrease by more than 20%.[3]

Annual incidence and mortality rates were 65,000 and 60,240 cases in Europe and 21,000 and 18,400 cases in the USA in 2008, respectively. It is estimated that by 2020 the number of cases will reach 78,000 and 27,000, respectively.[8] In Europe, hepatitis C virus (HCV) infection during 1940–60 and in the USA one decade later led to the current increase in HCC incidence. In Europe, the incidence and mortality rates reported are heterogeneous. During the last decades HCC mortality increased in males in most countries (*i.e.* Austria, Denmark, Germany, Greece, Ireland, Portugal, Norway, Spain, Switzerland, and United Kingdom), but decreased in some others (Finland, France, Italy, Netherlands, and Sweden).[9] In the USA, the rate of HCC deaths appears to have increased by about 40% from 1990 to 2004, in contrast to the overall rate of cancer deaths, which declined by about 18% during the same period.[10] This growth in incidence was due to the emergence of chronic liver disease, mainly chronic hepatitis C, but also to an increase in hepatitis B virus (HBV)-related HCC, particularly among immigrants from countries with endemic HBV infection, and the increasing incidence of non-alcoholic fatty liver disease (NAFLD). Projections of cancer incidence and deaths in the USA estimate that, in 2030, liver cancer will be the third leading cause of cancer-related deaths, surpassing breast, colorectal, and prostate cancers.[11,12] Conversely, in Japan, a country where the impact of HCV-related HCC was first noticed after World War II, a decline in HCC incidence has been noted for the first time since 1990.[6,7] Finally, the impact of universal infant vaccination against HBV has decreased the rate of HBV-related HCC in endemic countries, as reported for children and younger adults in Taiwan.[13,14]

Aetiology and risk factors

Approximately 90% of HCCs are associated with a known underlying aetiology[3] (Table 2), most frequently chronic viral hepatitis (B and C), alcohol intake and aflatoxin exposure. In Africa and East Asia, the largest attributable fraction is caused by hepatitis B (60%), whereas in the 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. However, these calculations are rough estimates which do not reflect co-morbidities and are likely to underestimate the impact of non-alcoholic steatohepatitis/metabolic syndrome.[3]

Cirrhosis is an important risk factor for HCC, and may be caused by chronic viral hepatitis, chronic alcohol abuse acquired and inherited metabolic diseases, such as NAFLD, as well as genetic haemochromatosis, or in some cases alpha-1-antitrypsin deficiency. All aetiologic forms of cirrhosis may be complicated by tumour formation, but the risk is higher in patients with chronic viral hepatitis. Overall, one-third of cirrhotic patients will develop HCC during their lifetime.[15] Long-term follow-up studies have found that approximately 1–8% of patients with cirrhosis develop HCC per year (*e.g.* 2% in HBV-infected cirrhotic patients and 3–8% in HCV-infected cirrhotic patients).[16] In general, features of liver disease severity (low platelet count of less than $100x10^9$/L, presence of oesophageal varices) in

Table 2. Geographical distribution of main risk factors for primary liver cancer world-wide.

	Alcohol (%)	HBV (%)	HCV (%)	Others (%)
Europe				
Western	32	13	44	10
Central	46	15	29	10
Eastern	53	15	24	8
North America	37	9	31	23
Andean Latin America	23	45	12	20
Asia				
East Asia	32	41	9	18
Asia-Pacific	18	22	55	6
South-East Asia	31	26	22	21
Africa				
North Africa, Middle East	13	27	44	16
Southern (sub-Saharan)	40	29	20	11
Western (sub-Saharan)	29	45	11	15

Contribution of hepatitis B, C, alcohol and other causes on absolute liver cancer deaths, both sexes, globally and by region 2015 (3). Data refer to all primary liver cancers (hepatocellular carcinoma, intrahepatic cholangiocarcinoma and liver cancer of mixed differentiation). HBV, hepatitis B virus; HCV, hepatitis C virus.

addition to older age and male gender correlate with development of HCC among patients with cirrhosis.[17] Recent studies have shown that liver cancer incidence increases in parallel to portal pressure, measured directly[18] or linked to the degree of liver stiffness as measured by transient elastography.[19–24]

Several studies have identified HBV-related factors as key predictors of HCC development in patients with chronic hepatitis B infection. Hepatitis B virus e antigen seropositivity,[25] high viral load,[26] and genotype C[27] are independent predictors of HCC development. In addition, hepatitis B viral load correlates with the risk of progression to cirrhosis.[28] Similarly, recent meta-analyses claimed that the risk of HCC development is increased in patients with HCV genotype 1b[29] or genotype 3.[30]

Dietary exposure to aflatoxin B1 is an important co-factor for HCC development in parts of Africa and Asia. Aflatoxin B1 exposure originates from fungal contaminations of staple foodstuffs preferentially in tropical and subtropical regions. Epidemiologic and molecular studies have shown a strong correlation between aflatoxin B1 exposure, *TP53* mutations (codon 249) and incidence of HCC, specifically in HBV-infected individuals.[31]

For patients with alcoholic liver cirrhosis, an increased risk of developing HCC has been reported for most parts of the world (with the exception of Northern Europe), including France[32] and Spain.[33] Regarding other risk factors, patients with haemochromatosis develop HCC in up to 45% of cases,[34] almost exclusively in stage III of the disease (cirrhosis).[35] HCC is more frequent in patients affected with acute hepatic porphyria[36] and porphyria cutanea tarda,[37] as well as being a well-documented complication of cirrhosis associated with alpha-1-antitrypsin deficiency.[38]

Growing evidence from retrospective investigations suggests an increased HCC incidence in patients with NAFLD associated with metabolic syndrome, diabetes,[39,40] and obesity.[41] Moreover, metabolic syndrome has an additive risk effect in those patients with chronic viral hepatitis.[42,43] Overall, NAFLD is becoming a relevant cause of HCC in developed regions[44–46] and it is estimated that in the USA between 500,000 and 900,000 new cases of HCC may develop as a result of the high prevalence of metabolic syndrome and NAFLD.[47] In NAFLD, the reported HCC incidence is very heterogeneous, ranging from 0.25% to 7.6%.[48] Furthermore, in a relevant proportion of patients, HCC develops in non-cirrhotic livers.[49,50] NAFLD may overlap with alcohol-related liver disease and future epidemiologic studies should address the relevance of this aspect of co-morbidity.[49] Epidemiologic evidence of a link between cigarette smoking and the occurrence of HCC was traditionally conflicting, but recent evidence supports that smoking is a significant co-factor.[51,52] The incidence of HCC is higher among patients with HIV infection than controls in the general population, and HIV appears to be an additive co-factor, increasing the risk of HCC in patients with chronic viral hepatitis.[53]

Prevention

Primary prevention of HCC can be achieved with universal vaccination against HBV infection.[14] Vaccination against hepatitis B is recommended by the World Health Organization for all newborns and high-risk groups.[54] 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-endemic countries (those with prevalence of hepatitis B surface antigen 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 endemic, injecting drug users, and people with multiple sex partners).

Antiviral treatment for patients with chronic hepatitis B and C infection should follow the recommendations of existing European Association for the Study of the Liver guidelines.[55,56] Pegylated interferon alfa, lamivudine, adefovir dipivoxil, entecavir, telbivudine, tenofovir disoproxil fumarate and tenofovir alafenamide are now available for HBV treatment, but long-term follow-up data assessing their efficacy in secondary prevention of HCC are only available for interferon, lamivudine entecavir, and tenofovir disoproxil fumarate treatment. Observational studies assessing the effect of interferon showed a potential effect in reduction of HCC incidence,[57] and long-term therapy with nucleotide or nucleoside analogues appears to favourably impact HCC incidence when data from randomised or matched controlled studies are considered.[58,59] After the first five years of entecavir or tenofovir disoproxil fumarate therapy, recent data suggest that HCC incidence is decreasing further, with the decrease more evident in patients with baseline cirrhosis.[60,61]

In hepatitis C viral infection, all-cause mortality and the risk of HCC is reduced among patients with HCV who achieve a sustained virological response (SVR) with interferon-based antiviral therapy.[62] Meta-analyses of interferon-based therapies showed a more than 70% reduction in HCC incidence (absolute risk reduction: 4.6%) after SVR,[63] independently of the grade of fibrosis. Patients with liver cirrhosis acquire a reduced HCC incidence after SVR, however, a relevant risk (<1.5% [0.3–2.4%]) remains.[64,65] Based on these data, SVR after HCV treatment leads to reduced HCC incidence, but surveillance of cirrhotic patients for HCC after SVR should be maintained as outlined below.[56,66] The advent of the new direct-acting antivirals (DAA) has been a major breakthrough because of their high efficacy, and their adequate safety profile which enabled their use in patients with advanced liver disease, in whom interferon-based regimens were not recommended. Based on previous studies assessing the benefits of interferon-based treatments, HCV eradication was expected to translate into a reduced incidence of *de novo* tumours in patients with HCV.

Furthermore, *recurrence* of HCC after initial anti-tumour treatment was also hoped to be reduced through HCV cure. However, some recent reports claimed that the HCC risk may remain higher in patients after DAA therapy than after interferon-based treatment. An alarm signal was released about a potentially increased risk of early tumour recurrence in successfully treated patients with HCC who received DAA therapy.[67,68] In addition, this appeared to be associated with a more aggressive tumour behaviour after therapy.[69] These observations were suggested to be related to the immune distortion associated with the rapid decrease in viral load, leading to changes in the inflammatory profile. This could translate into impaired immune surveillance, favouring the growth of already existing preclinical cancer clones. Another, more simplistic explanation could come from the broader spectrum of patients receiving antiviral therapy in the DAA era: more patients with a higher risk of developing HCC are treated, since DAA therapy can be offered to patients with more advanced liver disease who would not have been considered suitable for interferon treatment.

These studies led to several groups around the world publishing their experiences, but the limitations in several key aspects of the studies (retrospective assessment, absence of HCC screening, short follow-up and an excessive number lost to follow-up) impedes a robust conclusion.[70–76] Very recently, a meta-analysis concluded that there is no evidence that HCC occurrence or recurrence is different between patients receiving DAA or IFN therapy, but its strength is limited because of the inclusion of significantly heterogeneous studies without adequate follow-up for detecting HCC.[77] Another large retrospective cohort study of hepatitis C virus patients (n = 22,500) who were treated with DAA examining in the VA population demonstrated a reduction in the incidence of hepatocellular carcinoma in patients achieving a SVR.[78]

To adequately assess the risk of HCC recurrence/development, it is essential to determine if treated patients were properly screened for HCC before DAA initiation, how and for how long follow-up screening was performed and finally, if the incidence of HCC during follow-up was one of the endpoints of retrospective analysis.[79] Regrettably, in most of the previous studies these variables were not registered, limiting the strength of their conclusions. Therefore, further information about the HCC incidence after viral cure is still needed.

It is of great clinical relevance to point out that patients with HCV-associated cirrhosis and HCC treated with curative intent maintain a high rate of HCC recurrence even after subsequent DAA therapy. In these patients, close surveillance (tertiary prevention) is advised and the benefit of viral cure must be weighed against a potentially higher recurrence risk. The follow-up after HCC treatment with curative intent and subsequent successful DAA treatment implies 3–4-month imaging intervals for the first two years that can be extended to six-month intervals thereafter.

Numerous epidemiological studies have addressed the prevention of HCC in patients with chronic liver disease. Among these, only trials analysing the effect of coffee consumption have shown a consistently positive effect with regard to lowering HCC incidence. A large-scale population-based Japanese cohort study showed an association between coffee drinking and reduced risk of liver cancer. Individuals who consumed coffee on a daily basis had a lower HCC risk than those who almost never drank coffee (hazard ratio 0.49; 95% CI 0.36–0.66); this inverse association was confirmed in patients with chronic hepatitis C.[80] Similarly, a reduced HCC risk independent of its aetiology was found in Italy in a hospital-based case-control study[81] and confirmed in a meta-analysis of case-control studies and cohort studies from Japan and Southern Europe.[82,83] Recently, in the European Prospective Investigation into Cancer and Nutrition, a nested case-control study confirmed an inverse relationship between coffee intake and HCC (risk ratio of having four or more cups *vs.* less than two cups was 0.25; 95% CI 0.11–0.62).[84] The benefit of coffee consumption in liver disease is not limited to HCC; in the US Multi-ethnic Cohort (more than 215,000 people) high levels of coffee consumption were associated not only with reduced HCC incidence, but also with lower chronic liver disease mortality.[85] None of the studies have reported adverse hepatic effects of coffee consumption. Therefore, for the first time the panel has seen sufficient evidence to encourage patients with chronic liver diseases to drink coffee in order to decrease liver-related mortality and HCC development. A clear dose recommendation can currently not be given.

Surveillance

Recommendations

- Implementation of screening programmes to identify at-risk candidate populations should be improved. Such programmes are a public health goal, aiming to decrease HCC-related and overall liver-related deaths (**evidence low; recommendation strong**).
- Patients at high risk of developing HCC should be entered into surveillance programmes. Government health policy and research agencies should address these needs. Groups at high risk are depicted (Table 3) (**evidence moderate; recommendation strong**).
- The role of surveillance for patients with NAFLD without cirrhosis is unclear (**evidence low**).
- Surveillance should be performed by experienced personnel in all high-risk populations using abdominal ultrasound every six months (**evidence moderate; recommendation strong**)
- Tumour biomarkers for accurate early detection are still lacking. The data available show that the biomarkers tested (*i.e.* AFP, AFP-L3 and DCP) are suboptimal in terms of cost-effectiveness for routine surveillance of early HCC (**evidence low**).
- Patients on the waiting list for liver transplantation should be surveilled for HCC in order to detect and manage tumour occurrence or tumour response, and to help define priority policies for transplantation (**evidence low; recommendation strong**).

Surveillance consists of the periodic application of a diagnostic test to individuals at specific risk of 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 acceptability for the target population, and the availability of treatments and their effectiveness.[86] The

aim of surveillance is to obtain a reduction in disease-related mortality. This is usually achieved through a diagnosis of the disease at the early stage that, in turn, enhances the applicability and improves cost-effectiveness of therapies.

In the Western world, hepatocellular carcinoma (HCC) arises in a cirrhotic background in up to 90% of cases.[87] Cirrhosis not only hampers the application of tumour therapies, but it is itself a progressive disease that affects patient survival. A reduction in overall mortality represents the most appropriate endpoint to assess the efficacy of surveillance.

At present, there is insufficient evidence to modify the previously established definition of at-risk patients, but grey areas exist, requiring specific evidence. In particular, exact estimation of the HCC development risk in non-cirrhotic patients with non-alcoholic fatty liver disease (NAFLD) and in cirrhotic patients with long standing removal of the aetiological factors remains an unmet need, to be addressed by future research.

Ultrasound (US) is the method of choice and is often applied beyond HCC surveillance to monitor other conditions, such as the development of portal hypertension, including the onset of ascites or portal vein thrombosis, although its use in this setting has not been well defined.

Target populations

According to the general principles of surveillance, factors affecting the definition of the target population must consider the incidence of HCC in a specific set of patients and the probability that effective therapies, particularly radical ones, are suitable for these patients. Notably, in the setting of HCC, the incidence is higher in more advanced liver disease, but the probability of receiving radical (mainly surgical) therapies becomes lower, because of lower applicability of surgery, thus different incidence thresholds may apply to different target populations.

In fact, decision analysis and cost-effectiveness models suggest that an intervention is considered cost-effective if it provides life expectancy increases of at least three months with a cost below an established threshold. Conventionally the threshold adopted by most agencies in the last couple of decades has been US $50,000 per year of life saved,[88] although either slightly lower (£30,000) or significantly higher levels (up to $150,000) have been proposed to account for inflation, specific national healthcare resources and other factors.[89,90]

Cirrhotic patients

Cost-effectiveness studies indicate that an incidence of 1.5%/year or greater would warrant surveillance of HCC in cirrhotic patients,[91] irrespective of its aetiology.[92,93] However, the presence of cirrhosis with advanced liver failure (Child-Pugh class C) or decompensation in the Child-Pugh class B (with large ascites, hepato-renal syndrome or clinical jaundice) prevents effective HCC therapies from being employed when transplantation is not an option. Accordingly, surveillance for HCC is not cost-effective in these patients,[94] but must instead be carried out for patients on the waiting list for transplantation for cirrhosis, as HCC onset may modify both priority on the list and transplantability. Finally, although it seems intuitive that surveillance might not be cost-effective above a certain age cut-off, the lack of data prevents adoption of any specific recommendation: therefore, patients' conditions and the consequently estimated life expectancy should support the choice, rather than age alone.

Non-cirrhotic individuals

Patients with chronic hepatitis B virus (HBV) infection are at risk of HCC development even in the absence of cirrhosis, but the exact degree of risk is ill-defined and appears influenced by geographical region (higher in Asia and Africa than in Western Countries,[95,96] higher levels of HBV replication,[97,98] age and gender (males higher than female). These patients are at higher risk than the general population and at lower than patients with established HBV cirrhosis, but they are also more suitable for surgical treatments. Thus, cost-benefit modelling is needed in this scenario and expert opinion indicates that surveillance would be warranted if HCC incidence is at least 0.2%/year.[92,93,99] Therefore, even though regular six-month surveillance may not be indicated at initial observation, it may be recommended at a later time. Therefore, such patients should be regularly reassessed even though standard surveillance is not yet warranted. Additionally, fibrosis tends to progress to cirrhosis over time in untreated patients, but may benefit instead from antiviral therapies leaving a potential space of uncertainty in deciding upon start and continuation of surveillance and further claiming for HCC risk stratification.[99] Therefore, some prognostic models have been proposed to assess the risk of developing HCC, but none of the studies have universal applicability. Concerning immigrants to Europe from areas where HBV is endemic an individual risk assessment is required as the impact of migration on HCC risk has not been thoroughly investigated.

Patients with chronic hepatitis C and bridging fibrosis in the absence of cirrhosis (Metavir F3) are also at risk of being understaged and thus at significant risk of HCC.[17] Additionally, the fact that the transition from advanced fibrosis and cirrhosis cannot be accurately defined, led the European Association for the Study of the Liver to recommend surveillance for patients with bridging fibrosis. This panel continues to endorse such a policy. In this respect, transient elastography appears to be a promising tool that is able to stratify patients with active viral replication at different HCC risks.[19–24]

Information about the incidence of HCC in patients with non-viral chronic liver disease without cirrhosis, such as alcoholic and non-alcoholic steatohepatitis (NASH), autoimmune liver disease, genetic haemochromatosis, alpha-1-antitrypsin deficiency, and Wilson's disease is limited.[34–38] However, available evidence suggests that HCC usually arises in these contexts once cirrhosis is established.[87]

It is estimated that half of the cases of NASH-induced HCC arise in non-cirrhotic patients.[50,100] However, the incidence of HCC in these non-advanced patients is expected to be insufficiently high to deserve universal surveillance, given the large prevalence of NAFLD in the general population. However, it is important that patients at risk in the future are identified, in order to categorise those who should be screened for HCC. The obesity of these patients is another challenge, as it makes US screening more difficult. Radiological methods, such as computed tomography (CT) scans or magnetic resonance imaging (MRI), are available, but the surveillance programme would no longer be cost-effective. There is a clear need to prospectively acquire information on cohorts of patients with NASH, in order to define high-risk patients who should undergo surveillance.[101] Moreover, such patients are also more prone to obesity and cardiovascular disease, which may hamper a surgical approach. Therefore, no evidence-based recommendation about imple-

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

- Cirrhotic patients, Child-Pugh stage A and B **(evidence low; recommendation strong)**
- Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation (**evidence low; recommendation strong**)
- Non-cirrhotic HBV patients at intermediate or high risk of HCC* (according to PAGE-B† classes for Caucasian subjects, respectively 10–17 and ≥18 score points) (**evidence low; recommendation weak**)
- Non-cirrhotic F3 patients, regardless of aetiology may be considered for surveillance based on an individual risk assessment (**evidence low; recommendation weak**)

*Patients at low HCC risk left untreated for HBV and without regular six months surveillance must be reassessed at least yearly to verify progression of HCC risk.
†PAGE-B (Platelet, Age, Gender, hepatitis B) score is based on decade of age (16–29 = 0, 30–39 = 2, 40–49 = 4, 50–59 = 6, 60–69 = 8, ≥70 = 10), gender (M = 6, F = 0) and platelet count (≥200,000/μl = 0, 100,000–199,999/μl = 1, <100,000/μl = 2): a total sum of ≤9 is considered at low risk of HCC (almost 0% HCC at five years) a score of 10–17 at intermediate risk (3% incidence HCC at five years) and ≥18 is at high risk (17% HCC at five years).[114]

mentation of surveillance programmes in this setting can be made.

Some factors are associated with a higher risk of severe/fibrosis cirrhosis and HCC occurrence, such as the presence of diabetes mellitus, older age[102] and concurrent alcohol intake.[103] Furthermore, simple laboratory scores help identify patients at greater risk of severe fibrosis warranting more in-depth assessment. Studies of genetic factors suggested the PNPLA3 148 M variant at rs738409 to be associated with HCC development in obese individuals[104] and in patients with histologically proven NAFLD.[105] Whether a combination of these or other parameters may identify individuals at a risk of HCC high enough to deserve specific surveillance is still a matter of investigation. To summarise, patients with metabolic syndrome or NASH identified to be affected by severe fibrosis or cirrhosis either by histology or elastography should undergo surveillance,[106] in keeping with the general recommendation reported above, whereas the risk of HCC development is insufficiently established in individuals without severe fibrosis/cirrhosis to deserver universal surveillance for HCC.

Treated viral chronic hepatitis

Recent advances in therapy have led to relatively high rates of viral clearance or suppression among those being treated for chronic hepatitis B or C. Successful treatment leading to sustained virological response (SVR) in chronic hepatitis C, and hepatitis B e antigen seroconversion or sustained HBV-DNA suppression in chronic hepatitis B, decreases, but does not eliminate the risk of HCC.[58,63,107,108] Surveillance should be offered to treated patients with chronic hepatitis B who remain at risk of HCC development because of baseline factors, or those with hepatitis C virus (HCV)-induced advanced fibrosis or cirrhosis, even after achieving SVR. The value of shear wave elastography to identify patients with chronic hepatitis at greater risk of HCC has been proven in replicating HCV, but has been insufficiently validated in patients who achieved SVR after HCV eradication. In particular, the stiffness thresholds associated with sustained higher risk of HCC development, after achieving SVR with PegIFN-based therapies, ranged from 6.5 to 12.0 kPa.[109–111] Therefore, given the current knowledge there is no evidence for a timing or stiffness threshold to stop surveillance in patients who were included in surveillance programmes prior to interferon-based anti-HCV therapy. There is even less information in patients achieving SVR after direct-acting antiviral (DAA) therapies, therefore, there is no evidence to change the indication for surveillance. The limited data produced so far showed that HCC occurrence is not eliminated in patients at risk, at least in the short/mid-term after SVR of HCV with DAA, mandating continued surveillance.[68,112–114]

In connection with patients infected with HBV, one HCC risk stratification model includes also specific stratification of risks in Caucasian patients respectively starting nucleos(t)ide analogues (NUC) antiviral therapy or continuing long-term treatment beyond five years.[60,115] Data showed that Caucasian patients with cirrhosis at the time of initiating NUC therapy benefit from a decrease in HCC yearly incidence between the first five and second five years of treatment, specifically from 3.22% to 1.57%.[60] However, even the latter incidence remains higher than the recommended threshold for receiving surveillance. Therefore, these data confirm that surveillance is to be maintained in patients infected with HBV who have reached the stage of cirrhosis for no less than 10 years, regardless of receiving effective antiviral treatment. In connection with NUC-treated non-cirrhotic patients, the global incidence rate of HCC was shown to be lower than in cirrhotic patients, as expected,[60,115] but does not appear to decrease overall after five years of therapy (0.49% in the first five years *vs.* 0.47% in years 5 to 10),[60] remaining slightly higher than the recommended threshold for initiating HCC surveillance. However, this global incidence of HCC, only slightly higher than the surveillance threshold, can be further stratified into at least three different patient groups in Caucasian individuals (low, intermediate, high risk of HCC) according to the PAGE-B classification.[115] Patients in the low HCC risk class (PAGE-B score ≤9, Table 3), which represent about one-fourth of large case series of patients infected with HBV[115] hardly developed HCC up to 10 years after starting NUC[60,115] and therefore do not overcome the 0.2%/y threshold for starting surveillance. The PAGE-B score has not yet been validated in Asia, but other scores have been produced in this geographical region, such as the GAG-HCC,[116] CUHCC[116] and REACH-B[117] systems, which tend to include similar prognostic variables as the PAGE-B, but whose validation appeared suboptimal in Caucasian patients. Hence, only locally produced HCC risk stratification scores in HBV are to be applied in specific geographical regions, to reliably avoid surveillance treated HBV non-cirrhotic patients at low risk of HCC.[99]

Surveillance tests

Tests that can be used in HCC surveillance include serological and imaging examinations. The imaging test most widely used for surveillance is US, which has an acceptable diagnostic accuracy when used as a surveillance test (sensitivity ranging from 58 to 89%; specificity greater than 90%).[118] A meta-analysis including 19 studies showed that US surveillance detected the majority of HCC tumours 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%.[119]

The widespread popularity of US also relies on the absence of risks, non-invasiveness, good acceptance by patients and relatively moderate cost, and its capacity to detect the onset of other complications of cirrhosis early, such as subclinical ascites or portal vein thrombosis, which may also require prompt treatment. Nonetheless, US detection of HCC on a cirrhotic

background is a challenging issue, particularly in the instance of very coarse liver echotexture on US, which may impair identification of small tumours. 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 is recommended. The use of pure blood pool US contrast agents (commonly utilised in Europe) has not proven to increase the ability of US to detect small HCC tumours.[120]

Multidetector CT or dynamic MR imaging are not cost-effective for surveillance in general, because of the considerable rate of false-positive findings and the need to use contrast agents to achieve adequate sensitivity.[121] 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 also be 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 the high cost of MR and the need for contrast injection with the associated risks of allergic reaction and the recent reported brain accumulation of gadolinium[122] make their use in long-term surveillance highly debatable.

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.[123–125] 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.[126] Notably, AFP has mostly been 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 randomised study[127] and one population-based observational study[128] reached opposite results. The latter study provides a rationale for testing AFP in special populations or healthcare environments when US is not readily available.[128] However, when combined with US, AFP levels are only able to provide additional detection in 6–8% of cases not previously identified by US, also confirmed more recently.[129] 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.[130] Secondly, only a small proportion of tumours at an early stage (10–20%) present with abnormal AFP serum levels, a fact that has recently been correlated with a molecular subclass of aggressive HCCs (S2 class, EpCAM positive).[131–133] 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.[134] However, such information was mostly obtained in viraemic patients, in whom active hepatitis may act as a confounding factor. When such a factor is removed by pharmacological treatment, the diagnostic accuracy of AFP significantly increased because of the reduction of false-positive cases at lower AFP thresholds (as low as 12–20 ng/ml)[135–139] Despite great interest in these results suggesting a potential for AFP at least in this setting, there is still insufficient evidence to calculate the cost-effectiveness of AFP in the surveillance of patients with hepatitis B virus at risk of HCC in Western countries and whether this oncomarker has any additional role and impact on survival in comparison to US alone. Hence, research efforts to this end are highly warranted. Similar analyses have not yet been provided for patients with hepatitis C virus, because of the very recent introduction of direct-acting antivirals able to effectively eradicate HCV in large populations of cirrhotic patients.

Specific evidence about the utility of AFP for early tumour detection when used to complement US surveillance in patients with unsatisfactory liver US explorability does not exist and thus no recommendation can be made.

All other serum markers have usually been evaluated, alone or in combination, in a diagnostic or prognostic, 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.[140] In addition, DCP levels have been associated with portal vein invasion and advanced tumoural stage, a fact that prevents the usage of this marker for early detection.[141] A similar situation occurs with AFP-L3 fraction levels.[142] At present, none of these tests can be recommended for surveillance of patients at risk of developing *de novo* HCC.

In conclusion, US can be seen as the most appropriate test to perform surveillance. The combination with AFP is not recommended in patients with active liver inflammation, as the 6–8% gain in the detection rate does not counterbalance the increase in false-positive results, ultimately leading to an approximately 80% increase in the cost of each small HCC diagnosed.[119,143] It is worth remarking that insufficient data are available regarding the diagnostic accuracy of AFP in patients with adequate treatment of the aetiological cause of liver disease (effective antivirals, abstinence from alcohol, *etc.*), making any calculation of the cost-effectiveness impossible to date.

Surveillance efficacy

Only one randomised controlled trial was published on HCC surveillance with US. This was a population-based study with cluster randomisation (randomising entire villages) comparing US and AFP measurements every six months *vs.* no surveillance in a population of Chinese patients with chronic hepatitis B infection regardless of the presence of cirrhosis.[144] Despite suboptimal adherence to the surveillance programme (55%), HCC-related mortality was reduced by 37% in the surveillance arm because of increased applicability of resection in detected cases.

Other types of evidence include population and non-population-based cohorts and cost-effectiveness analysis which mostly reinforce the benefits of regular US schemes.[94,119,145–151] However, these studies are heterogeneous as far as stage and aetiology of liver disease, and surveillance protocols. Moreover, almost all suffer from methodological biases such as lead-time bias (apparent improvement of survival because of an anticipated diagnosis) and length time bias (over-representation of slower-growing tumours). While the latter is unavoidable in this type of study, lead-time bias can be minimised using correction formulas. Nonetheless, in a recent retrospective case-control study from Italy, lead-time bias accounted for most of the surveillance benefit, but only until the third year of follow-up after HCC diagnosis.[152] Moreover, after

lead-time adjustment, estimated in 6.5 months, semi-annual surveillance maintained a survival benefit over symptomatic diagnosis.[152]

Surveillance interval

The ideal interval of surveillance for HCC should be dictated by two main features: rate of tumour growth up to the limit of its detectability, and tumour incidence in the target population. Based on the available knowledge on mean HCC volume doubling time;[145,146,148] a six-month interval represents a reasonable choice, since a shorter interval of three months did not translate into any clinical benefit[149] and a longer interval of 12 months appears cost-effective, but with fewer early-stage HCC diagnoses[153] and shorter survival.[150]

Finally, cost-effectiveness studies have shown that semi-annual US-based surveillance improves quality-adjusted life expectancy at a reasonable cost.[154] In light of available knowledge, a six-month scheduled surveillance is the preferable choice. Further trials in this setting would be difficult to implement.

Diagnosis

Recommendations

- Diagnosis of HCC in cirrhotic patients should be based on non-invasive criteria and/or pathology (**evidence high; recommendation strong**).
- In non-cirrhotic patients, diagnosis of HCC should be confirmed by pathology (**evidence moderate; recommendation strong**).
- Pathological diagnosis of HCC should be based on the International Consensus recommendations using the required histological and immunohistological analyses (**evidence high; recommendation strong**).
- Non-invasive criteria can only be applied to cirrhotic patients for nodule(s) ≥1 cm, in light of the high pre-test probability and are based on imaging techniques obtained by multiphasic CT, dynamic contrast-enhanced MRI (**evidence high; recommendation strong**) or CEUS (**evidence moderate; recommendation weak**). Diagnosis is based on the identification of the typical hallmarks of HCC, which differ according to imaging techniques or contrast agents (APHE with washout in the portal venous or delayed phases on CT and MRI using extracellular contrast agents or gadobenate dimeglumine, APHE with washout in the portal venous phase on MRI using gadoxetic acid, APHE with late-onset (>60 s) washout of mild intensity on CEUS).
- Because of their higher sensitivity and the analysis of the whole liver, CT or MRI should be used first (**evidence high; recommendation strong**).
- FDG PET-scan is not recommended for early diagnosis of HCC because of the high rate of false negative cases (**evidence low; recommendation strong**).

Imaging-based diagnosis

Imaging is an essential part of hepatocellular carcinoma (HCC) diagnosis, contributing to primary liver tumour typing and HCC staging. Non-invasive imaging diagnosis of HCC in the setting of a cirrhotic liver was accepted in 2001, when dynamic imaging explorations demonstrated the typical diagnostic pattern[155] (updated in 2005[156]). Imaging-based diagnosis relies on the peculiar vascular derangement occurring during hepatic carcinogenesis[157] and of the high pre-test probability of HCC in the setting of cirrhosis,[158–161] although the frequency of intrahepatic cholangiocarcinoma (CC) and combined HCC/CC is also increased in cirrhosis.[162] The higher pre-test probability is also the reason why a non-invasive diagnosis is only accepted by the European Association for the Study of the Liver (EASL) in cirrhotic patients, appreciating that there are non-cirrhotic patients at significant risk of developing HCC. Contrast-enhanced imaging methods are necessary for the diagnosis of HCC and are based on vascular phases (lesion appearance in the late arterial phase, in the portal venous phase, and in the delayed phase).[159,161,163] The typical hallmark is the combination of hypervascularity in late arterial phase (defined as arterial phase hyperenhancement [APHE] according to LI-RADS [Liver Imaging Reporting and Data System] classification) and washout on portal venous and/or delayed phases, which reflects the vascular derangement occurring during hepatocarcinogenesis.[157] The previous EASL-European Organisation for Research and Treatment of Cancer (EORTC) guidelines have raised concerns focussed particularly on two aspects of HCC diagnosis: the diagnostic criteria according to tumour size and the imaging modality. As studies have shown a dramatic drop in sensitivity when two coincidental imaging techniques were required in HCCs between 10 and 20 mm,[159] the 2012 EASL-EORTC guidelines have proposed one conclusive imaging in centres of excellence with high-end radiological equipment. In these centres, the use of a sequential algorithm maintained high specificity while increasing the sensitivity for nodules of 1–2 cm.[161] Concerning the contrast-enhanced imaging techniques, only multiphasic computed tomography (CT) and magnetic resonance imaging (MRI) were recommended. As the biodistribution of the ultrasound (US) contrast agent available in Europe (confined to the intravascular space) differs from the iodinated contrast-CT and extracellular gadolinium-based MRI contrast agent, tumours other than HCC (such as cholangiocarcinoma) may display homogeneous contrast enhancement in the arterial phase followed by washout on contrast-enhanced US (CEUS).[164,165]

Diagnostic performance of CT and MRI

Since the previous EASL/EORTC guidelines, many studies and several meta-analyses have assessed the diagnostic performance of multiphasic contrast-enhanced CT and MRI.[166–168] In most studies, there was a trend towards higher sensitivity of MRI compared to CT, with specificity ranging between 85% and 100%.[167] Indeed, results vary according to HCC size, with MRI performing better than CT particularly in small lesions (sensitivity of 48% and 62% for CT and MRI, respectively, in tumours smaller than 20 mm *vs.* 92% and 95% for CT and MRI, respectively, in tumours equal or larger than 20 mm).[168] Sensitivities are even lower when explanted liver is used as the reference standard and in prospective studies.[168] A recent prospective multicentric study, including 381 patients with

544 nodules, shows a sensitivity and specificity of 72.3% and 89.4% for MRI using extracellular contrast agents, and 71.6% and 93.6% for CT in lesions between 20–30 mm, respectively.[169] In lesions of 10–20 mm size, sensitivities and specificities were 70.6% and 83.2% for MRI using extracellular contrast agents, and 67.9% and 76.8% for CT, respectively.[169] In lesions of 10–20 mm in size, the combination of CT and MRI had a specificity of 100%, but a sensitivity of 55.1%.[169] These results reinforce the imaging hallmark for the non-invasive diagnosis of HCC, with a slight decrease in specificity for small nodules with either CT or MRI. These results do not support the use of coincidental imaging in small lesions.

Many other imaging findings have been described in HCCs at CT and at MRI and occur more commonly in HCCs than in regenerative or dysplastic nodules: hyperintensity on T2-weighted MRI, hyperintensity on diffusion-weighted MRI, intra-lesional fat, lesional iron sparing, corona enhancement, presence of capsule, mosaic architecture, nodule-in-nodule architecture, intralesional haemorrhage.[170] Indeed, they increase the likelihood of a lesion being an HCC. However, they do not have a specificity approaching 100% and therefore do not allow a conclusive diagnosis of HCC.

Comparison of CT *vs.* contrast-enhanced MRI using hepatobiliary contrast agents

Multiple studies have compared the diagnostic performance of multiphasic CT with gadoxetic acid-enhanced MRI.[171–179] They have all shown gadoxetic acid-enhanced MRI to have higher sensitivity than multiphasic CT and similar specificity, the difference being significant in small lesions.[166,180–182] Only one prospective study compared multiphasic CT with gadobenate dimeglumine-enhanced MRI using dynamic and dynamic plus hepatobiliary phases.[183] Here, dynamic plus hepatobiliary phase MRI had a higher sensitivity and negative predictive value than multiphasic CT and dynamic phase MRI alone.

Comparison between extracellular MR agents and gadoxetic acid or gadobenate dimeglumine

Large prospective comparisons of diagnostic performance for HCC between extracellular MRI and either gadoxetic-enhanced MRI or gadobenate dimeglumine MRI are missing.[184] Several meta-analyses have looked at the sensitivity of MRI using extracellular or hepatobiliary contrast agents (gadoxetic acid or gadobenate dimeglumine).[166,168,185] All have found MRI using hepatobiliary contrast agents to be associated with higher sensitivity than with extracellular agents, particularly in small HCCs, but large, prospective, head-to-head comparative studies are still lacking.

Specific issue with gadoxetic-enhanced MRI

Gadoxetic acid is unique in that approximately 50% of the administrated dose is taken up by the hepatocytes and excreted into the bile ducts, while the other half is excreted by the kidneys, allowing for functional evaluation of the hepatocytes. Such biokinetics have several consequences for diagnostic issues: firstly, the classically late dynamic phase obtained at 3 min should be renamed the transitional phase, as signal intensity is a combination of extracellular and hepatocellular concentrations and lesion hypo-intensity on that phase is not synonymous with a washout; secondly, hypo-intensity on hepatobiliary phase is related to a decrease in membrane transporters and is again not a washout phenomenon. Therefore, on gadoxetic acid-enhanced MRI, washout can only be diagnosed on portal venous phase and hypo-intensity on hepatobiliary phase is regarded as an ancillary finding favouring malignancy, either primary or secondary. As most HCCs (80%–90%) are hypo-intense in the hepatobiliary phase, this feature may contribute to the differentiation of HCC from benign nodules developed on chronic liver diseases.[186,187] When hypo-intensity on the transitional phase and/or the hepatobiliary phase is used as an alternative to washout, the sensitivity for diagnosis of HCC is increased, but unfortunately the specificity is decreased.[168,188–191] Remarkably, gadoxetic acid-enhanced MRI has advantages over extracellular contrast agents. Despite the lower specificity for HCC diagnosis, gadoxetic acid-enhanced MRI has a higher sensitivity for detecting nodules that are either HCC not displaying the typical features of imaging hallmarks or high-grade dysplastic nodules. This increased sensitivity for detecting lesions/HCCs may be of particular value in patients thought to harbour single HCC, finally improving patient management. The increased sensitivity in lesion detection was reported to translate into a reduction in the risk of disease recurrence.[192] Lesion signal intensity on hepatobiliary phase is also a prognostic factor.[193] Lastly, non-hypervascular, non-HCC nodules that are hypo-intense on hepatobiliary phase have a higher risk of progression to typical HCC than iso- or hyper-intense nodules.[194] Regrettably, most data about the usefulness of gadoxetic acid come from Eastern countries, where most HCCs arise in patients chronically infected with hepatitis B virus, with relatively well-preserved liver function. Confirmatory studies in the West including more advanced liver disease secondary to alcohol abuse, NAFLD and hepatitis C virus infection are awaited.

The injection of gadoxetic acid was claimed to be associated with an increased risk of transient respiratory motion artefacts in the arterial phase that could reduce image quality. The presence of such artefacts has been reported in a wide range of patients depending on the case series (from 2.4% to 18%).[195–197] Whether these artefacts hamper the detection of lesion vascularity on arterial phase has not been not clearly established yet.

Contrast-enhanced ultrasound

The usage of CEUS was questioned in the previous EASL guideline because of the potential risk of misdiagnosis in the instance of CC, which appeared to occur at a rate of 2–5% of all new nodules in cirrhosis.[164,165,198] Indeed, the pattern of global APHE followed by washout at CEUS is not specific for HCC and occurs in about 50% of mass-forming CC in cirrhosis, leading to a risk of misdiagnosis of around 1% of nodules arising in cirrhosis.[164,165] However, following these reports, subsequent studies demonstrated that the onset of washout takes place earlier than 60 s after contrast injection in the vast majority of CCs (50 to 85%),[199–204] while this is rarely observed in HCC, and that the intensity of washout in the portal phase is more marked in CC than in HCC.[205] This has led to a refinement of the definition of the typical hallmark for HCC at CEUS, which therefore would be APHE followed by late (>60 s) washout of mild degree.[206,207] This definition improves the capacity of CEUS to identify malignant lesions such as CC (which are often not identified as definitively malignant by CT and MRI using the conventional vascular criteria.[208–210] This new CEUS criteria for HCC has already been adopted in Italy (Italian Association for the Study of the Liver[211] and by the American

College of Radiology in the USA.[206,212] A very recent large retrospective study in more than 1,000 lesions in cirrhosis, showed this new definition of the typical HCC pattern (corresponding to the LR5 classification according to LI-RADS for CEUS) has a positive predictive value for HCC of almost 99% (higher than the one achieved using the previous EASL and American Association for the Study of Liver Diseases (AASLD) criteria, corresponding to 94%) and positive likelihood ratio of 15.5, with no case of misdiagnosis with intrahepatic CC.[198] Such improvement in diagnostic capacity was associated with only a slight decrease in sensitivity in comparison to the previous EASL and AASLD criteria (from 67% to 62%).[198] Furthermore, in a recent prospective multicentric study, in the 10–20 mm nodules, CEUS had a specificity of 92.9% *vs.* 76.8% and 83.2% for CT and MRI, respectively.[169] Also, in the 10–20 mm nodules, the positive likelihood ratio of CEUS for diagnosing HCC was 5.6 while it was 2.9 and 4.2 with CT and MRI, respectively.[169] Finally, after a first inconclusive CT or MRI, CEUS as a second imaging technique had the highest specificity with only a slight drop in sensitivity for the 10–20 mm nodules and the highest sensitivity and specificity for 20–30 mm nodules.[169] However, when CEUS is compared with either CT or MRI, its sensitivity is significantly lower, especially in nodules of 10 to 20 mm because of a lower detection rate of washout than with CT or MRI.[159,213–215] Accordingly, CEUS can be effectively utilised to characterise lesions in cirrhosis. However, CEUS with pure blood pool contrast agents, such as those containing sulfur hexafluoride or octafluoropropane with a phospholipid shell, utilised in Europe and North America for liver investigations, is not a panoramic technique, because the arterial phase is too short to allow adequate exploration of the entire liver and deeply seated lesions may be difficult to visualise. Consequently, it was reported to miss around 13% of HCC visible on CT or MRI.[213] CEUS, can be utilised to characterise one or very few nodules visible at conventional baseline US. CEUS also suffers from the difficulty of reviewing images acquired in another centre, unlike CT or MRI. Furthermore, it is not recommended as a first-line imaging technique or for recall strategies in terms of cost-effectiveness, because CT or MRI will be needed for staging, but it can be utilised when both CT and MRI are contraindicated or are inconclusive for the HCC diagnosis.[214,215] Notably, if MR or CT suggest a malignant lesion other than HCC, this panel recommends obtaining a pathological confirmation.

Lesion size

The radiological hallmarks of HCC only occur in a minority of patients with small tumours (<2 cm),[216] regardless of which imaging modality is utilised. HCC not showing APHE on imaging cannot be regarded as less aggressive than typical HCC.[217] Therefore, postponing other diagnostic modalities to the expected six-month surveillance interval, after a first inconclusive imaging technique, without attempting to reach a definitive diagnosis is contraindicated, even in very small lesions. Delaying a definitive diagnosis of a suspicious lesion until it exceeds 2 cm in diameter leads to increased treatment failures or recurrences, regardless of whether the lesion is ablated or resected,[218] since the development of satellite nodules and microscopic vascular invasion increases exponentially beyond this size cut-off.[219] Therefore, it is crucial to provide reliable diagnostic tools for a final diagnosis below the size of 2 cm.

Although nodules <10 mm should not prompt the start of the recall strategy, they may be found on imaging performed for other nodules ≥10 mm in size. When these small nodules do not display the typical imaging hallmarks of HCC, their presence should not affect the treatment strategy planned, although they cannot be ignored in the case of surgical resection or ablative treatment. The optimal management for nodules <1 cm showing the typical HCC pattern has not yet been clarified. According to the LI-RADS classification, which endorses a conservative approach, a definitive diagnosis of HCC cannot be established, but they must be considered as probable HCC.[220] A clear recommendation cannot be given and the EASL panel recommends local multidisciplinary board discussion for the management of patients found to host such tiny apparently typical lesions.

Despite advances in contrast-enhanced imaging and particularly MRI, at present, the EASL panel does not endorse imaging options to predict any diagnosis apart from definitive HCC (*e.g.* low-/high-grade dysplastic nodule or large regenerative nodules, *etc.*). In connection with this issue, the EASL panel highlights that the diagnosis of HCC using the ACR LI-RADS system[220] differs from the EASL guidelines when CT or MRI are considered. The LI-RADS system also integrates the use of imaging features not related to tumour enhancement, such as the presence of tumour capsule or significant tumour growth over time, which have not been prospectively validated and are not accepted by EASL. Conversely, the diagnosis of HCC by CEUS is coincident when using the current EASL or LI-RADS criteria. Additionally, the LR2, LR3 and LR4 LI-RADS classes might be helpful to further stratify the risk of HCC in individual nodules (corresponding respectively to low, intermediate or high probability of HCC), but none of these classes rule out the presence of HCC,[221] thus a biopsy should be performed whenever technically feasible, at least in the dominant nodule. One interesting aspect of the LI-RADS system is the standardisation of the reporting and data collection of imaging techniques that improves communication and understanding between imaging operators and clinicians. Further efforts are warranted to adopt standardised and unique definitions worldwide for the diagnosis of HCC[207] and to harmonise different systems.

Characterisation of portal vein thrombosis

Macrovascular invasion (mostly observed in the portal vein) is a major prognostic factor frequently seen in large HCC, but sometimes present in oligo-nodular small HCC as well. Cirrhotic patients also tend to develop portal vein thrombosis, with a yearly incidence as high as 16% in Child-Pugh B-C patients.[222] Therefore, portal vein thrombosis may also complicate diagnosis of cirrhotic livers harbouring HCC, causing a burning diagnostic challenge to differentiate portal vein thrombosis from tumour portal vein invasion, which has prognostic and therapeutic implications.

Contrast-enhanced imaging techniques can distinguish portal vein thrombosis from tumourous portal vein invasion with high accuracy. Two imaging findings are quite specific for tumour portal invasion: presence of APHE and high signal intensity within the obstructed vessel on diffusion-weighted MRI with high b-values.[223–226]

Value of FDG-PET in HCC diagnosis

HCC is not a very avid tumour for FDG-PET as uptake is observed in less than 40% of the cases,[227] and most well differentiated HCCs are ^{18}F-FDG PET negative. Some other tracers

have been suggested such as ^{11}C-choline. However, the overall detection rate of PET/CT with these tracers cannot compare with contrast-enhanced CT and MRI.[228] Yet, uptake on ^{18}F-FDG-PET seems to be of potential prognostic value. It is associated with poor prognosis, increased serum alpha-fetoprotein and vascular invasion. Therefore, it may facilitate the selection of patients for surgical resection or liver transplantation.[229,230]

Diagnosis of HCC in a non-cirrhotic liver

Imaging features of HCC developing in a non-cirrhotic liver are not different from those in cirrhosis. HCC in non-cirrhotic livers tend to be larger at diagnosis as patients are not enrolled in surveillance programmes. Yet, the specificity of the imaging hallmarks (AHPE and washout on portal venous and/or delayed phases) is lower than in cirrhosis as alternative diagnoses are seen more commonly (*e.g.* hepatocellular adenoma, and hypervascular metastases). Therefore, the diagnosis of HCC requires pathologic proof in non-cirrhotic livers.

Pathological diagnosis

As classification of liver cancer is based on morphological parameters, pathohistological diagnosis is the gold standard in defining HCC and its differential diagnoses. Pathohistological diagnosis of HCC is based on the criteria of the World Health Organization (WHO) classification[231] and the International Consensus Group for Hepatocellular Neoplasia.[232] Morphological staging of HCC in resection and transplantation specimens relies on accurate macroscopic and histological assessment of the tumourous lesions and has to be performed according to the valid TNM-classification including resection margin assessment.[233] Usually grading of the tumour is provided, although there is no worldwide uniform agreement on which grading scheme to use and data on the independent prognostic value of grading in HCC are inconclusive.

Pathologic differential diagnostic assessment of focal liver lesions in cirrhosis includes distinction of HCC from other primary (intrahepatic cholangiocarcinoma, combined HCC/CC) and secondary malignancies of the liver (especially neuroendocrine tumours, squamous cell carcinoma metastases, lung cancer metastases). Usually differential diagnosis can be made on the basis of regular and special histological stains. Especially in cases of poorly differentiated, solid growing carcinomas or tumours of presumed mixed/intermediate/precursor cell differentiation (combined HCC/CC) immunohistological markers (especially for lineage differentiation) can be helpful to support or define the diagnosis. While differential diagnosis of HCC and intrahepatic CC is expected to be conclusive on the basis of these diagnostic measures, differential diagnosis of HCC from combined HCC/CC is not clear cut and may leave uncertainty in a few cases. Generally, clear cut CC differentiation of any size or unequivocal signs of mixed/intermediate differentiation in more than 10% of the tumour should induce the diagnosis of combined HCC/CC.

Recently, HCC subtypes that can be defined by morpho-molecular analyses and that display specific biological behaviour have been identified, such as fibrolamellar and chromophobe subtypes.[234,235] Currently, HCC subtyping has no major impact on clinical decision making, however, most clinical trials exclude the fibrolamellar subtype.

Histological assessment is also essential for the distinction of benign and premalignant precursor lesions from (mostly highly differentiated) HCC. This is relevant for the distinction of premalignant dysplastic nodules from highly differentiated HCC, mostly in the instance of background cirrhosis and the question of malignant transformation of ß-Catenin mutated hepatocellular adenoma. Distinction of dysplastic nodules from HCC involves absolute (vascular and interstitial invasion) and several relative parameters (trabecular disarray, increased nuclear/cytoplasmic ratio), and should be supplemented by immunohistological markers (see below). Especially hepatocellular adenomas with ß-catenin mutations in exon 3 carry a high risk of transformation into HCC and need to be identified.[234,236] Beside morphological parameters of malignancy (see above) analysis for human telomerase reverse transcription (*hTERT)* mutations may help to diagnose existing malignant transformation.[237] Diagnosis and management of hepatocellular adenoma are described extensively elsewhere in another EASL guideline.[237]

Specificity of liver biopsy based diagnosis of HCC has been reported to reach up to 100%,[238] although in routine diagnostics these numbers may not be reached because of the differential diagnostic challenges in highly differentiated hepatocellular tumours. Sensitivity of liver biopsy-based diagnosis of HCC depends on location, differentiation, and size of the lesion, as well as the expertise of the person performing the biopsy and the pathologist, it is reportedly in the range of 90% for all tumour sizes. Pathological diagnosis is generally more challenging for nodules <2 cm in size,[239] since these lesions often represent well differentiated tumours. In a prospective study, the first biopsy was reported positive in ~60% of cases for tumours less than 2 cm.[159]

Since the histopathological criteria of malignancy in hepatocellular tumours, namely significant cytological and histological atypia and interstitial and vascular invasion, can be missed by biopsy specimens,[159] the diagnosis of early and well differentiated HCC should be further supplemented by immunohistological analyses for markers linked to malignant transformation of hepatocytes. A combination of three different immunomarkers –HSP70 (HSPA7), glypican 3 (GPC3), and glutamine synthetase (GS) — has been shown to further support the diagnosis of highly differentiated HCC in surgically resected specimens (sensitivity and specificity of 72% and 100%, respectively),[240] and its specificity was externally validated in samples obtained by percutaneous biopsy[241–243] although its use does not significantly increase the sensitivity of HCC diagnosis in an expert setting.[243] Both, the International Consensus Group of Hepatocellular Neoplasia and the WHO have adopted this three-marker panel in their recommendations.[231,232] There is still a need to increase the sensitivity of these panels by defining new markers correlating with malignant transformation. Staining for neovascularisation may provide additional help. In addition, immunohistological markers may help to identify HCCs with poorer prognosis (cytokeratin 19 [CK19]).[244] Furthermore, it should be emphasised that diagnostic accuracy in difficult biopsy cases can be increased by sending formalin-fixed paraffin-embedded tissue blocks or slides to expert liver pathologists for a second opinion.

Several gene expression signatures have been proposed to support diagnosis, and to subtype HCCs with a potential for

prognostic assessment.[245–247] However, the clinical usefulness of such analyses has not been proven and has not entered routine diagnostics, so far. Molecular markers have been assessed on HCC tissues for their predictive potential and have been used as inclusion criteria in clinical trials.[248] As the number of clinical trials increases, the availability of HCC tissue has become more relevant for including patients. Although always an individual decision integrating clinical (palliative *vs.* curative) and patient specific factors (age, *etc.*), several centres have introduced more active biopsy strategies into their policies.

Potential risks of liver tumour biopsy are bleeding and needle track seeding. In a meta-analysis, the risk of tumour seeding after liver biopsy was reported to be 2.7% with a median time interval between biopsy and seeding of 17 months,[249] but this study probably suffers from publication bias and even lower rates are expected in experienced centres. It has further been reported that needle track seeding can be treated well, *e.g.* by excision or radiation and does not affect outcome of oncological treatment[250] and overall survival.[249] In a meta-analysis of the bleeding risk of liver tumour biopsies, mild bleeding complications range around 3–4%, while severe bleeding complications requiring transfusions are reported in 0.5% of cases.[251] In conclusion, it is now widely accepted that the potential risks, bleeding and needle track seeding, are infrequent, manageable and do not affect the course of the disease or overall survival. In general, they should not be seen as a reason to abstain from diagnostic liver biopsy.

Synthesis of radiological and histopathological diagnosis/ synopsis

Diagnostic assessment of hepatic lesions suspected of being HCC in a specific patient is influenced by the size and location of the lesion, the state of the non-tumourous liver, the clinical status of the patient, the imaging patterns, the expertise of the diagnostic physicians, the extent of therapeutic options, and general conditions of the respective healthcare system. Generally proposed diagnostic algorithms may not be able to address all parameters. The certainty of diagnosis represents a high priority; its impact is rising with extent and effectiveness of therapy in HCC and its differential diagnoses.

In cirrhotic patients, the diagnosis of HCC is often based on contrast-enhanced imaging as shown in the diagnostic algorithm (Fig. 2). Biopsy of the lesion is indicated when the imaging-based diagnosis remains inconclusive, especially in lesions smaller than 2 cm in diameter where the diagnostic performance of contrast-enhanced imaging is lower. Considering a degree of uncertainty with imaging-based HCC diagnosis (around 5–10%), even when classical diagnostic parameters are fulfilled, biopsy has to be considered if a higher level of certainty is required. Furthermore, several centres have introduced

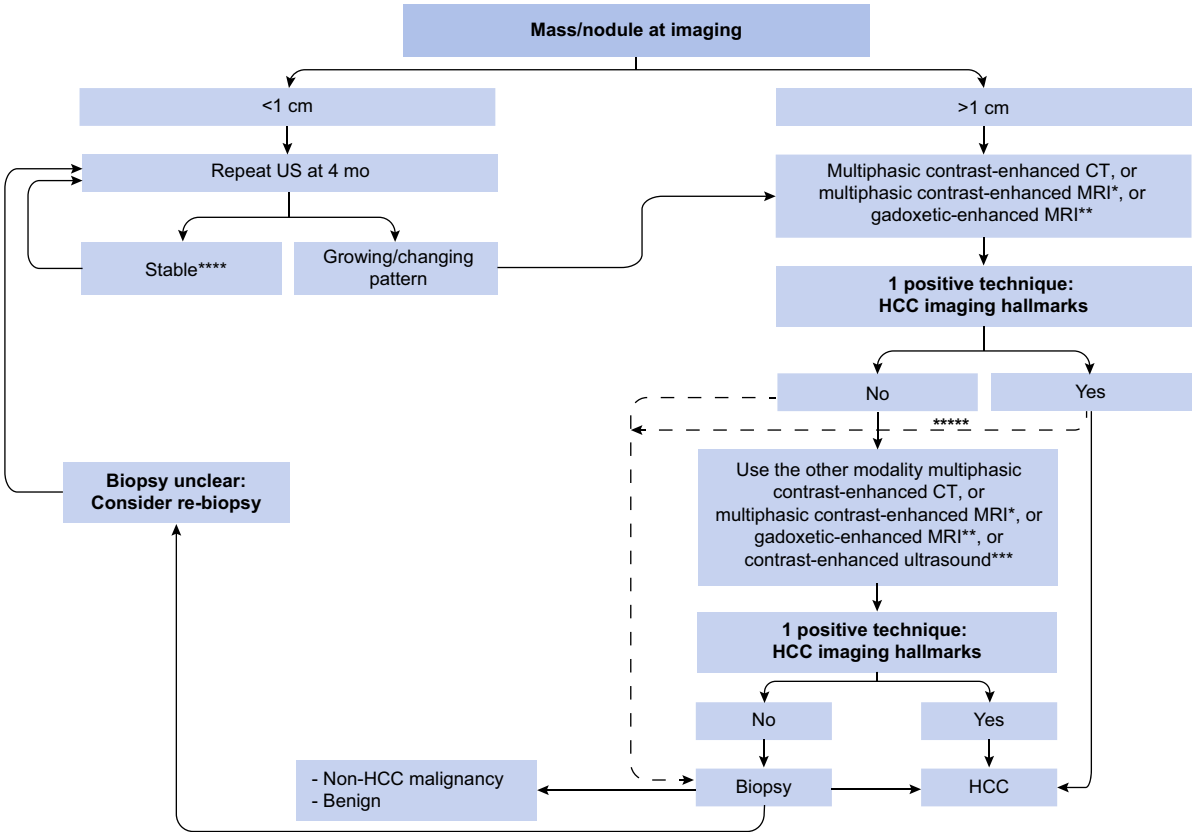


Fig. 2. Diagnostic algorithm and recall policy in cirrhotic liver. *Using extracellular MR contrast agents or gadobenate dimeglumine. **Using the following diagnostic criteria: arterial phase hyperenhancement (APHE) and washout on the portal venous phase. ***Using the following diagnostic criteria: arterial phase hyperenhancement (APHE) and mild washout after 60 s. ****Lesion <1 cm stable for 12 months (three controls after four months) can be shifted back to regular six months surveillance. *****Optional for centre-based programmes.

a more active biopsy strategy in order to address different trial and experimental treatment options, especially for systemic therapies. Potential complications of liver biopsy are rare and manageable and do not justify abstaining from diagnostic biopsy. Broader availability of liver biopsy in HCC has the potential to provide suitable patients access to more clinical trials, enlarging the treatment options and supporting research measures expected to improve the therapeutic situation in liver cancer in the future.

In non-cirrhotic liver, imaging alone is not considered sufficient and histological assessment is required to establish the diagnosis of HCC. It must be acknowledged that the diagnosis of liver cirrhosis might be difficult in some cases; therefore, the diagnostic process for HCC in patients where cirrhosis is uncertain should be carried out as in non-cirrhotic patients. Therefore, liver biopsy is recommended and has the additional advantage of providing further information regarding the non-tumourous liver tissue.

Recall policy

Recommendations

- In patients at high risk of developing HCC, nodule(s) less than 1 cm in diameter detected by ultrasound should be followed at ≤4-month intervals in the first year. If there is no increase in the size or number of nodules, surveillance could be returned to the usual six-month interval thereafter (**evidence weak; recommendation weak**).
- In cirrhotic patients, diagnosis of HCC for nodules of ≥1 cm in diameter can be achieved with non-invasive criteria and/or biopsy-proven pathological confirmation (**evidence strong; recommendation strong**).
- Repeated bioptic sampling is recommended in cases of inconclusive histological or discordant findings, or in cases of growth or change in enhancement pattern identified during follow-up, but with imaging still not diagnostic for HCC (**evidence low; recommendation strong**).

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 hepatocellular carcinoma (HCC) at a very early stage (2 cm or less), when radical treatments can be applied with the highest probability of long-term cure.[87] In the case of HCC surveillance, abnormal ultrasound results are either a newly detected focal lesion or a known hepatic lesion that enlarges and/or changes its echo pattern.[252]

Pathological and radiological studies show that the majority of nodules smaller than 1 cm that can be detected in a cirrhotic liver are not malignant[159,219] and adequate bioptic sampling of such tiny lesions is challenging. Moreover, the initial growth is usually only of slow expansion in the early phases, even in the instance of HCC, and complete response to therapy is almost always achievable in lesions up to 2 cm.[253,254] Thus, a strict follow-up is a reasonable approach 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. These new nodules should trigger the recall strategy for diagnosis with non-invasive or invasive (biopsy) criteria, as described in the section on diagnosis. If a definitive diagnosis cannot be reached with non-invasive radiological criteria because of a lack of the typical radiographic hallmarks of HCC, then biopsy is recommended. If even biopsy does not show malignancy (or very rarely a definitive haemangioma), then at least strict follow-up every 3–4 months is recommended. However, repeat bioptic sampling is directly recommended in cases of inconclusive histological findings or when apparently conclusive non-malignant histological findings are overtly discordant with the suggested imaging diagnosis (*e.g.* histological finding of cirrhosis in the instance of a well demarcated focal lesion with arterial hyperenhancement) since percutaneous biopsy bears the risk of false negative results.[159] A new biopsy is also recommended in case of growth or change in the enhancement pattern identified during follow-up, but with imaging still not diagnostic for HCC. Upon detection of a suspicious nodule, the recommended policy is to evaluate the patient in a referral centre with appropriate human and technical resources.

Staging systems and treatment allocation

Recommendations

- Staging systems for clinical decision making in HCC should include tumour burden, liver function and performance status (**evidence high; recommendation strong**).
- The BCLC staging system (Fig. 3) has been repeatedly validated and is recommended for prognostic prediction and treatment allocation (**evidence high; recommendation strong**). The levels of evidence for treatments according to strength and magnitude of benefit are summarised (Fig. 9).
- Treatment stage migration concept applies.
- Refinement of BCLC classes (particularly B and C) by clinical data, molecular classes or biomarker tools should further facilitate understanding of outcome data, treatment allocation and trial stratification. This needs to be validated in a clinical setting.
- Patients should be discussed in multidisciplinary teams to fully capture and tailor individualised treatment options (**evidence low; recommendation strong**).

Staging systems

Once the diagnosis is established, prognostic assessment is a critical step in the management of hepatocellular carcinoma (HCC). 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 tumours, the co-existence of two life-threatening conditions, such as cancer and cirrhosis,

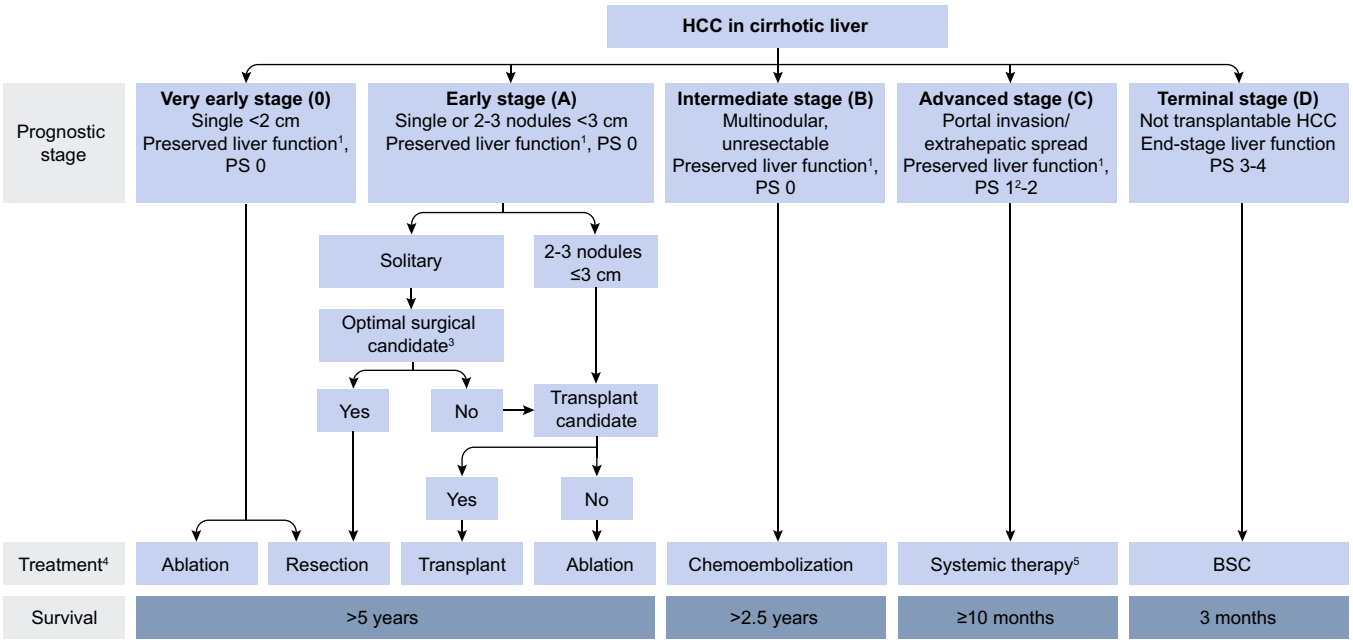


Fig. 3. Modified BCLC staging system and treatment strategy. [1]"**Preserved liver function**" refers to Child-Pugh A without any ascites, considered conditions to obtain optimal outcomes. This prerequisite applies to all treatment options apart from transplantation, that is instead addressed primarily to patients with decompensated or end-stage liver function. [2]**PS 1** refers to tumour induced (as per physician opinion) modification of performance capacity. [3]**Optimal surgical candidacy** is based on a multiparametric evaluation including compensated Child-Pugh class A liver function with MELD score <10, to be matched with grade of portal hypertension, acceptable amount of remaining parenchyma and possibility to adopt a laparoscopic/minimally invasive approach. The combination of the previous factors should lead to an expected perioperative mortality <3% and morbidity <20% including a postsurgical severe liver failure incidence <5%. [4]The **stage migration strategy** is a therapeutic choice by which a treatment theoretically recommended for a different stage is selected as best 1st line treatment option. Usually it is applied with a left to right direction in the scheme (*i.e.* offering the effective treatment option recommended for the subsequent more advanced tumour stage rather than that forecasted for that specific stage). This occurs when patients are not suitable for their first line therapy. However, in highly selected patients, with parameters close to the thresholds defining the previous stage, a right to left migration strategy (*i.e.* a therapy recommended for earlier stages) could be anyhow the best opportunity, pending multidisciplinary decision. [5]As of 2017 sorafenib has been shown to be effective in first line, while regorafenib is effective in second line in case of radiological progression under sorafenib. Lenvatinib has been shown to be non-inferior to sorafenib in first line, but no effective second line option after lenvatinib has been explored. Cabozantinib has been demonstrated to be superior to placebo in 2nd or 3rd line with an improvement of OS from eight months (placebo) to 10.2 months (ASCO GI 2018). Nivolumab has been approved in second line by FDA but not EMA based on uncontrolled phase II data. ASCO, American Society of Clinical Oncology; BCLC, Barcelona Clinic Liver Cancer; EMA, European Medicines Agency; FDA, Food and Drug Administration; MELD, model for end-stage liver disease; PS, performace status; OS, overall survival. Modified with permission from[87].

complicates prognostic assessments.[87,255] In addition, the presence of cancer-related symptoms has consistently shown an impact on survival. Finally, any system aimed at being clinically meaningful should link prognostic prediction to treatment indication.

Staging systems for HCC should be designed with data from two sources. Firstly, prognostic variables obtained from studies describing the natural history of cancer and cirrhosis. Secondly, treatment-dependent variables obtained from evidence-based studies providing the rationale for assigning a given therapy to patients in a given subclass.

The main clinical prognostic factors in patients with HCC, based on studies reporting the natural history of the disease, are related to tumour status (defined by number and size of nodules, presence of vascular invasion, extrahepatic spread), liver function (defined by Child-Pugh's class, bilirubin, albumin, clinically relevant portal hypertension, ascites) and general tumour-related health status (defined by the Eastern Cooperative Oncology Group [ECOG] classification and presence of symptoms).[256–260] Aetiology has not been identified as an independent prognostic factor.[260]

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 8th TNM edition in accordance with the American Joint Committee on Cancer,[233] which was obtained from the analysis of a series of patients undergoing resection, has several limitations.[261,262] Firstly, 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. Finally, its prognostic value in non-early tumours is limited.[262] Among more comprehensive staging systems, six have been broadly tested, three European (the French classification,[263] the Cancer of the Liver Italian Program [CLIP] classification,[257] and the Barcelona-Clínic Liver Cancer [BCLC] staging system[87,264]) and three Asian (the Chinese University Prognostic Index [CUPI] score,[265] the Hong-Kong Liver Cancer [HKLC] staging system[266] and the Japan Integrated Staging [JIS], which was refined including biomarkers (alpha-fetoprotein [AFP], des-γ-carboxyprothrombin [DCP] AFP-L3) (bm-JIS)[267]). CUPI and the CLIP scores largely sub-classify patients at advanced stages, with a small number of effectively treated patients. Overall, most of these systems or scores have been externally validated, but only three include the three types of prognostic variables (BCLC, CUPI, and HKLC) and only two assign treatment allocation to specific prognostic subclasses (BCLC and HKLC). HKLC was derived from a large cohort of patients (n = 3,927, mostly HBV-related), and

identifies nine stages and sub-stages. Regrettably, this proposal has some limitations: survival among different stages overlaps, there is no external validation in Western countries evaluating its performance in a population including all stages of the disease,[268] and the population used for developing the HKLC staging was already treated and the outcome retrospectively analysed, introducing an unintentional selection bias against transarterial chemoembolisation (TACE) in comparison to resection.[269]

The current European Association for the Study of the Liver Clinical Practice Guidelines endorse the BCLC classification for several reasons. It includes prognostic variables related to tumour status, liver function and health performance status along with treatment-dependent variables obtained from cohort studies and randomised trials. It has been externally validated in different clinical settings[260,270–273] and is an evolving system that links tumour stage with treatment strategy in a dynamic manner, enabling the incorporation of novel advances in the understanding of the prognosis or management of HCC. In this regard, the seminal classification reported in 1999[264] was updated with the incorporation of stage 0 (very early HCC) and chemoembolisation for intermediate HCC in 2003,[274] further modified in 2008 to incorporate sorafenib as a first-line treatment option in advanced tumours,[275] the consideration of ablation as first-line treatment in selected patients with solitary HCC smaller than 2 cm,[276] and finally included other systemic therapies and the elimination of the Child-Pugh score as a tool for evaluating liver function.[87] As discussed later, further refinements in class stratification (for instance to incorporate biomarkers) or treatment allocation resulting from positive high-end trials are expected in the coming years.

Tissue and serum biomarkers predicting prognosis have been less explored in patients with HCC. Strict rules for incorporating prognostic or predictive markers into clinical practice have been published.[277] According to these rules, acceptable biomarkers should be obtained from randomised investigations, as is the case with RAS 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 incorporating biomarkers for the management of HCC when the following requirements are met: i) Demonstrate prognostic prediction in properly powered randomised studies or in training and validation sets from cohort studies; ii) Demonstrate independent prognostic value in multivariate analysis including known clinico-pathological predictive variables; iii) Confirm 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.[278]

There is room for further refinement of prognosis evaluation. Liver function has traditionally been assessed through the Child-Pugh classification, which is known to have limited predictive power as temporary events not fully captured (renal failure, spontaneous bacterial peritonitis, hyponatremia, recurrent encephalopathy or malnutrition) may indicate end-stage liver disease, requiring transplant. If a transplant is not feasible, HCC should be categorised as terminal stage (BCLC D) and best supportive care should be offered. Furthermore, the assessment of Child-Pugh score includes some subjective variables (for instance, ascites detected by imaging) that might impair its clinical applicability. The combination of albumin and bilirubin (ALBI score) has been shown to stratify patients across BCLC stages[279] and allows subgrouping of Child-Pugh A patients, but its role in clinical decision making or stratification in research trials is not defined. Both parameters are already included in the evaluation of patients and hence, while statistically significant it may be clinically irrelevant.[280]

Regarding serum markers, increased AFP is associated with poorer prognosis. Elevated AFP levels have been shown to predict risk of tumour recurrence after resection,[281,282] risk of drop-out in patients on the waiting list for liver transplantation,[283–285] survival and risk of tumour recurrence after liver transplantation,[286–290] response to loco-regional therapies,[291–293] and survival in advanced HCC.[294,295] Other markers such as vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang2) have been shown to have independent prognostic value in large cohorts of untreated advanced tumours.[294] The heterogeneity of the above studies prevents the formulation of a clear recommendation, but it is advised that AFP levels >200 and/or >400 ng/ml be tested as prognostic factors of poor outcome in research investigations.

Outcome prediction and treatment allocation

The treatment allocation recommended in these guidelines is modified from the BCLC classification and is summarised (Fig. 3). Patients with HCC are classified into five stages (0, A, B, C and D) according to pre-established prognostic variables, and therapies are allocated according to treatment-related status. Prognosis prediction is defined by variables related to tumour status (size, number, vascular invasion, N1, M1), liver function (bilirubin, portal hypertension, liver function preservation) 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.

Very early HCC (BCLC stage 0) is defined as the presence of a single tumour <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% because of the widespread implementation of surveillance programmes.[296] From pathological studies, though, two subclasses of tumours 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%.[239] Therefore, some tumours smaller than 2 cm are prone to disseminate locally, but others behave as carcinoma *in situ* and those are defined as stage 0. Recent data have shown a five-year survival in 80–90% of patients with solitary HCC smaller than 2 cm treated with resection.[297,298] Since radiofrequency ablation (RFA) is able to offer a complete tumour necrosis with a safe margin in the majority of cases, it is likely that resection and RFA are similar in terms of outcome. A recent Markov model for very early tumours (BCLC 0) created to simulate a randomised trial between resection *vs.* RFA followed by resection for cases with initial local failure, concluded that both approaches were nearly identical in terms of survival.[299] A systematic review and meta-analysis including seventeen studies (3,996 patients treated

with resection and 4,424 patients treated with ablation) with an associated cost-effectiveness analysis using a Markov model concluded that, for very early HCC (single nodule <2 cm) in Child-Pugh class A patients, RFA provided similar life expectancy and quality-adjusted life expectancy at a lower cost.[218] Finally, several cohort studies have reported five-year survival beyond 70% after RFA in well-selected patients with very early HCC.[253] The only advantage of surgical resection would be the opportunity to assess the risk of early recurrence by pathology (microvascular invasion, poor differentiation or presence of satellites). If a high risk of recurrence is detected in the specimen, liver transplant might be indicated (the so-called "*ab initio*" indication).[300,301] If a patient is not a candidate for liver transplant, the availability of the pathology characteristics will not change the treatment strategy and thus, RFA might become the first-line option (see chapter 'resection'), leaving surgery for those patients with nodules not suitable for RFA, or who fail treatment.[276,302] Regrettably, no randomised controlled trial addressing this issue has been reported so far and comparison of cohort studies suffers from selection bias favouring surgical resection.

Early HCC (BCLC stage A) is defined in patients presenting with single tumours >2 cm or three nodules <3 cm in diameter, ECOG-0 and preserved liver function. Median survival of patients with early HCC reaches 50% to 70% at five years after resection, liver transplantation or local ablation in selected candidates. The natural outcome of these cases is ill-defined because of the scarcity of data reported, but median survival is estimated to be around 36 months.[303] An improvement in survival is universal when applying the so-called treatment-dependent variables to the selection of candidates.

Tumour status is defined by the size of the main nodule and multi-centricity (single lesion, three nodules ≤3 cm), each of these categories showing significantly different outcomes. As discussed below, for single tumours beyond 5 cm surgical resection is still considered as a first option, because if modern MRI is applied in preoperative staging, the fact that solitary large tumours remain single and have no macrovascular involvement - which might be common in HBV-related HCC - reflects a more benign biological behaviour.

Variables related to liver function are relevant for candidates considered for resection. Absence of clinically relevant portal hypertension (defined as HVPG ≤10 mmHg) and normal bilirubin are key predictors of survival in patients with single tumours undergoing resection.[304–306] Similarly, Child-Pugh class A is the strongest prognostic variable in patients undergoing local ablation,[292,297,307,308] along with tumour size and response to treatment.[309] Since liver transplantation may potentially cure both the tumour and the underlying liver disease, variables mostly related with HCC have been clearly established as prognostic factors (single tumours ≤5 cm or three nodules ≤3 cm), defining the so-called Milan criteria.

Intermediate HCC (BCLC stage B): Median survival for untreated patients at an intermediate-stage (BCLC-B – multinodular asymptomatic tumours without vascular invasion or extrahepatic spread) is 16 months,[310,311] or 49% at two years.[260] According to the positive results in terms of survival benefit of two randomised controlled trials,[312,313] and a cumulative meta-analysis,[310] TACE is considered the first-line treatment, while recent cohort studies have reported a median survival of around 40 months in well-selected candidates with a state of the art technique and a super-selective approach.[293,314,315]

The current intermediate HCC definition includes a wide range of patients according to liver function and tumour burden. This has triggered a major controversy and willingness to further stratify the BCLC-B category according to tumour burden and liver function.[316,317] Some of these proposals classify large solitary HCC beyond 5 cm with an expansive growth as intermediate-stage, although vascular invasion or tumour dissemination has been excluded after proper imaging evaluation. However, if technically feasible they may benefit from surgical resection, and these patients should be classified as BCLC-A.[1,87,318] Another rare subgroup are patients with large multifocal HCC affecting both lobes, without vascular invasion or extrahepatic spread, as major tumour burden is usually associated with cancer-related symptoms and thus, these patients correspond to a more evolved tumour stage either C or D instead of a poor prognostic subclass of intermediate-stage. Finally, Child-Pugh A-B may include patients with refractory ascites, and events such as spontaneous bacterial peritonitis, hyponatremia or recurrent encephalopathy, which predict poor outcome in the absence of transplantation.[255,319] In such instances, liver transplantation should be considered and if HCC exceeds the accepted criteria for the patient to be listed, then the patient must be classified as BCLC D. While studies analysing the natural history and prognostic factors may include such patients,[316] therapeutic trials usually exclude them because of their high short-term mortality.

Advanced HCC (BCLC stage C): Patients with cancer-related symptoms (symptomatic tumours, ECOG 1-2), macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases) bear a poor prognosis, with expected median survival times of 6–8 months,[260,310,311] or 25% at one year.[260] Nonetheless, it is obvious that this outcome varies according to liver functional status and other variables. In the last decade, major advancements have occurred in the field of advanced HCC. Until 2007, there was no FDA-approved first-line treatment for patients with advanced HCC. This scenario has changed as a result of data showing survival benefits in patients receiving sorafenib – a multi-tyrosine kinase inhibitor - in advanced cases.[320,321] The results of these randomised controlled trials represented a breakthrough in the management of HCC, as it is discussed in the systemic therapies section of this document, impacting on the survival of patients with advanced disease. The positive results of sorafenib opened the door for evaluation of other targeted agents. Regrettably, all subsequent phase III trials evaluating new agents alone or in combination with sorafenib, in first-line or in second-line treatment, failed to demonstrate a survival benefit. Only very recently, regorafenib, an oral multikinase inhibitor with a similar mechanism of action to sorafenib, demonstrated an impact on survival in a phase III trial in patients with HCC who progressed but were tolerant to sorafenib and had Child-Pugh A liver function and performance status 0 or 1.[322] According to this study, regorafenib is recommended in second-line in those patients who progressed but were tolerant to sorafenib. Very recently, lenvatinib, an inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth

factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT, demonstrated non-inferior survival to sorafenib in an open-label, multicentre, non-inferiority, randomised trial.[323] Finally, cabozantinib, a MET, VEGFR2 and RET inhibitor approved for thyroid and renal cancer, has shown survival benefit compared to placebo in second-line.[324]

End-stage HCC: Patients with end-stage disease are characterised by very poor performance status (Eastern Cooperative Oncology Group 3–4) that reflects a severe tumour-related disability. Their median survival is 3–4 months or 11% at one year.[260] Similarly, Child-Pugh C patients with tumours 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 these cases, the patient should be offered 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 chemoembolisation. Similarly, patients at BCLC-B stage with contraindications or with untreatable progression on chemoembolisation,[325,326] should be offered sorafenib, as reported in the SHARP trial.[320]

Refinement of BCLC classification

Some studies challenged the capacity of BCLC to precisely stratify patients for trial design. These studies mostly included patients at BCLC-C stage of the disease.[268,327] The panel of experts acknowledges that the range of survival reported for patients at BCLC-B and -C warrants consideration. Further stratification of patients within each class according to liver function (Child-Pugh A *vs.* B, ascites, ALBI score, *etc.*), prognostic molecular biomarkers, or evolutionary events (pattern of progression, development of side effects during systemic therapy, *etc.*) should be explored.

Response assessment

Recommendations

- Assessment of response in HCC should be based on mRECIST for loco-regional therapies (**evidence moderate; recommendation strong**). For systemic therapies both mRECIST and RECIST1.1 are recommended (**evidence moderate; recommendation weak**). The use of changes in serum biomarker levels for assessment of response (*i.e.* AFP levels) is under investigation.
- Multiphasic contrast-enhanced CT or MRI are recommended for assessment of response after resection, loco-regional or systemic therapies (**evidence moderate; recommendation weak**). Follow-up strategies for detection of recurrence after different treatments are outlined in the specific treatment sections.

For details see the chapter Trial design and endpoints (paragraphs response rate and response assessment tools, objective response in loco-regional therapies and objective response in systemic therapies).

Liver resection

Recommendations

- Surgical resection is recommended as treatment of choice in patients with HCC arising on a non-cirrhotic liver (**evidence low; recommendation strong**).
- Indications for resection of HCC in cirrhosis should be based on multi-parametric composite assessment of liver function, portal hypertension, extent of hepatectomy, expected volume of the future liver remnant, performance status and patients' co-morbidities (**evidence high; recommendation strong**).
- Perioperative mortality of liver resection in cirrhotic patients should be less than 3% (**evidence high; recommendation strong**).
- LR is recommended for single HCC of any size and in particular for tumours >2 cm, when hepatic function is preserved, and sufficient remnant liver volume is maintained (**evidence moderate; recommendation strong**).
- In properly trained centres, LR should be considered via laparoscopic/minimally invasive approaches, especially for tumours in anterolateral and superficial locations (**evidence moderate; recommendation weak**).
- HCC presenting with two or three nodules within Milan criteria may be eligible for LR according to patient performance status, co-morbidities and preservation of liver function and remnant volume (**evidence low; recommendation weak**).
- HCC-related macrovascular invasion is a contraindication for LR. Intervention on distal portal invasion – at segmental or sub-segmental level – deserves investigations within prospectively designed protocols (**evidence moderate**).
- Neoadjuvant or adjuvant therapies are not recommended because they have not been proven to improve the outcome of patients treated with resection (**evidence high; recommendation strong**). Further clinical trials with new agents are encouraged.
- Follow-up after resection with curative intent is recommended because of high rates of treatable recurrence (**evidence high; recommendation strong**). Follow-up intervals are not clearly defined. In the first year, 3–4 month intervals are practical.

Surgery is the mainstay of hepatocellular carcinoma (HCC) treatment, leading to the best outcomes of any treatment available in well-selected candidates (five-year survival of 60–80%). Liver resection (LR) and liver transplantation (LT) represent the first option in patients with early tumours on an intention-to-treat perspective. Surgical interventions can often be extended to other stages of HCC, once effective tumour downstaging is achieved by non-surgical means.

Several technical and methodological updates in HCC resection and transplantation have been implemented in the last five years. In the updated guidelines, a comprehensive review of the current standards of surgery in patients with HCC has been undertaken, with special focus on innovations and selection criteria that bear a demonstrable impact on patient outcomes, providing availability and access of the proposed refinements to the whole community of health providers dealing with HCC.

Liver resection in non-cirrhotic liver

Hepatic resection is the treatment of choice for HCC in non-cirrhotic patients (5% of cases in the West, 40% in Asia),[328] where even major resections can be performed with low rates of life-threatening complications and acceptable outcome. Definition of HCC in normal liver may vary and can be challenging at times. In the elusive field of non-cirrhotic liver the emerging indication for LR is represented by resection of HCC in non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome, in which HCC may in fact occur in the absence of cirrhosis or severe fibrosis.[50,100,329] Results of LR in patients with NAFLD and metabolic syndrome are burdened by a significant rate of severe complications, ranging from 13 to 20%, although post-surgical mortality in this group is contained within 2%. Therefore, LR in NAFLD and metabolic syndrome is a surgical procedure with a risk profile closer to cirrhotic rather than to truly normal livers. Curative potential of LR for HCC-related to NAFLD/metabolic conditions (*i.e.* long-term survival) seems to be higher than that observed in hepatitis virus-related tumours.[330,331] However, co-morbidities such as dyslipidemia, hypertension, diabetes, obesity, heart and lung chronic dysfunction are commonly observed in these patients and play a significant and negative prognostic role.

Liver resection in cirrhotic liver

Several refinements in techniques, perioperative management and case selection have improved surgical interventions for liver cancer in patients with chronic liver disease and cirrhosis. Since no single surgical modality fits all HCC presentations, a multidisciplinary approach to surgical intervention is mandatory. This should be focussed on the key conditions affecting decision making in the area of surgical HCC, resulting in a multi-parametric approach to cancer and non-cancer components in the single patient. Criteria presented in the previous European Association for the Study of the Liver (EASL)/European Organisation for Research and Treatment of Cancer (EORTC) Clinical Practice Guidelines in 2012[1] (*i.e.* solitary tumours and very well-preserved liver function, hepatic vein to portal system gradient ≤10 mmHg or platelet count ≥100,000/ml) describe the "ideal" candidates for LR in cirrhosis. Such prescription remains confirmed, especially in a non-experienced context.

However, in the last few years patients exceeding one or more of the described criteria have been approached with LR in experienced centres, providing accurate balance of the relative weight of each determinant of prognosis. This has been enabled by general optimisation of surgical technique, pre-resection imaging planning, ultrasonic and bipolar dissector devices, intermittent hilar clamping (Pringle manoeuvre), low central venous pressure maintenance, mini-invasive approaches and intensive post-operative management. Indirect confirmation of improved perioperative management of the surgical patient emerges from the reported decrease in blood transfusion during LR in cirrhosis, from 80% to 90% to less than 10% in two decades.[332] Overall, outcome results achieved in patients undergoing LR in experienced centres (*i.e.* post-operative mortality and severe post-surgical morbidity of <3% and <30%, respectively) seem to favour the use of extended criteria for LR, namely of HCCs in which one or more conventional selection criteria for LR summarised in the 2012 EASL/EORTC Guidelines are not satisfied.

A consensus on "extended criteria" for LR in cirrhosis has not been reached, even though any expansion in patients' selection criteria should consider, measure and combine at least three groups of variables:

1. Liver function assessment

Although liver function determined by Child-Pugh stage[333,334] remains the most practiced method for measuring liver reserve – with stage A allowing LR within safe limits – other parameters such as model for end-stage liver disease (MELD) or MELD-Na score, indocyanine green kinetics, liver stiffness measurement (LSM) and cholinesterase/bilirubin ratio, have shown a significant role in improving patient selection, especially in those with borderline liver function.[335–339] Non-invasive comprehensive assessment of fibrosis grade by LSM with transient elastography, and dynamic liver function determination by means of the hepatic indocyanine green kinetic (ICG test), are additional very informative tools for LR planning. Significant risk of post-hepatectomy liver failure[340] can be predicted by liver stiffness above 12–14 kPa.[336,341,342] LSM can also be used to estimate a safe liver remnant volume.[343] A retention rate of ICG at 15 min (ICG_{R15}) after i.v. administration of 0.5 mg/kg body weight of such an inert, water-soluble fluorescent substance can be measured at bedside with non-invasive pulse dye densitometry devices. Various cut-offs of ICG_{R15} can be part of the decision making algorithm for liver resective procedures in cirrhotic patients, limiting resection and segmentectomy to patients with ICG_{R15} below 20–25% and 30–35%, respectively.[344,345]

2. Portal hypertension

Although clinically relevant portal hypertension (CRPH; (defined as HVPG >10 mmHg) is a significant prognostic factor affecting survival in both surgical and medical patients with HCC in cirrhosis,[306] its relevance as an independent determinant of post-surgical outcomes has been questioned.[305] As limited resection in patients with preserved liver function and moderate CRPH yields competitive survival outcomes,[346,347] the role of portal hypertension in decision making for eligibility to resection of HCC should be always balanced with the extent of hepatectomy and liver function indicators, such as the MELD score[348] and the availability and predicted effectiveness of alternative HCC therapies. Simplified decisional algorithms, like the one presented (Fig. 4) are of help in predicting the risk of post-surgical decompensation in cirrhotic patients on the basis of pre-surgical, non-invasive, objective parameters. Such algorithms can also be applied in the Western context.

3. Extent of hepatectomy and surgical invasiveness

According to tumour size, number of detectable tumour satellites, intrahepatic tumour location at intraoperative ultrasound and the available surgical experience, LR can be performed by conventional means (*i.e.* open: laparotomic) or through minimally invasive operations (*i.e.* close: laparoscopic-robotic). Furthermore, LR can be anatomic (*i.e.* providing systematic removal of the tumour-bearing portal territories, with exposure of the landmark veins framing the segmental territory) or non-ana-

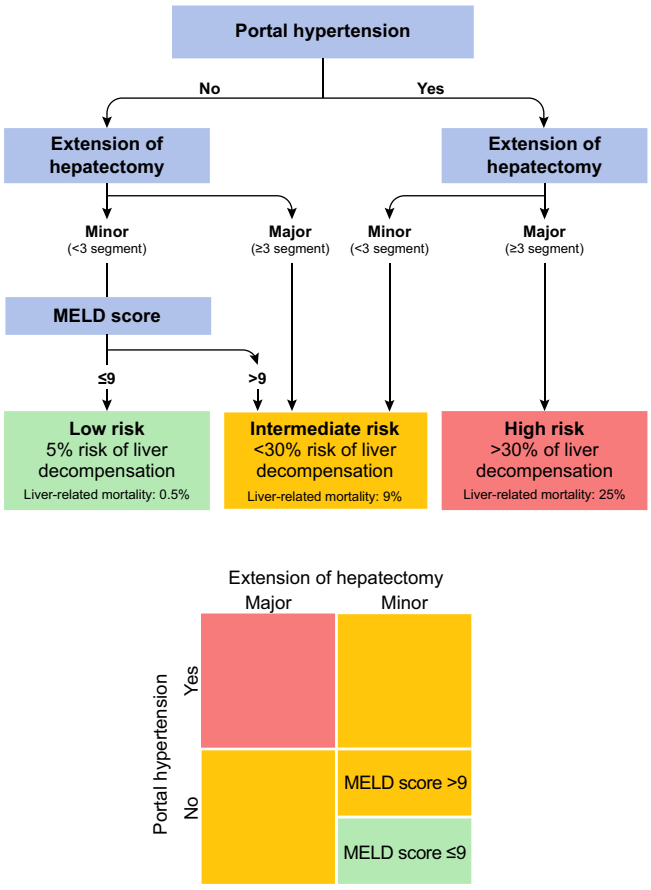


Fig. 4. Multi-parametric assessment of the risk of liver decompensation after LR for HCC in cirrhosis. Simplified decisional algorithm identifying high (red), intermediate (yellow) and low (green) risk of liver decompensation, according to a hierarchic interaction of the three main determinants of liver insufficiency: portal hypertension, extent of resection and liver function. HCC, hepatocellular carcinoma; LR, liver resection. Adapted from[348] with permission.

tomic (Fig. 5). The extent and precise definition of LR (hepatectomies) should be correctly reported according to international terminology.[349]

The extent of LR can be accurately planned ahead of surgery by means of CT/MRI volume calculation of the removed and the remnant parts of the liver, to be adjusted on liver function, grade of portal hypertension and body weight (see above). Retrospective studies linking anatomic resections and better outcome should be interpreted with caution, because of the propensity to perform wider interventions in patients with well-preserved liver function. With respect to size, anatomic resections should be preferred for HCC nodules of at least 2 cm in size,[350] with a very large retrospective series[351] and newer less invasive laparoscopic-resections questioning the superiority of anatomic LR in HCC of larger size.[352–354] Limited resections conducted through laparoscopic-robotic techniques in large volume centres are feasible and indicated for curative LR in selected groups of HCC with borderline liver conditions (*i.e.* Child B7, moderate PH or bilirubin around 2 mg/dl) and several studies have demonstrated that laparoscopic-robotic resections of HCC in cirrhosis are associated with reduced risk of post-operative liver decompensation.[298,355,356] That widens the curative perspective offered by modern LR approaches, particularly in hepatitis C virus (HCV)-related cirrhotic patients in which pre/post-resection treatment with direct-acting antivirals (DAAs) may optimise liver function control.

On top of the previous considerations, LR for HCC – as with any surgical procedure –patients' general condition, performance status and co-morbidities must be considered ahead of any intervention. Age should not be a contraindication *per se*, if adequate performance status and no major co-morbidities are confirmed in patients undergoing LR for HCC. In particular, post-surgical survivals compared to age-sex-matched reference populations suggest that LR can be offered in patients >70 years old, who are in fact exposed to a smaller loss of their individual lifespan in comparison with their younger counterparts.[357]

When liver-preservation principles are met, and patient's general conditions have been scrutinised as permissive for surgical intervention, LR should be tailored on HCC characteristics and presentation. In this respect, at least four major considerations should contribute to decide the best approach to LR in case of single HCC in cirrhosis:

a. Tumour size and intrahepatic tumour location influence decision on surgical approach. For single HCCs ≤2 cm deeply/centrally located, radiofrequency ablation (RFA) offers competitive results with respect to LR (see paragraph on local ablation). Conversely, laparoscopic-robotic LR for HCC located in superficial-peripheral positions of the liver provides optimal survival outcomes while minimising complications and hospital stay (Fig. 6);

b. LR can be offered to single HCC regardless of its size. Although patients with a single HCC of *any size* can be offered LR with a definitive survival advantage over other treatments – especially for tumour >5 cm – surgical feasibility may vary according to the liver volume and function-preservation principles summarised previously. However, studies have confirmed that post-resection outcome decreases as tumour size increases. It is worth noting that while HCCs beyond 5 cm still qualify as an early stage eligible for LR – if technically feasible, according to Barcelona Clinic Liver Cancer (BCLC) classification – the 5 cm cut-off defines tumours trespassing into the intermediate-stage in other classifications[266] and also defines the limit in size for which an HCC is excluded from liver transplantation according to conventional criteria. In practice, tumours >5 cm are surgically actionable as early HCC (BCLC-A), but appear to bear a worse prognosis than BCLC-A <5 cm HCC. Some authors have suggested designating this subgroup as BCLC-AB stage.[358]

c. Minimal invasive LR can be an effective option in very early (≤2 cm) and early HCC. Although ablation is the first-line treatment for the majority of tumours ≤2 cm because of its higher cost-effectiveness[218] and of milder liver function impact, especially for deeply/centrally located tumours, studies demonstrate that patients treated with laparoscopic-robotic LR for very early and early HCC mainly located in superficial or antero-lateral liver positions suffer less complications and shorter hospital stays, with respect to traditional open resection, while achieving competitive oncologic outcome with respect to ablation.[359–362] No differences in operative time, blood loss, intraoperative

complications, hospital stay, and morbidity were found in laparoscopic LR for cirrhotics compared with non-cirrhotics and in fact a laparoscopic approach appears to reduce the incidence of post-operative ascites, liver failure and morbidity with no difference in overall or disease-free survival at two years.[363] In selected patients with suboptimal/difficult indications for a percutaneous approach, or in cases of concomitant minimally invasive liver procedures, laparoscopic tumour ablation should be considered a doable option. Although three randomised controlled trials (RCTs) did not show superiority of LR over RFA for tumours up to 4–5 cm[364–366] other studies[367] and meta-analyses[368,369] emphasised superior results of LR – either open or minimally invasive – on local tumour control and on subsequent patient survival. A more objective model based on a large data set showed LR to be progressively superior to percutaneous ablation, as the maximal tumour size increased from 2 cm.[370] Reported morbidity and mortality in major laparoscopic-robotic LR series collected in very early and early HCC are 10–15% (including laparotomic conversions) and 1%, respectively.[371,372]

d. For single HCC >3 cm LR is cost-effective. When the perspectives on treatment effectiveness and cost are combined and meta-analysed to replace the absence of RCTs in patients receiving resection or ablation for early tumours, LR prevails over ablation in single HCC above 3 cm, while uncertainty still remains for nodules 2–3 cm in size.[218] Also, from the perspective of interventional radiology, competitive local control and long-term patient outcome favour LR – provided the maintenance of the liver preservation principles and absence of co-morbidities described above are considered – in patients with HCC above the 3 cm threshold.[373]

If patient performance status and co-morbidities allow surgical consideration, and if liver function and remnant liver volume-preserving principles are met, HCCs presenting with multiple nodules are not a contraindication *per se* for surgical intervention. In particular, HCC with multiple nodules within Milan criteria (≤3 nodules, each ≤3 cm in size) belong to the early-stage category (Fig. 3) and thus, at least in theory, could be approached with LR, if eligibility for ablation and liver transplant is suboptimal or excluded. There is a lack of research comparing LR with the large span of therapeutic alternatives usually proposed for multifocal HCC.[211,374,375] However, LR applied to multifocal HCC achieves competitive survival rates in several studies[211,376] and compared to TACE.[377,378] While in large groups of Western patients a net survival benefit in favour of LR with respect to non-surgical loco-regional treatments has been observed across all stages of tumour presentation.[358] Regrettably, these retrospective comparisons were almost certainly associated with selection bias, as the patients who were selected for resection over TACE probably had clinical characteristics that gave the surgeon confidence of a good outcome, whereas those selected for TACE likely lacked such features, immediately introducing a bias against TACE. In BCLC-A patients with multifocal tumour within Milan criteria, LR might be effective if sufficient liver function (Child-Pugh A and MELD ≤9) and good performance status (Eastern Cooperative Oncology Group 0–1) were present, and its efficacy compared to available loco-regional therapies should be evaluated in prospective studies.

HCC-related portal vein invasion

A substantial proportion of patients with HCC present with tumour-related portal vein thrombosis (PVTT) either at onset of disease or as result of HCC recurrence or progression, leading the disease to an advanced stage not amenable to curative treatments.[379] The observed increase in PVTT detection rate may be related to technical improvements in imaging techniques over time. Similarly, the better outcomes reported for resected HCC in recent years might be explained by the exclusion of patients that in the past were not diagnosed as PVTT, especially at segmental and sub-segmental level. Patients with HCC and PVTT may present as asymptomatic and within Child-Pugh stage A, although in most instances have a significant degree of synthetic dysfunction and an impending liver decompensation that precludes any attempt at surgical cure. PVTT can be graded as PV1 (segmentary), PV2 (secondary order branch), PV3 (first-order branch), PV4 (main trunk/contralateral branch).[380] The extension of PVTT is known to directly affect patients prognosis whatever treatment is attempted,[381,382] including LR, especially in the presence of elevated alpha-fetoprotein and large tumours. Propensity matched-cohorts analysis by the Liver Cancer Study Group of Japan demonstrated, however, that as long as the PVTT is limited to the first-order branch (PV1), LR can offer a longer survival outcome than non-surgical treatment,[383,384] offering median survival intervals exceeding four years. Also, in Western series, a remarkable prognosis after LR for patients with HCC and PVTT has been demonstrated.[385–388] Nonetheless, no prospective comparison of LR *vs.* systemic treatments or radioembolization has ever been reported, thus how much the remarkable survival was related to a super-selection of the population remains unclear. Therefore, LR can only be considered for PV1/2 extension of HCC, and only then as an option to be tested within research settings and not to be considered a standard of practice.

Neoadjuvant or adjuvant therapies

Tumour recurrence complicates 70% of cases at five years, reflecting either intrahepatic metastases (true recurrences) or the development of *de novo* tumours. No clinical definition of both entities has been established, but the cut-off of two years has been adopted to grossly classify early and late recurrences.[275] Several strategies to prevent and treat recurrence have been tested in the setting of randomised studies. In the past decade, before the advent of DAAs for treatment of HCV infection, different meta-analyses evaluated the effect of interferon in improving recurrence-free survival and late recurrence of HCC after LR.[389,390] Other strategies tested, including chemotherapy, chemoembolisation, internal radiation and retinoids, did not provide any benefit in terms of prevention of relapse.[391] Adoptive immunotherapy reduced HCC recurrence, whilst increasing recurrence-free survival[392] and overall survival after curative treatment,[393] which is of interest in light of future studies on modern therapies with immune checkpoint inhibitors, including the CTLA-4, PD-1, and PD-L1 inhibitory pathways and other checkpoint proteins. A randomised controlled trial (RCT) testing sorafenib *vs.* placebo as adjuvant therapy after LR or ablation failed to demonstrate any positive effect.[394] Considering the currently available information, the panel does not recommend adjuvant therapy after LR, and prospective studies in this setting are strongly encouraged.

Liver transplantation

Recommendations

- LT is recommended as the first-line option for HCC within Milan criteria but unsuitable for resection (**evidence high; recommendation strong**). Milan criteria are the benchmark for selection of patients with HCC for LT and the basis for comparison with other suggested criteria.
- Consensus on expanded criteria for LT in HCC has not been reached. Patients beyond the Milan criteria can be considered for LT after successful downstaging to within Milan criteria, within defined protocols (**evidence moderate; recommendation weak**).
- Composite criteria that consider surrogates of tumour biology – among which AFP is the most relevant – and response to neoadjuvant treatments – to bridge or downstage tumours – in combination with tumour size and number of nodules, are likely to replace conventional criteria for defining transplantability. Composite criteria should be investigated and determined *a priori*, validated prospectively and auditable at any time (**evidence low; recommendation strong**).
- Tumour vascular invasion and extrahepatic metastases are an absolute contraindication for LT in HCC (**evidence high**).
- The use of marginal cadaveric grafts for LT in patients with HCC has no contraindication (**evidence moderate**). Prioritising a cadaveric graft allocation, for patients with or without HCC, within a common waiting list, is complex and no system can serve all regions. Prioritisation criteria for HCC should at least include tumour burden, tumour biology indicators, waiting time and response to tumour treatment (**evidence moderate; recommendation strong**).
- Transplant benefit may need to be considered alongside the conventional transplant principles of urgency and utility in decision making, regarding patient selection and prioritisation, depending on list composition and dynamics (**evidence moderate; recommendation weak**)
- In LT candidates with HCC, the use of pre-transplant (neoadjuvant) loco-regional therapies is recommended if feasible, as it reduces the risk of pre-LT drop-out and aims at lowering post-LT recurrence – particularly when complete or partial tumour response are achieved (**evidence low; recommendation strong**).
- Although the contribution of living donation to LT for HCC in Europe is still marginal, living donor LT for HCC remains an option to be explored in selected patients and in experienced centres, according to waiting list time and dynamics, and within donor-recipient double equipoise principles (**evidence low**).

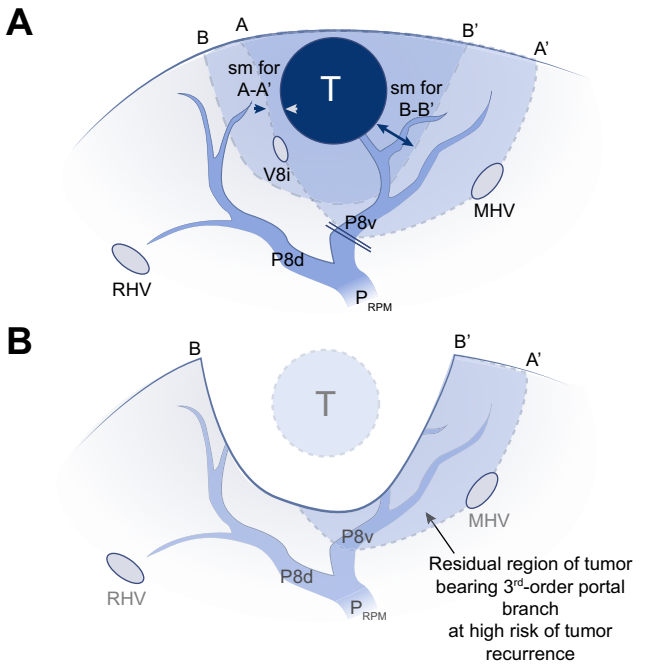


Fig. 5. Principles of anatomic *vs.* non-anatomic liver resection for HCC. (A) Anatomic resection (A-A1) removes entirely the tumour-bearing portal branches bordered by the landmark veins, while non-anatomic resection (B-B1) is any other type of resection in which the tumour-bearing 3rd order portal region is not fully removed. (B) After non-anatomic resection of HCC some part of the tumour-bearing portal region is left, which is at high risk of tumour recurrence This picture is reproduced from Shindoh J *et al. J Hepatol* 2016 (with permission). HCC, hepatocellular carcinoma; MHV, middle hepatic vein; P8v, ventral branch of P8; P8d, dorsal branch of P8; PRPM, right paramedian pedicle; RHV, right hepatic vein; V8i, intermediate vein for segment VIII.

Hepatocellular carcinoma (HCC) is the only generally accepted indication for solid organ transplantation in cancer and yet, liver transplantation (LT) for HCC represents a prototype for other transplant indications in various cancer conditions affecting the liver.[395,396]

Four areas have been addressed by the panel in the context of LT for patients with HCC: i) Patient selection; ii) Organ allocation and priority for patients with HCC with respect to non-HCC candidates; iii) Neoadjuvant therapies and their impact on LT for HCC; (4) Living donor LT for HCC.

Patient selection

Currently, patients with HCC in cirrhosis represent about 30%–35% of the waiting list population in Europe, with large variations from northern to southern Europe (Scandinavian Countries: 15%–18%, Mediterranean Countries up to 40%–44%). HCC is the fastest growing indication for LT worldwide, together with NASH/NAFLD liver insufficiency.[397]

The expected five-year survival rates of LT for HCC meeting conventional Milan criteria (single tumour ≤5 cm or multiple tumours ≤3 nodules ≤3 cm in size, without vascular invasion)[398] are 65%–80%, and patients meeting the Milan criteria have a significant survival advantage (hazard ratio 1.68) over patients beyond the criteria.[399,400] The Milan criteria works as the most

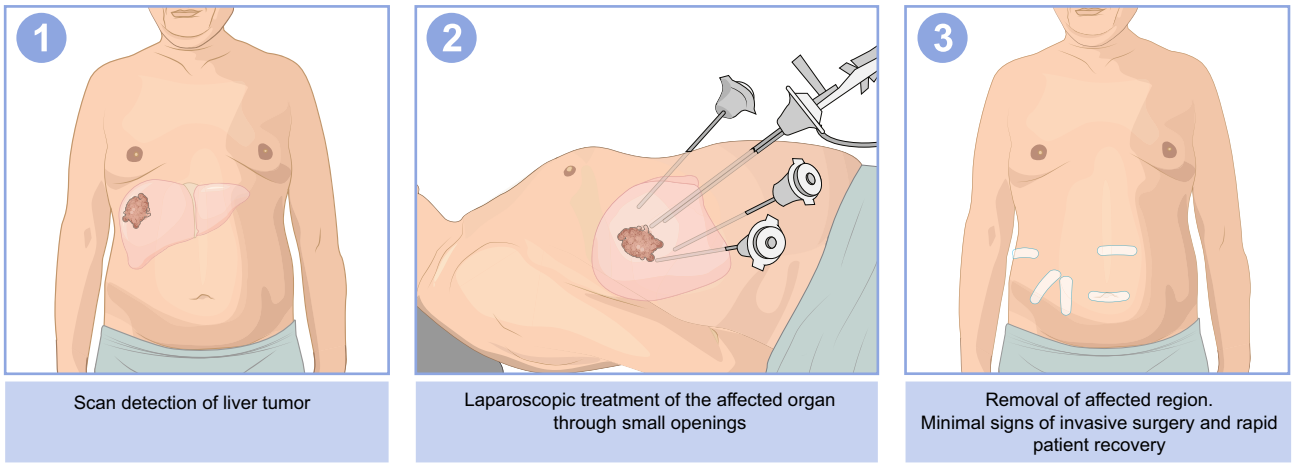


Fig. 6. Principles of mini-invasive/laparoscopic liver resection for HCC. HCC, hepatocellular carcinoma.

reliable border for transplantability in case of HCC both in Western and Eastern guidelines. Patients within Organ Procurement and Transplantation Network (OPTN) T2 stage (Milan) criteria are considered eligible for LT, while those beyond Milan can be offered LT only after successful downstaging into Milan criteria.[401]

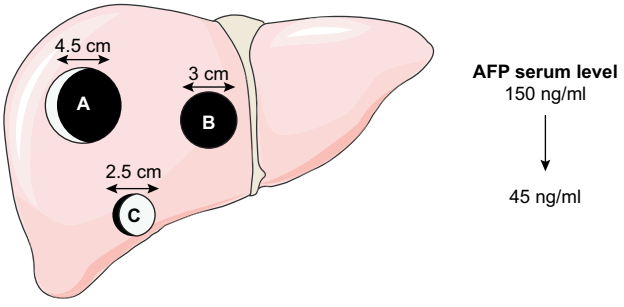
Expanded criteria

Prospective trials comparing different criteria for LT in HCC are unlikely to be conducted.

Criteria beyond Milan that have claimed non-significant differences compared to the Milan criteria in terms of post-LT survival, and that have been externally validated are: *UCSF criteria* (*i.e.*: single nodule ≤6.5 cm or 2–3 nodules ≤4.5 cm and total tumour diameter ≤8 cm,[402,403] *Up-to-7 criteria* (*i.e.*: those HCCs having the number 7 as the sum of the size (cm) of the largest tumour and the number of tumours,[404] *Total tumour volume (TTV) criteria + alpha-fetoprotein (AFP)* (*i.e.*: total tumour volume <115 cm^3 and AFP <400 ng/ml,[288,405] and the *AFP-French model* (*i.e.*: points system based on tumour size, number of tumours and AFP cut-off levels at 100 ng/ml and 1,000 ng/ml.[286] Among other expanded criteria from the East (Asian criteria) originally developed for living donor LT, only the Hangzhou criteria[406] and the Seoul criteria[407] consider AFP level (below 400 ng/ml) among the variables contributing to eligibility for LT, similarly to the prospective downstaging criteria tested in the Bologna centre.[408]

In fact, several AFP cut-offs have been proposed for incorporation into transplant criteria: 100 ng/ml,[286,409,410] 200 ng/ml,[230] 400 ng/ml,[288,408,411] 1,000 ng/ml[286,412,413] but no consensus has been reached on how to combine them with the morphological characteristics of HCC. When treated as continuous variables, AFP and variations in tumour morphology may be used to estimate post-LT survival probability, within an individualised incremental risk of death after LT. Using a calculator available at the address: www.hcc-olt-metroticket.org the individual post-transplant outcome of any patient with HCC considered for listing can be calculated on radiology parameters collected at any time, as well as after receiving neoadjuvant/downstaging treatment.[290]

Notably, in published criteria and in prediction models the size of HCC rather than the number of tumour nodules has the major prognostic role,[404,405] with nodules <1 cm usually not considered in the calculations of number of active tumours. It has been proposed that when predicting post-LT outcome in patients with HCC treated with neoadjuvant therapies, each tumour nodule should be defined as active if showing at dynamic radiological imaging (contrast-enhanced CT scan or MRI) an enhancement in the arterial phase with venous washout, even if this is only a part of an otherwise necrotic nodule.[290] In other words, for the specific prediction of post-LT outcome in HCC, each tumour nodule should be measured as totally vital (*i.e.*, including in the tumour size calculation any concomitant necrotic area) even if a partial enhancement is detectable after neoadjuvant/downstaging treatment. Conversely, fully necrotic HCC should count zero in such a prognostic computation (Fig. 7). Whatever criteria are applied, data on ten-year survival



Selection criteria	Pre-treatment	Post-treatment
Milan	OUT	OUT
UCSF	OUT	IN
TTV + AFP	IN	IN
Up-to-7	OUT	IN
French model	OUT (3 points)	IN (1 point)
HALT-HCC score	High risk (score 21)	Low risk (score 17)
Metroticket 2.0	55% at 5 yr (if HCV-negative)	70% at 5 yr (if HCV-negative)

Fig. 7. Computation of HCC nodules treated with neo-adjuvant therapies in light of liver transplantation. Post-treatment stage migration of this HCC according to commonly used criteria for transplant selection is indicated (see also text). HCC, hepatocellular carcinoma. Example of multifocal (three nodules) HCC presented for transplant consideration after neo-adjuvant treatments (downstaging). On last pre-LT imaging, tumour nodules are considered as fully necrotic (black) or still vital if presenting even minimal amount of enhanced tumour tissue (white). For transplant consideration this case should be rated as a two nodules HCC of 4.5 cm and 2.5 cm in size, with decrease in AFP from 150 to 45 ng/ml.

is scarce, and the panel endorses the practice of reporting these figures for transplantation in HCC, in order to better discriminate differences in outcome and in benefit of transplant with respect to non-transplant therapies.

Extrahepatic tumour spread cannot be cured by an extreme loco-regional treatment such as LT and represents a clear contraindication for LT.

Macrovascular tumour invasion – either at portal vein or hepatic veins level – is an absolute contraindication for LT, since it is the most important and independent risk factor for post-transplant HCC recurrence and for significant decrease in survival.[414] As for liver resection, tumour invasion of distal portal branch at sub-segmental level remains a debated issue, since peripheral tumour invasion can be detected today more frequently than in the past – because of improved imaging. Segmental/sub-segmental portal thrombosis with partial/complete regression after loco-regional/systemic treatments is not currently an indication for LT, but may be considered as part of dedicated prospective investigations.

Marginal cadaveric grafts

Meta-analyses have confirmed LT as the therapy with the highest chances of curing HCC.[415] Therefore, LT should be considered in any HCC treatment strategy whenever possible, unless age and co-morbidities advise against transplant. The major limiting factor of LT in HCC is the scarcity of donated organs, with the additional problem of balancing the distribution of available organs equally among cancer *vs.* non-cancer indications. With the aim of enlarging the available organ pool to meet the growing demand of transplantation in patients with HCC, several surgical techniques have been developed. All these techniques produce the so-called "marginal graft" (also defined as "extended criteria livers").[416,417]

Marginal grafts definition includes: i) *living donor right lobe graft, cadaveric split livers* (in which an organ from cadaveric donors is divided and made available for two recipients of different size), ii) *organs with severe steatosis*, iii) organs recovered not only from *donation after brain death (DBD donors)* but also *after circulatory death (DCD donors)*.

As patients with HCC frequently show better liver function and lower model for end-stage liver disease (MELD) scores in comparison to patients undergoing LT for advanced cirrhosis, marginal grafts are preferentially proposed for HCC recipients according to the donor-recipient match principle, aimed at balancing the risks of organ and LT failures. Although initially concerns were raised regarding the use of marginal grafts for patients with HCC, recent reports have confirmed that marginal livers are currently used in up to 60% of HCC European recipients.[418,419] With respect to the use of donors after circulatory death, it has been recently shown that recipients who are transplanted with a good quality DCD liver do no worse than those transplanted with livers from DBD donors.[420] Notably, the DCD experience and results are improving, thanks to a new generation of resuscitation/recondition perfusion machines.

Although a retrospective study with competing-risk regression analysis has demonstrated that donor-related factors of poor quality livers, such as donor >60 years old, body mass index >35, diabetes and severe steatosis are associated with an increased rate of HCC recurrence after liver transplant,[421] the risk-benefit ratio of post-LT survival remains in favour of the use of marginal donors for patients with HCC.

Organ allocation and priority for HCC

Objective decisions on organ allocation within common waiting lists (prioritisation policies between HCC *vs.* non-HCC patients) are driven by various factors, whose relative weight is frequently modified according to local/regional contexts.[417]

The most frequent drivers of a balanced organ distribution among different transplant indications are based on exception points. Exception points assignment for patients with HCC listed for LT are currently based on:

- Tumour burden and presentation (see selection criteria paragraph above);
- Point progression over time (with/out cap and stand-by period before some categories of HCC receive points);[422–424]
- MELD score and MELD-combined scores such as HCC-MELD,[425] deMELD;[285] $MELD_{EQ}$;[408,426]
- Response to loco-therapies against the tumour, based on bridging or downstaging aims.[427–430]

Several studies have demonstrated that response to loco-regional therapies for HCCs while waiting for transplantation is correlated to post-LT cancer recurrence and can be used as a surrogate of tumour biology in outcome predictions.[431]

Novel MELD exception point systems for HCC, based on tumour characteristics and dynamics have been implemented in Europe and America, because of differential post-treatment responses and a risk of drop-out over time.[432,433] This evolution in HCC priority systems, together with the predicted relative increase in cadaveric graft availability due to a reduction in hepatitis C virus (HCV)-related diseases because of direct-acting antiviral treatment, are likely to increase the number of HCC considered for LT in the near future.[434–436] The issue must be considered and prospective protocol investigations on HCC transplant patients with HCV are required.

Any outcome prediction of LT in HCC must deal with the double and differential prognosis of cirrhosis and cancer. Main drivers for decision making in this contest are based on *Urgency* (*i.e.*, focussed on *pre-transplant* risk of dying without transplant) and *Utility* principles (*i.e.*, focussed on maximisation of *post-transplant* outcome). Those principles apply differently whether or not HCC appears on top of liver cirrhosis,[437] as summarised (Table 4).

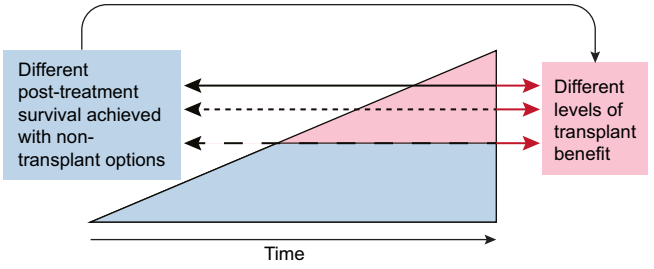
Studies have shown that additional specificities must be considered at the time of LT listing for HCC, as competitive non-transplant options exist for the large majority of patients with well-preserved liver function.[437,438] Particularly, transplant benefit (TB) considerations should be added to the conventional principles of urgency and utility when decisions on patients with HCC are made. TB is the net benefit in survival achieved by subtracting the survival that could be achieved by non-transplant options from the absolute post-LT survival[439] (Fig. 8). According to a pure transplant benefit approach, the LT indication in HCC may be counterintuitive, serving more effectively intermediate/advanced stages of HCC.[440] Also, the use of TB is limited by the fact that is difficult to be properly quantified ahead of transplant. However, it has been demonstrated that TB plays a strong important role in prioritising at least four conditions involving patients with HCC:[292,427,441,442]

- Decompensated cirrhosis (MELD >15–20) or non-cancer-related MELD exceptions with HCC within conventional Milan criteria (see above);

Table 4. Application of urgency and utility principles in liver transplantation for cirrhosis with or without HCC.

Cirrhosis	HCC + cirrhosis
High pre-transplant mortality	Low pre-transplant mortality
High post-transplant long-term recovery	Variable post-transplant cure, depending on tumour stage at operation
Predictable outcome with no transplant (MELD)	Composite prognostic factors and variable biology influencing outcome
No competitive options besides transplantation	Competitive options in selected patients subgroups
↓	↓
Urgency principle	**Utility principle**
Focussed on pre-transplant risk of dying without transplant	Focussed on maximisation of post-transplant outcome

HCC, hepatocellular carcinoma.



Allocation models considered for liver transplantation

Model	Definition
Urgency	Focused on pretransplant risk of dying: patients with worse outcome on the waiting list are given higher priority for transplantation (based on Child or MELD score)
Utility	Based on maximisation of post-transplant outcome, takes into account donor and recipient characteristics: mainly used for HCC since the MELD score poorly predicts post-transplant outcome in HCC due to the absence of donor factors and lack of predicting tumour progression while waiting
Benefit	Calculated by subtracting to the survival achieved with LT the survival obtained without LT. Ranks patients according to the net survival benefit that they would derive from transplantation and maximise the lifetime gained through transplantation. If applied to HCC without adjustments, it may prioritise patients at highest risk of recurrence.

Fig. 8. Models governing decision-making on prioritisation of liver transplant candidates with cirrhosis and HCC. HCC, hepatocellular carcinoma. Adapted from,[437] with permission.

- Barcelona Clinic Liver Cancer B patients (multifocal HCC) within validated expanded criteria (see above) and with disease control after having achieved objective response with downstaging treatment (Fig. 7) and not eligible for further treatments;[39]
- Recurrent/persistent HCC after potentially curative treatment (liver resection or ablation), if the persistent/recurrent tumour burden remains within conventional LT criteria (*i.e.*: the so-called "salvage LT"[301,443,444]);
- Patients within Milan criteria who are untreatable with liver resection or loco-regional therapies.

Notably, TB principles tends to prevail when cancer-related risk of drop-out and response to loco-regional treatments are taken into account. In fact, waiting list candidates slightly beyond the accepted limits of transplantability are significantly more likely to die or be removed from the waiting list than less advanced candidates (Milan Criteria) but – if prioritised and transplanted early by means of exception points – show similar survival in comparison to less advanced HCC.[428] As response to pre-LT treatment influences the risks of drop-out, LT eligibility and priority for HCC may not be determined completely up front, but come into focus after the best available therapy has been applied and discussed, within an adaptive approach also based on TB considerations.[430,432,433]

Neoadjuvant therapies in LT and downstaging within Milan criteria

LT candidates with HCC – if not treated – are inherently at risk of cancer progression while waiting, with an incremental risk of tumour progression and post-transplant cancer-related mortality related to HCC presentation and AFP variation over time.[290,404,445,446] Several studies and meta-analyses on loco-regional treatment have demonstrated significant advantages of neoadjuvant therapies in reducing the drop-out risk due to tumour progression.[412,422,447–449] Neoadjuvant protocols are very heterogeneous among centres, but hierarchic use of ablation and transarterial therapies in various combinations is almost universal, especially when expected waiting time is above six months.[450,451]

When defining neoadjuvant treatments, "*bridging*" describes treatment of accepted transplant candidates within Milan criteria while on the waiting list, while "*downstaging*" describes treatment used to bring patients whose tumour burden is outside accepted criteria for transplantation to within acceptable criteria. Acceptable criteria are defined as those criteria achieving an expected survival after LT equal to patients who meet transplant criteria without downstaging.[399] In the large majority of studies, patients are accepted as LT candidates when their HCC, presenting at an intermediate/advanced stage, is successfully down-staged to within the Milan criteria.[412,452,453] The consensus on the Milan criteria as an endpoint for downstaging protocols is influenced by the current MELD system, that assigns additional exception points to patients down-staged to within Milan criteria.

Response to bridging and downstaging treatments significantly influences not just drop-outs, but also the rate of post-transplantation tumour recurrences.[412,444] Interestingly, good response to downstaging is frequently related to the presence of histology markers of good prognosis in the treated HCC (*i.e.*: absence of microvascular invasion and satellites, low tumour grading), similarly to patients receiving LT within Milan criteria at presentation.[400,412] Thus, response to downstaging has an important role in predicting tumour aggressiveness. Ultimately, response to downstaging represents a selection tool for defining eligibility for transplant and refining priority in patients with different HCC presentations.[454–457]

As downstaging designates a selection strategy, its applicability depends on the context in which it is applied and on whether more restrictive *vs.* more relaxed criteria are defined

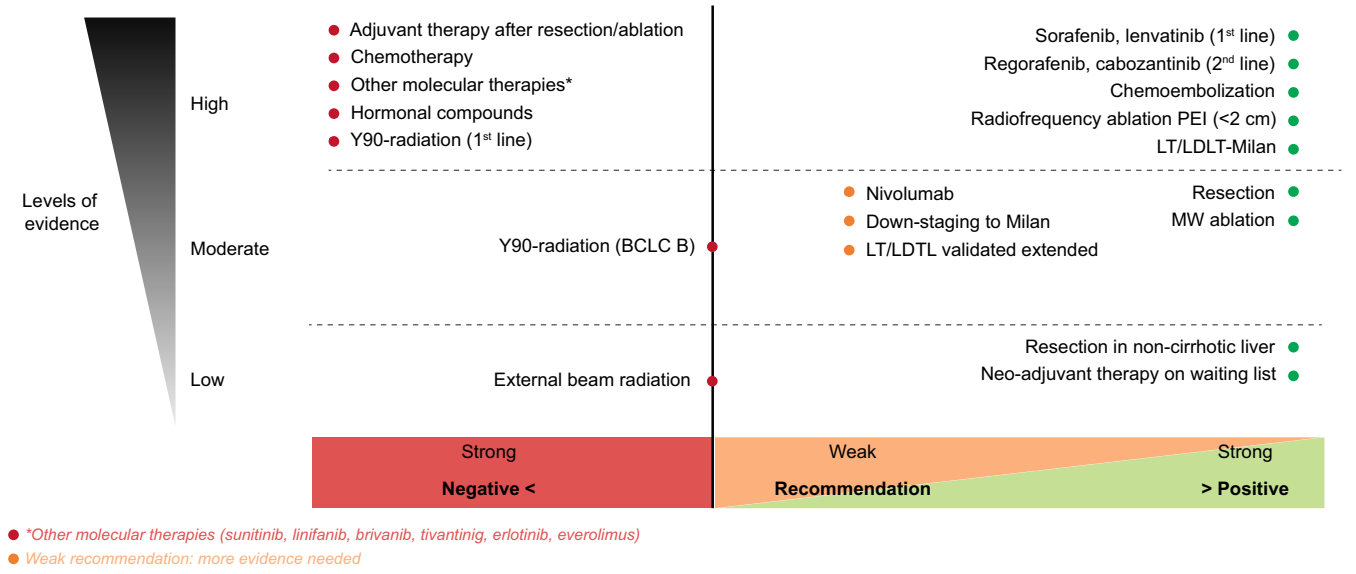


Fig. 9. Representation of EASL recommendations for treatment according to levels of evidence and strength of recommendation (adaptation of the GRADE system). LDLT, living donor liver transplantation; LT, orthotopic liver transplantation; MW, microwave; PEI, percutaneous ethanol injection; RF, radiofrequency ablation.

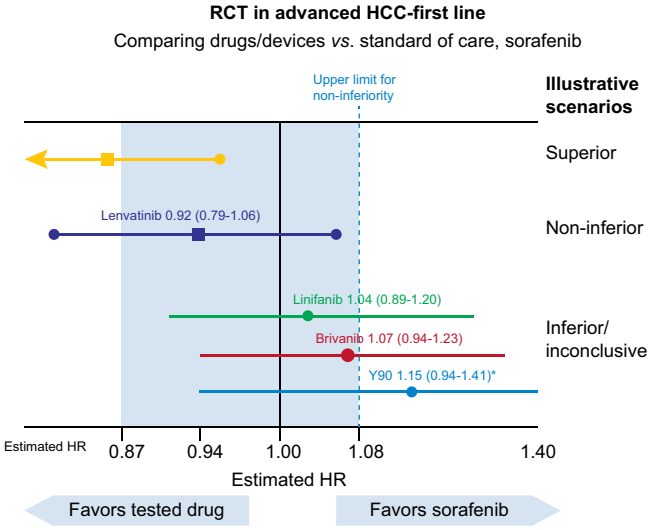


Fig. 10. Understanding non-inferiority results in advanced HCC. It is estimated that RCT testing drugs head-to-head to sorafenib in first line might have three potential results a) drug is superior to sorafenib if the HR (95% CI) boundaries do not cross the unity (no example so far). b) The drugs are non-inferior compared to sorafenib, if the HR (95% CI) boundaries fall between 1 and 1.08 (lenvatinib case), and C) the drug is inferior to sorafenib if the HR (95% CI) boundaries cross the 1.08 upper limit for non-inferiority (linifanib and brivanib cases). Also, the negative results of Y-90 *vs.* sorafenib are shown. To claim non-inferiority a specific trial needs to be conducted. (Modified from Llovet, *CCR 2014*). *These treatments are inferior or inconclusive. If the RCT have been designed for superiority (*i.e.* Y90 *vs.* sorafenib) a specific RCT with non-inferiority design is needed to claim non-inferiority. HCC, hepatocellular carcinoma; HR, hazard ratio; RCT, randomised controlled trial.

for starting and ending the strategy itself. The choice of Milan criteria as the endpoint for downstaging has been influenced by the MELD system that assigns additional exception points to patients down-staged to within Milan criteria. Incidentally, only two studies have determined upfront selection criteria for starting downstaging in patients carrying HCC beyond Milan Criteria. In those studies, HCCs eligible for downstaging were defined by the following size-and-number parameters: a) single lesion >5 cm but ≤6 cm, or 2 lesions ≤5 cm with total tumour diameter of ≤8 cm, or 4–5 nodules ≤4 cm with total tumour diameter ≤12 cm, plus AFP <400 ng/dl[408] or b): single lesion ≤8 cm, or 2–3 lesions ≤5 cm with total tumour diameter of ≤8 cm, or 4–5 nodules all ≤3 cm with total tumour diameter ≤8 cm, plus AFP <1,000 ng/ml.[412] With those restrictions, the drop-out rate from the protocols was limited to 10% and 34.7% respectively, namely within a much lower range compared to those studies in which more liberal access to downstaging was allowed, and in which the drop-out rate from the downstaging strategy itself was 44%–76%.[458,459] Therefore, restricting eligibility for downstaging protocols is recommended, in order to limit futile treatments and improve the success rate of the strategy. Prospective studies to address this issue are suggested.

Living donor LT for HCC

Living donor liver transplantation (LDLT) is the elective procedure for liver replacement in large parts of Asia, because of a shortage of deceased organ donation and higher incidence of HCC, possibly due to a higher frequency of viral hepatitis. In Europe LDLT still represents a debated second-line option, if cadaveric donation is not feasible or waiting time is prohibitively prolonged, with the procedure reserved to very experienced resection and transplantation centres. One may notice that after about 20 years of practice, LDLT in Europe has not been fully embraced and in some countries even abandoned. Currently LDLT represent 6–7% of the total number of LT performed yearly in Europe (data from ELTR and Eurotransplant 2017). The reasons for that are multifactorial and attain to donor risk, technical challenges both in the donor and the recipient operation, suboptimal cultural acceptance of possible failures, introduction of the MELD score and increased utilisation of marginal donors.[460] The risks and benefits of LDLT should be accurately evaluated in both donor and recipient, a concept known as *double equipoise*.[399,461]

Although there are no reasons to maintain substantial differences in donor source for HCC recipients, selection criteria for

cadaveric LT *vs.* LDLT differ and so does the rate of reported survival at five years. Overall, tumour size and number of tumour nodules considered suitable for LT are less restrictive for LDLT. This causes on average a reduction in expected survival that, however, is recognised as acceptable when the donation process is treated as a personal gift, rather than a resource to be distributed in the community. In Asia patients with LDLT beyond Milan criteria, including far advanced HCC, accounted for about 30% to 40% of total LDLT,[462] with exceptions also offered to patients with macrovascular invasion.[463] Notably, no prospective study on extended indications or transplant benefit advantages have been produced in this population. In Europe, LDLT remains a challenging transplant alternative in selected cases of HCC in which extended transplant indications may be explored.

Local ablation and external radiation

Recommendations

- Thermal ablation with radiofrequency is the standard of care for patients with BCLC 0 and A tumours not suitable for surgery (**evidence high; recommendation strong**). Thermal ablation in single tumours 2 to 3 cm in size is an alternative to surgical resection based on technical factors (location of the tumour), hepatic and extrahepatic patient conditions.
- In patients with very early stage HCC (BCLC-0) radiofrequency ablation in favourable locations can be adopted as first-line therapy even in surgical patients (**evidence moderate; recommendation strong**).
- Microwave ablation showed promising results for local control and survival (**evidence low**). Other ablative therapies are under investigation.
- Ethanol injection is an option in some cases where thermal ablation is not technically feasible, especially in tumours <2 cm (**evidence high; recommendation strong**)
- External beam radiotherapy is under investigation. So far there is no robust evidence to support this therapeutic approach in the management of HCC (**evidence low; recommendation weak**).

Over the past 30 years, several methods for chemical or thermal tumour destruction have been developed and clinically tested.[373] The seminal technique was percutaneous ethanol injection (PEI), which induces coagulative necrosis of the lesion as a result of cellular dehydration, protein denaturation, and chemical occlusion of small tumour vessels. Subsequently, thermal ablative therapies emerged, and are classified as either hyper-thermic treatments (heating of tissue at 60°–100 °C) – including radiofrequency ablation (RFA), microwave ablation (MWA), 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.

In parallel to the improvements in tumour ablation techniques, the efficacy of imaging-guidance tools, important for the procedures technical success, has recently been shown. Indeed, the accurate placement of an electrode or an applicator in the tumour is essential for achieving complete tumour control. According to personal experience, ultrasound, computed tomography (CT), and Cone-beam CT are the modalities of choice for guidance and immediate assessment. Fusion imaging enables the overlay of multiple imaging, such as real-time ultrasound and CT. It is most helpful in tumours barely visible on ultrasound and has been shown to decrease the risk of mistargeting.[464] Electromagnetic tracking guiding systems allow faster electrode placement into the target than conventional methods and could reduce the risk of bleeding complications.[465] Indeed, controlling the presence and volume of tumour necrosis at the end of the procedure is of the utmost importance in order to achieve complete ablation. This can be done with administration of IV contrast agents using ultrasound, Cone-beam CT, CT or magnetic resonance imaging (MRI).[466,467]

Percutaneous ethanol injection is a well-established technique for the treatment of nodular-type HCC that leads to complete necrosis in 90% of tumours <2 cm.[291,309] Yet, PEI is associated with incomplete necrosis in most HCCs >2 cm and suffers a high local recurrence rate, which may reach 49% in lesions exceeding 2 cm.[468] The distribution of alcohol inside the lesion cannot be well governed and usually does not extend beyond the cirrhotic fibrous tissue surrounding the tumour. Accordingly, all meta-analyses that have included randomised controlled trials that compared PEI with RFA have favoured RFA over PEI in terms of overall survival (OS), disease-free survival, and recurrence.[469–471] Another chemical ablation technique, percutaneous acetic acid injection, has not offered substantial advantages to PEI.[472,473]

The mechanisms of cell death in RFA are based on the frictional heat generated using high-frequency alternating current. Heat produces coagulative necrosis of the tumour and allows extension of the necrosis to a "*safety ring*" in the peri-tumoural tissue, which might eliminate small-undetected satellites. RFA has been evaluated as first-line therapy in early HCCs. In a series of 162 patients with cirrhosis, the OS and recurrence-free survival, were 67.9% and 25.9%, respectively.[474] A meta-analysis showed OS of 76% at three years for single HCCs <3 cm, with recurrence-free rates of 46%.[218] Significant predictors of poor OS are Child-Pugh class B, elevated serum alpha-fetoprotein level, and presence of portosystemic collaterals.[253,309,474] The only significant predictive factor of local tumour progression, which is approximately 30% at three years, is tumour size with a clear threshold at 2 cm in diameter.[253,307–309,474] OS in very early HCC (<2 cm) treated by RFA was demonstrated to be at least equal to surgical treatment in a Markov model[299] and in a cost-effective analysis based on data from a systematic review.[218]

Sub-capsular HCCs

Tumour location has been a matter of debate in RFA for two reasons: firstly, the technical success (whether a sub-capsular location is a risk factor of reduced effectiveness and local tumour progression) and secondly the risk of complications that could be higher in superficial tumours. Since the release of previous guidelines, a large study using propensity score matching has compared the long-term outcome of RFA in subcapsular or

non-subcapsular HCCs.[475] Various authors have shown that there were no significant differences in OS, local tumour progression, and major complication rates between the two groups.[475,476] It is worth remembering that some tumour location issues could be overcome by use of artificial ascites or by performing laparoscopy assisted ablation. However, in some instances a safe ablation of subcapsular tumours is unfeasible, depending on the location (*e.g.* close to the gallbladder or in cases of previous abdominal surgery preventing detaching of liver capsule from bowel loops, *etc.*). Clearly, the retrospective nature of the above studies suffers from inclusion bias, excluding subcapsular lesions considered at excessive risk of complications.

Intermediate HCCs

Selected patients with tumours larger than 3 cm, oligo-nodular multiple (>3 nodules <3 cm) tumours or advanced compensated liver failure (Child-Pugh B not clinically decompensated) can be reasonably treated with RFA on an individual basis or with a combination of two treatment modalities. Although these treatments provide good results, they are unable to achieve response rates and outcomes comparable to those observed in small HCCs. Yet, the large tumours benefit from improvements in tumour ablation technique and especially the multipolar approach.[477–479] In large HCC, another approach is to combine RFA with transarterial chemoembolisation. Recent meta-analyses have shown that the combination of RFA with transarterial chemoembolisation significantly increases OS and recurrence-free survival, without a significant difference in major complications, but the combination is technically and resource demanding, and external validation in Western countries is awaited.[480–482]

RFA *vs.* surgery

There have been several studies, trials and meta-analyses that have compared RFA with surgical resection as a first-line treatment for patients with small, solitary HCC,[482] as well as a recent Cochrane review.[483] The Cochrane review included four trials, representing 574 patients, comparing RFA to surgery in patients with early resectable HCC. The authors did not find evidence of a difference in mortality at maximal follow-up between the two treatments. The proportion of patients with HCC recurrence in the liver was lower in the surgery group than in the RFA group, while the number of serious adverse events and any adverse events was lower in the RFA group than in the surgery group. The length of hospital stay was shorter in the RFA group than in the surgery group. None of the trials reported health-related quality of life. Finally, on the basis of a systemic review of the literature, RFA was shown to be the most cost-effective therapeutic strategy in very early HCC (single nodule <2 cm) and in the presence of two or three nodules ≤3 cm.[218] When deciding between surgery and ablation, it must be considered that similar prognostic factors affect RFA and surgery, namely liver dysfunction and tumour size, but with significantly different weightings and rates of progression between the two treatment modalities. Prognosis after surgery is more heavily affected by the progression of liver dysfunction (as expressed by the model for end-stage liver disease score) than RFA, even in compensated patients in Child-Pugh A, whereas RFA suffers a more abrupt drop in effectiveness with increasing tumour size than surgery.[370] Additionally, in daily practice, tumour location has highly important consequences on the choice between thermal ablation or surgery, as only a limited number of cases are equally suitable for both techniques.[484]

RFA *vs.* microwave ablation

In RFA, an electric current in the RF range is delivered through one or several needle electrodes (monopolar or multipolar) producing heat-based thermal cytotoxicity. MWA uses electromagnetic energy that heats the tissue and is less prone to heat sink effect, meaning that treatment efficacy is less affected by vessels located in the proximity of the tumour. In the previous EASL/EORTC guidelines, MWA microwave was under investigation. Since 2011, we have found 15 articles, which have compared RFA with MWA (Table S1). All but one are retrospective, most of them were percutaneous procedures, and the number of patients included varies from 35 to 879 patients. In all series, OS was not significantly different between RFA and MWA. The rate of complete response was not significantly different. In 10 studies that evaluated the rate of local recurrence, MWA showed a significant decrease in local recurrence in four studies, while results were not different between the two techniques in the other six studies. The rate of complications was not different.

Similarly, recent meta-analyses indicate a similar efficacy between the two percutaneous techniques, with one study showing possible superiority of MWA in larger HCCs.[485,486] It is worth pointing out that different devices with single RF electrodes (*e.g.* cool tip *vs.* various hooked needles) were shown to produce similar rates of adverse events and similar necrosis volumes,[487] whereas different MWA devices seem to produce substantially different ablation volumes and shapes.[488]

Treatments under investigation

Laser ablation and cryoablation have been proposed for local ablation in HCC. Since the previous guidelines, only one randomised trial has compared RFA with laser ablation in patients with HCC, within Milan criteria, with a non-inferiority design. Laser ablation results were not inferior to RFA in complete tumour ablation, time to local progression, and OS.[489] However, laser ablation requires higher operator skills than RFA or MWA because of the need to position multiple fibres inside the same tumour, with adequate spatial distribution, although it might be safer in difficult locations.[490]

So far one randomised controlled trial has compared cryoablation with RFA in 360 patients with HCC. No differences were observed between the two techniques concerning OS, and tumour-free survival. Local tumour progression was significantly lower in the cryoablation group than the RFA group.[491] Yet the complication rate is not negligible, particularly because of the risk of "*cryoshock*", a life-threatening condition resulting in multi-organ failure, severe coagulopathy and disseminated intravascular coagulation following cryoablation.

Irreversible electroporation (IRE) is a novel form of tissue ablation that uses high-current electrical pulses to induce pore formation of the cell lipid bilayer, leading to cell death. It is not affected by heat sink and may result in less collateral damage based on its mechanism of action. In a short series of

patients with HCC who underwent liver transplantation, most tumours showed complete pathologic necrosis without any viable tumour cells, with preservation of bile ducts within the treatment area.[492,493] However, delivery of IRE requires general anaesthesia with deep muscular blockade, given the muscular contraction induced by IRE stimuli, making its performance more demanding than RFA/MWA, and making it costlier in terms of resources.

The other non-chemical non-thermal ablation techniques are still undergoing clinical investigation. High-intensity focussed ultrasound is a novel ablative approach reported in cohorts of patients with small tumours, but no randomised studies are available.[494,495]

External radiation therapy

Many series and some trials have been reported on the efficacy and tolerability of different techniques of external beam radiotherapy in different stages of HCC,[496] but we do not have any well conducted prospective trial to consider radiotherapy as an efficient and proven option.

Most trials and series tested the interesting combination of external beam radiotherapy with TACE or other intra-arterial treatments. A systematic review and meta-analysis focussed on trials comparing TACE with or without radiotherapy[497] reported 25 trials (including 11 randomised controlled trials) involving 2,577 patients and concluded that patients receiving the combined treatment had a better survival and response rate than those treated with TACE alone, at the price of more gastroduodenal ulcers and transient increases in aminotransferases and bilirubin. But in a systematic review of randomised studies, comparing TACE alone *vs.* TACE plus external beam radiotherapy, all trials were rated as low to very low quality.[498]

Results of a planned interim analysis (analysing 69 patients) of an ongoing prospective randomised trial comparing TACE to proton beam radiation therapy in patients within Milan or San Francisco transplant criteria,[499] showed a trend toward improved local control and progression-free survival with radiotherapy.

Many other therapeutic areas have been tested including radiotherapy in first-line treatment, particularly in Korea.[500] Patients with portal vein thrombosis were considered as a good target,[501] with some cases of secondary liver transplantation.[502,503] A Surveillance Epidemiology End Results (SEER) database analysis comparing ablative techniques and external radiation in solitary nodules,[504] showed significantly better results for ablative techniques in nodules over 3 cm in diameter, for those under 3 cm there was no significant difference, but there was a major trend in favour of ablative techniques. Stereotactic body radiotherapy was safely used as a bridge to liver transplantation in patients with HCC in a large Canadian series, with comparable drop-out rates and survival to TACE and RFA, from time of listing.[505]

The consensus of experts and a recent review[506,507] concluded that despite signs of efficacy and safety, there was a compelling need for large prospective studies and particularly randomised phase III trials evaluating the role of radiotherapy. Notably, a recent phase II clinical trial, mostly in patients with HCC (69/90), tested 'individualised adaptive stereotactic body radiotherapy' in patients at high risk of liver damage based on indocyanin green retention at 15 min (assessed at different phases of the treatment). This new strategy needs further evaluation, but its tolerability seems very good.[508]

Transarterial therapies

Recommendations

- TACE is recommended for patients with BCLC stage B and should be carried out in a selective manner (**evidence high; recommendation strong**). The use of drug-eluting beads has shown similar benefit to conventional TACE (cTACE; gelfoam-Lipiodol® particles) and either of the two can be utilised (**evidence high; recommendation strong**). TACE should not be used in patients with decompensated liver disease, advanced liver and/or kidney dysfunction, macroscopic vascular invasion or extrahepatic spread (**evidence high; recommendation strong**). There is insufficient evidence to recommend bland embolisation, selective intra-arterial chemotherapy and lipiodolisation (**evidence moderate**).
- TARE/SIRT using yttrium-90 microspheres has been investigated in patients with BCLC-A for bridging to transplantation, in patients with BCLC-B to compare with TACE, and in patients with BCLC-C to compare with sorafenib. Current data show a good safety profile and local tumour control but fail to show overall survival benefit compared to sorafenib in BCLC-B and -C patients. The subgroup of patients benefitting from TARE needs to be defined (**evidence moderate**).
- There is insufficient evidence to recommend scores that better select BCLC-B candidates for first TACE or for subsequent sessions (**evidence moderate**).

Transarterial chemoembolisation

Transarterial chemoembolisation (TACE) is the most widely used primary treatment for unresectable HCC,[325,509] and was the recommended first-line therapy for patients with intermediate-stage disease in the previous guidelines.[1] HCC exhibits intense arterial neo-angiogenic activity during its progression. The rationale for TACE is that the intra-arterial infusion of a cytotoxic agent followed by embolisation of the tumour-feeding blood vessels will result in a strong cytotoxic and ischaemic effect targeted to the tumour since this tends to become entirely fed by arterial inflow, unlike the surrounding parenchyma which receives the majority of inflow through the portal system. TACE should be distinguished from chemo-lipiodolisation, which involves the delivery of an emulsion of chemotherapy mixed with Lipiodol®, bland transcatheter embolisation (TAE), where no chemotherapeutic agent is delivered, and intra-arterial chemotherapy, where no embolisation is performed. Details on the distinct types and definitions of image-guided transcatheter embolisation have been reviewed elsewhere.[510,511]

Conventional TACE

This procedure is also called Lipiodol TACE. It involves transcatheter delivery of chemotherapy emulsioned with Lipiodol, followed by vascular stagnation achieved with particle embolisation. The combination of Lipiodol drug emulsion followed by particle embolisation demonstrates a better pharmacokinetic effect over Lipiodol/drug emulsion without particle embolisation or drug alone and induces substantially greater tumour necrosis compared to injection of Lipiodol alone or as a drug

emulsion without particle embolisation.[512] Moreover, the combination of Lipiodol/drug emulsion with particles also demonstrates better long-term survival than injection of Lipiodol/drug emulsion without particles.[513] Retention of Lipiodol can also be regarded as an additional imaging biomarker.[512]

The most common drugs used during conventional TACE, either as single agents or in combination regimens, are doxorubicin or epirubicin, cisplatin or miriplatin.[514] These anticancer drugs have been tested amongst others on three human HCC cell lines. The most effective drug was idarubicin which is currently under evaluation in clinical trials.[515,516]

Survival benefits of TACE compared to best supportive care were demonstrated by two randomised controlled trials,[312,313] one of which identified treatment response as an independent predictor of survival,[312] and several meta-analyses.[310,517] As a result of these investigations, TACE is the standard of care for patients who meet the criteria for the intermediate-stage of the BCLC staging system, *i.e.* those with multinodular and/or large HCC, absence of cancer-related symptoms and no evidence of vascular invasion or extrahepatic spread. In 2011, a meta-analysis by Cochrane investigators challenged the efficacy of TACE.[518] Several biases contained in this assessment, including the use of trials with inappropriate control arms or target populations leading to poor outcomes, call into question the impact of this investigation.

Recently, a systematic review on conventional TACE has included 101 articles, with a total of 10,108 patients.[514] The objective response rate was 52.5% (95% CI 43.6–61.5), and the overall survival (OS) was 70.3% at one year, 51.8% at two years, 40.4% at three years, and 32.4% at five years with a median OS of 19.4 months (95% CI 16.2–22.6). The five most common adverse events were liver enzyme abnormalities (18.1%), fever (17.2%), haematological/bone marrow toxicity (13.5%), pain (11%), and vomiting (6%), which are related to the occurrence of postembolization syndrome. Overall mortality rate was 0.6% and the most common cause of death was related to acute liver insufficiency. Very recently, an RCT suggested that the combination of intravenous steroids with antiemetics for three days at the time of TACE reduce the incidence of the postembolization syndrome in comparison to antiemetics alone,[519] with a good safety profile, but external validation is required before any such policy can be endorsed.

TACE with drug-eluting beads

Strategies to improve anti-tumoural activity and clinical benefits with chemoembolisation have been launched. The ideal TACE scheme should allow maximum and sustained intratumoural concentration of the chemotherapeutic agent with minimal systemic exposure, along with calibrated tumour vessel obstruction.

Embolic microspheres have the ability to sequester chemotherapeutic agents and release them in a controlled mode over a one-week period. TACE with drug-eluting beads (TACE-DEB) using calibrated doxorubicin-carrying microspheres has shown more sustained and tumour-selective drug delivery and permanent embolisation.[520] A randomised phase II study comparing the short-term outcomes of TACE-DEB and conventional TACE indicated some advantages of TACE-DEB in terms of toxicity and radiologic tumour response, particularly in fragile subgroups, such as Child-Pugh B and performance status >0 patients, and in those with bilobar or recurrent tumours.[521] However, the leading safety issue favouring TACE-DEB was alopecia. Another RCT compared TACE-DEB and conventional TACE in patients followed-up for at least two years or until death. There were no differences in OS (one- and two-year survival rates were 86.2% and 56.8% after TACE-DEB and 83.5% and 55.4% after conventional TACE, respectively). There were no differences according to the median number of procedures (two in each arm), in-hospital stay and local and overall tumour response (median TTP of nine months in both arms). The incidence and severity of adverse events did not differ between the arms, except for post-procedural pain, which was more frequent and severe after conventional TACE.[522] This result was confirmed by a meta-analysis based on seven studies (693 patients) that demonstrated that the two procedures had equivalent results.[523] Conversely, a retrospective study has shown that biliary injuries, intrahepatic bilioma, and global hepatic damage were significantly higher following TACE-DEB than with conventional TACE, especially in patients with advanced cirrhosis.[524] Accordingly, at present there is insufficient evidence to recommend one TACE technique over another and the choice is left to the operator.

Patient selection

The indication for TACE should consider tumour burden, underlying liver disease, and performance status. Patients with declining performance status (Eastern Cooperative Oncology Group PS ≥2) or severe hepatic decompensation (Child-Pugh C or Child-Pugh B decompensated cirrhosis) are unlikely to benefit from TACE, which is often detrimental in such patients. Inadequate hepatic function, such as serum bilirubin >2 mg/dl, and a tumour burden >50% of total liver volume, increase the risk of hepatic decompensation after TACE.[325,512] Macrovascular invasion of the main portal branches or the main portal vein are contraindications for TACE.[313] Impaired portal vein blood flow (for example, a portal vein thrombus, hepatofugal blood flow) is considered an absolute contraindication for TACE, although it can be performed safely in patients with segmental or sub-segmental portal vein obstruction if the treatment is selective.[525] However, TACE is not recommended in patients with segmental portal vein tumour invasion. Such indications should be discussed in multidisciplinary team sessions, in light of TARE and alternative first and second-line systemic treatments. Patients with biliary-enteric anastomosis or biliary stent are at higher risk of hepatic abscess, therefore other treatments should be preferred. As Barcelona Clinic Liver Cancer (BCLC) stage B represents a heterogeneous group of patients, a subclassification was proposed in order to select patients most likely to benefit from TACE treatment.[316] According to the available information, the best candidates are those patients with uni- or pauci-nodular disease without vascular invasion or metastases, who are asymptomatic and have a Child-Pugh stage of ≤B7. In such patients, the median survival after TACE in modern series is 40–50 months.[293,314,315]

Technical factors

Super-selective chemoembolisation is recommended to increase treatment efficacy and minimise the ischaemic insult to non-tumoural tissue. Then, identification of tumoural feeders is crucial to better target the tumour and obtain complete necrosis. It can be done prior to the procedure on arterial phase contrast-enhanced CT and is best in the angiographic suite with 3D-angiography obtained with a rotational flat panel detector

system (cone-beam CT). Additionally, dedicated computer-aided software may help identify tumour feeders.[526] Contrast-enhanced cone-beam CT imaging obtained immediately after TACE enables assessment of treatment success.

Treatment schedule

To date, no solid data suggest that scheduled TACE at regular intervals is more or less effective at improving patient survival than on demand TACE according to tumour response assessment. However, the repetition of TACE procedures according to an aggressive schedule (*i.e.* TACE every two months) might induce liver failure in an unacceptable proportion of patients.[527] Given the improvement in imaging techniques in detecting residual viable tissue, at present a subsequent course of TACE appears recommended only when residual viable HCC is documented by contrast-enhanced imaging, CT, rather than planned upfront regardless of the outcome of the first TACE session.

After initial TACE success, the treated tumours gain vascularisation and may be re-treated. The decision on when TACE therapy should be interrupted is complex. In recent years, several scores have been proposed to guide the decision to re-treat.[528–531] Regrettably, their applicability is controversial and such scoring systems probably identify patients who were poor candidates for TACE at baseline, as defined in these guidelines.[532–535] TACE should not be repeated when substantial necrosis is not achieved after two rounds of treatment or when follow-up treatment fails to induce marked necrosis at sites that have progressed after an initial tumour response. Additionally, TACE should not be repeated upon 'untreatable progression' defined as tumour progression associated with a clinical profile that prevents re-treatment. Definitions of untreatable progressions may include major progression –extensive liver involvement, extrahepatic metastasis or vascular invasion – but also minor intrahepatic progression associated with impaired liver function and performance status.[326] Finally, doxorubicin like any other anthracycline may induce cardiotoxicity. It is mostly a dose-dependent chronic cardiomyopathy. Left ventricular ejection fraction should be checked by echocardiogram in patients receiving multiple TACE sessions and the cumulative dose should not exceed 450 mg/m.[2]

Combination of TACE and RFA

In patients with HCC, the combination of TACE and RFA is associated with significantly higher OS and recurrence-free survival, than RFA monotherapy, without a significant difference in major complications. This benefit is more important in HCC larger than 3 cm in diameter,[480,536,537] however the combination of the two techniques on the same occasion is quite demanding in terms of resources.

Combination of TACE and antiangiogenics

The local hypoxia and ischaemic necrosis achieved by TACE results in activation of hypoxia-inducible factors (HIFs) and increased levels of vascular endothelial growth factor (VEGF). Accordingly, the combination of TACE with anti-angiogenic agents might constitute an effective strategy to improve outcomes. Sorafenib, which inhibits the vascular endothelial growth factor receptor receptors, has been extensively evaluated in combination with TACE. This combination therapy has shown an acceptable safety profile, but conclusive efficacy has not been demonstrated.[538–540] Similarly, negative results were obtained for brivanib, an inhibitor of VEFGR2 and the fibroblast growth factor receptor, as an adjuvant to TACE in patients with HCC.[541] Likewise, Orantinib combined with cTACE did not improve overall survival in patients with unresectable hepatocellular carcinoma.[542]

Transarterial embolisation

Four meta-analyses compared the outcomes of TACE *vs.* TAE.[517,543–545] All of them showed that the OS was statistically similar between the two groups. More recently, a randomised trial of 101 patients did not find differences between TACE and TAE in terms of tumour response, progression-free survival and OS,[546] but nearly half of the patients recruited were at an advanced stage, limiting the results' reliability. These results are in line with a Cochrane review on TACE advocating for more adequately powered and bias protected trials.[518] Yet, the standard of care for patients with intermediate HCC is TACE in the vast majority of institutions, while very few will perform TAE only.

Other indications of TACE

TACE is also used in patients with early-stage HCC as a bridge to liver transplantation or when liver transplantation, hepatic resection, and image-guided ablation are not possible, in keeping with the stage migration strategy.[547] Actually, two surveys, an Italian one and an international one, have shown that TACE is widely used outside intermediate HCCs.[509,548] Both demonstrated that TACE represents a major part of daily clinical practice in patients with HCC worldwide. Although TACE is the first-line treatment option for intermediate-stage HCC, in real life approximately 40% of TACEs are performed in either early or, more rarely, advanced stages.[293,314,315,546,549]

Selective internal radiation therapy

Selective internal radiation therapy (SIRT) also called radioembolization is defined as the infusion of radioactive substances such as 131-Iodine-labelled Lipiodol[550] or microspheres containing yttrium-90 (Y90)[511] or similar agents into the hepatic artery. Given the hypervascularity of HCC, intra-arterial-injected microspheres are preferentially delivered to the tumour-bearing area and selectively emit high-energy, low-penetration radiation to the tumour. Currently, the most popular technique uses resin or glass microspheres coated with Y90, a ß-emitting isotope. This treatment requires a close collaboration between interventional radiologists, nuclear medicine specialists, radiopharmacists, and physicists. Patients undergo preliminary angiography of the hepatic artery, and protective coiling of extrahepatic branches if necessary. In the same session, 99Tc macroaggregated albumin is injected into the hepatic artery using the same catheter position chosen for the scheduled SIRT session. Calculation of the dose to the tumour, dose to the adjacent liver, hepato-pulmonary shunt fraction, and tracer distribution are evaluated with macroaggregated albumin single-photon emission CT imaging. Severe lung shunting and extrahepatic uptake contraindicate the procedure. Patients are usually readmitted for SIRT one or two weeks later. SIRT is performed in a lobar, sectorial, or segmental approach according to tumour size and location. In patients with HCC developed on chronic liver disease, whole-liver treatment in one session is discouraged. Because of the minimally embolic effect of Y90 microspheres, treatment can be safely used in patients with portal vein thrombosis.[551] Cohort studies reporting long-term outcomes showed a median survival time of 16.9 months to

17.2 months for patients at intermediate stages and 10 months to 12 months for patients at advanced stages with portal vein invasion.[382,552–554] Objective response rates range from 35% to 50%.[382,552,554] Around 20% of patients present liver-related toxicity and 3% treatment-related death,[552] but adverse events are neither more common nor more severe in elderly patients, and survival is no shorter.[555]

SIRT *vs.* sorafenib

One of the most common indications of SIRT is treatment of patients with locally advanced HCC. Two RCTs comparing efficacy and safety in patients treated with SIRT *vs.* sorafenib have completed patient enrolment and have been presented.[556,557] In both studies, designed for superiority of SIRT, the primary endpoint was not reached as no statistically significant differences in OS were observed in intention-to-treat or per-protocol populations. In both studies, tumour response rate was significantly higher with SIRT, although this finding did not translate into longer survival. In both trials, the applicability of Y-90 was limited to 72–77% of patients because of treatment contraindications. In the SIRveNIB trial,[557] progression-free survival and time to progression were significantly higher in the SIRT group than in the sorafenib group in the treated population. In the SARAH trial,[556] the total and median number of treatment-related adverse events per patient were twice as frequent with sorafenib *vs.* SIRT including Grade ≥3 treatment-related adverse events. However, the course of the adverse event (rate of remission in the two arms) was not reported. A head-to-head RCT of SIRT *vs.* sorafenib is ongoing, and the added value of sorafenib in patients treated with SIRT is being evaluated in another RCT (SORAMIC trial). Another phase III clinical trial (STOP-HCC) evaluating yttrium-90 trans-arterial radioembolization (TheraSphere®) prior to sorafenib *vs.* Sorafenib alone in the treatment of patients with unresectable HCC is ongoing. At present, the survival benefit of SIRT compared to sorafenib in advanced HCC is still not proven, and its use either alone or in combination with systemic therapy should only be adopted after multidisciplinary board discussion.

SIRT *vs.* TACE

Up to now, all studies comparing SIRT with TACE have been retrospective with a small number of patients. Compared to TACE, SIRT induces less toxicity (possibly because of better patient selection in those treated with SIRT than those treated with TACE), provides significantly longer time to progression and better tumour control, and maintains higher quality of life, although it does not provide longer survival.[558–560] Regrettably, its performance is more demanding than TACE and it is less available.

Other indications

Few studies have evaluated SIRT as a bridge to liver transplant. In a small series, patients treated with SIRT showed better tumour control and a higher proportion received liver transplantation than those with TACE, leading to speculation that SIRT could reduce drop-out from transplant waiting lists.[560] SIRT has also been tested in patients with borderline resectable HCC. Besides its effect on tumour control, SIRT might prepare or select patients for surgery as it induces substantial hypertrophy in the liver lobe contralateral to the target.[561]

Systemic therapies

Recommendations

- Sorafenib is the standard first-line systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh A) and with advanced tumours (BCLC–C) or earlier stage tumours progressing upon or unsuitable for loco-regional therapies (**evidence high; recommendation strong**).
- Lenvatinib has been shown to be non-inferior to sorafenib and is also recommended in first-line therapy for HCC given its approval. It is indicated for patients with well-preserved liver function (Child-Pugh A class), good performance status and with advanced tumours – BCLC-C without main portal vein invasion – or those tumours progressing upon or unsuitable for loco-regional therapies (**evidence high; recommendation strong**).
- There are no clinical or molecular biomarkers established to predict response to first or second-line systemic treatments (**evidence moderate**).
- Regorafenib is recommended as second-line treatment for patients tolerating and progressing on sorafenib and with well-preserved liver function (Child-Pugh A class) and good performance status (**evidence high; recommendation strong**). Recently, Cabozantinib has shown survival benefits *vs.* placebo in this setting.
- Based on uncontrolled but promising data, immune therapy with nivolumab has received FDA approval in second-line treatment, pending phase III data for conventional approval. At present, the data are not mature enough to give a clear recommendation (**evidence moderate; recommendation weak**).
- Treatments that failed to meet their endpoints in randomised trials are not recommended. Further clinical trials are needed to confirm claims of non-inferiority (Fig. 10), or any trends of better outcome identified in subgroup analysis (**evidence high**). TARE in combination with systemic therapy is under investigation.
- Patients at BCLC D stage, who are not candidates for liver transplantation should receive palliative support, including management of pain, nutrition and psychological support. In general, they should not be considered for clinical trials (**evidence low; recommendation strong**).

Molecular pathogenesis and targets for therapies

Molecular targeted therapies have changed the landscape of cancer management. Molecular subclasses of hepatocellular carcinoma (HCC) have been proposed as proliferation/non-proliferation, and the key drivers of this cancer have been identified after sequencing more than 1,500 samples in several studies.[562] The most prominent drivers (TERT, CTNNB1 and TP53) are currently not actionable mutations. Potential targets for precise therapies with monoclonal anti-bodies and tyrosine kinase

inhibitors (TKIs), such as high-focal amplification FGF19 or VEGFA, have a prevalence of less than 10%.[563,564] Three systemic drugs have shown survival benefits in the setting of phase III studies for advanced HCC, sorafenib and lenvatinib in first-line treatment and regorafenib in second-line.[320–323] These drugs are multi-kinase inhibitors, abrogating several pathways simultaneously. At ASCO GI in January 2018 a fourth drug, cabozantinib (60 mg po qd) showed superiority over placebo in second- and third-line treatment with an improved overall survival from 8.0 months to 10.2 months.[324] Promising signals of efficacy have been reported in large phase II studies with the checkpoint inhibitor nivolumab.[565] So far, no proof-of-concept biomarker-enriched study has yet demonstrated efficacy for precision medicine in HCC.

Treatments for advanced HCC

Hepatocellular carcinoma is recognised as among the most chemo-resistant tumour types, and until 2007 no systemic drug was recommended for patients with advanced tumours, 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 tumours.[320,321] Following the approval of sorafenib, several substances were tested for either non-inferiority (brivanib, linifanib)[566,567] or superiority (sunitinib, erlotinib plus sorafenib)[568,569] but most of them did not reach their primary endpoint. Furthermore, systemic chemotherapy with doxorubicin[570] or FOLFOX[571] did not demonstrate survival benefits. Moreover, two recent phase III superiority trials comparing internal radiation with Y-90 resin microspheres *vs.* sorafenib did not hit the primary endpoint.[556,557] Meanwhile, phase III trials investigating brivanib, everolimus, ramucirumab, and tivantinib in second-line therapy failed to show improved outcome compared to placebo.[295,572–574] Toxicity in the setting of impaired liver function, lack of efficacy of the investigational substance, and an imbalance in prognostically relevant factors in the different study arms have all been discussed as reasons for the large number of unsuccessful phase III trials.[575]

It took 10 years from the approval of sorafenib for a second phase III trial to be positive, defining a role for another TKI, regorafenib, for patients progressing on sorafenib.[322] Very recently, lenvatinib, an anti-angiogenic TKI was found to be non-inferior to sorafenib, offering another upfront therapy for patients with HCC.[323] Furthermore, the positive results of cabozantinib *vs.* placebo in second-line (CELESTIAL trial) were presented in January 2018 at ASCO GI.[324] High expectations characterise recently published and ongoing trials investigating checkpoint inhibitors, the current mainstay of immune oncology, as a new treatment option for HCC. Until now, only uncontrolled data exist, however, the objective response rates (15–20%) and the median survival reported (16 months) for nivolumab, a programmed cell death protein-1 (PD-1) immune checkpoint inhibitor, are unseen with other therapies and raise hope for a rapid broadening of the therapeutic armamentarium in HCC beyond TKIs.[565]

First-line therapies

Sorafenib

Sorafenib, an oral multi-TKI, was the first drug to demonstrate a survival benefit in patients with advanced HCC. Following an initial phase II study showing a signal of efficacy,[576] a large double-blinded placebo-controlled phase III investigation was conducted, leading to positive survival results.[320] In this trial, the median overall survival (OS) of patients in the sorafenib group was 10.7 months compared to 7.9 months in the placebo group (HR, 0.69; 95% CI 0.55–0.87; $p = 0.00058$), representing a 31% decrease in the relative risk of death. 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.[321] Sorafenib is well tolerated, the most common grade 3 drug-related adverse events observed are diarrhoea and hand-foot skin reaction, which occurred in 8–9%, and 8–16% of patients, respectively. Discontinuation due to adverse events was 15% in the sorafenib arm and 7% in the placebo. As a result, sorafenib received approval by regulatory agencies in 2007. Following the approval of sorafenib, several phase III trials compared sorafenib with investigational agents, resulting in a median OS of around 10 months (range between 6.5 and 11.8 months [Table 5]). In addition, several post-marketing studies produced real-life data and reported OS for Barcelona Clinic Liver Cancer (BCLC) B patients of 15.6–20.1 months and for BCLC-C of 8.4–13.6 months.[577–580]

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 tumours, BCLC-C, or tumours progressing on loco-regional therapies (concept of treatment stage 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,[581,582] however, the reported outcome for Child-Pugh B patients from the non-interventional GIDEON trial was poor.[583] Sorafenib treatment should be maintained at least until radiographic progression, and beyond that point second-line treatment with regorafenib is recommended.

Sorafenib has been tested in the adjuvant setting after resection or complete local ablation for early HCC stages and in combination with chemoembolisation for intermediate stages.[394,538,540] These trials did not support the use of sorafenib as an adjuvant agent nor in combination with TACE.

Lenvatinib

Lenvatinib is an oral multi-kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR1-3); fibroblast growth factor receptor (FGFR1-4); platelet-derived growth factor receptor α (PDFGRα), RET, and KIT.[584] Lenvatinib was investigated in an open-label, phase III, multicentre, non-inferiority trial involving patients (two-thirds from the Asia-Pacific region) with advanced HCC (excluding main portal vein invasion and >50% tumour to total liver volume occupancy), Child-Pugh A, performance status 0/1, randomised to lenvatinib (body weight ≥60 kg: 12 mg/day; <60 kg: 8 mg/day) *vs.* sorafenib (Table 5). The study met its primary endpoint of non-inferiority in OS (median OS: lenvatinib, 13.6 months *vs.* sorafenib, 12.3 months; hazard ratio [HR]: 0.92; 95% CI 0.79–1.06). Lenvatinib also improved progression-free survival (7.4 months *vs.* 3.7 months on sorafenib) and TTP (8.9 months *vs.* 3.7 months on sorafenib). In terms of response, the objective response rate defined by modified Response Evaluation Criteria In Solid Tumours (mRECIST) was significantly better for lenvatinib (24.1% *vs.* 9.2% sorafenib; $p < 0.001$). Grade ≥3 TEAEs were more common with lenvatinib *vs.* sorafenib (57% *vs.* 49%, respectively). The most common grade 3/4 treatment-related AEs with lenvatinib and sorafenib, respectively, were hypertension (23% *vs.* 14%),

decreased weight (8% *vs.* 3%), decreased platelet count (6% *vs.* 3%), elevated aspartate aminotransferase (5% *vs.* 8%), decreased appetite (5% *vs.* 1%), diarrhoea (4% *vs.* 4%), and palmar-plantar erythrodysesthesia (3% *vs.* 11%). Median time on lenvatinib and sorafenib was 5.7 months and 3.7 months, respectively. These results indicate that lenvatinib is an active drug that provides clinically significant benefits to patients with advanced HCC or those progressing to chemoembolisation.[323] The open-label design makes it difficult to interpret other differences related to patient reported outcomes. No cost-effectiveness studies comparing both drugs are available. In summary, the panel recommend its use in the indicated populations once the drug is approved by regulatory agencies.

Treatments with no benefit in first-line

Sunitinib is an oral multi-TKI approved for the treatment of renal cell carcinoma, gastrointestinal stromal tumours and pancreatic neuroendocrine tumours. A multicentre, open-label sorafenib-controlled randomised phase III trial was prematurely discontinued for safety issues and futility reasons.[568] This drug is presently not recommended for treatment of HCC.

Brivanib alaninate, an oral VEGFR and FGFR TKI, was evaluated in two phase II studies in first and second-line patients with advanced stage HCC. The median OS was 10 months in the first-line treated group and 9.8 months in the second-line treated group, with manageable adverse events.[585] Three phase III trials testing brivanib in first-line blinded to sorafenib,[566] in second-line blinded to placebo[572] and in combination with chemoembolisation[541] resulted in negative results for primary endpoints.

Linifanib, an oral TKI targeting VEGF and PDGF, and ramucirumab, a monoclonal antibody against VEGFR2[586] failed in phase III studies in first-line and second-line indications, respectively.[295,567] 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 (MAP2K1) inhibitors, transforming growth factor-beta (TGFβ) and Janus kinase 2 (JAK2) inhibitors are being tested in early clinical investigations.[587]

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 immunocompromised patients, like cirrhotics. HCC has also been shown to be chemo-resistant to the most common chemotherapies, which as single agents have caused modest anti-tumoural responses.[310,588–590] Systemic doxorubicin has been evaluated in more than 1,000 patients in clinical trials with an objective response rate of around 10% and negative or inconclusive survival benefits. Furthermore, a recent phase III trial combining doxorubicin and sorafenib *vs.* sorafenib alone did not meet its primary endpoint. The addition of doxorubicin to sorafenib resulted in higher toxicity but did not improve OS[570] (Table 5).

Three other regimens have also shown negative results: PIAF regimen (Cisplatin/Interferon α2b/Doxorubicin/Fluorouracil-PIAF regimen), FOLFOX and hepatic intra-arterial chemotherapy (HIAC) with cisplatin and 5-FU. The phase III trial comparing PIAF *vs.* doxorubicin showed median survival of 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 and treatment-related mortality of 9%.[590] A second randomised controlled trial (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 favouring the FOLFOX group (median survival 6.4 months *vs.* 4.9 months; $p = 0.07$) associated with a better time to progression (2.9 months *vs.* 1.7 months).[571] Finally, HIAC with cisplatin and 5-FU combined with sorafenib did not meet the primary endpoint of better survival compared to sorafenib alone (Table 5) Chemotherapy for HCC in non-cirrhotic patients is an underexplored area.[591] Thus, considering the available evidence, systemic chemotherapy is not recommended for the treatment of HCC, nor as a control regimen for any trial because of its well-known toxic effects, although the panel acknowledges that inappropriate patient selection and trial design have contributed to the failure of appropriate drug development for chemotherapy. Chemotherapy for HCC in non-cirrhotic patients needs to be further investigated.[591]

Hormonal compounds

Hormonal compounds have not shown survival benefits in HCC. A meta-analysis of seven RCTs comparing tamoxifen *vs.* conservative management, comprising 898 patients, showed neither anti-tumoural effects nor survival benefits for tamoxifen.[310] Two large RCTs were reported afterwards assessing tamoxifen[592,593] with negative results in terms of survival. Thus, this treatment is discouraged in advanced HCC. Anti-androgen therapy is not recommended.[594]

Other treatments

A large RCT compared seocalcitol – a vitamin-D like anti-proliferative molecule – with placebo in 746 patients and showed no differences in OS (9.6 months seocalcitol *vs.* 9.2 months placebo).[311] Finally, negative results were also reported with a tubulin inhibitor (T-67) in a large multicentre RCT.[595]

Second-line therapies

Regorafenib

Regorafenib is an oral multi-kinase inhibitor that blocks the activity of protein kinases involved in angiogenesis, oncogenesis, and the tumour microenvironment.[596] Regorafenib (160 mg po once daily 3 weeks on / 1 week off) showed survival benefits compared to placebo in the phase III RESORCE trial in patients with HCC who tolerated and progressed on sorafenib[322] (Table 5). The trial included patients with good liver function (Child-Pugh A) who previously tolerated sorafenib (defined as receiving sorafenib ≥400 mg daily for at least 20 of the last 28 days of treatment). The latter avoided unexpected toxicity as sorafenib and regorafenib have a comparable safety profile. The primary endpoint OS was met and regorafenib improved the median OS from 7.8 months on placebo to 10.6 months (HR 0.63; 95% CI 0.50–0.79); $p < 0.0001$). Radiographic objective response was 10.6% (mRECIST; 6.6% RECIST 1.1) and disease control rate 65.2% (mRECIST; 65.7% RECIST 1.1). Adverse events were manageable and consistent with the known regorafenib safety profile, leading AEs were hand-foot-skin-reaction, fatigue and hypertension. Median times on regorafenib or placebo were 3.6 months and 1.9 months, respectively. The FDA and EMA have approved regorafenib in patients with HCC who have been previously treated with sorafenib. The panel recommends regorafenib for this indication.

Immunotherapy
The recent success of checkpoint inhibitors in different tumours has stimulated several ongoing clinical trials of different checkpoint inhibitors in HCC. Most advanced is nivolumab, that targets PD-1 and has been tested in a dose escalation and expansion trial in patients with advanced HCC. Nivolumab's interference with the PD-1 receptor restores T-cell–mediated anti-tumour activity. A large phase II study in patients in front-line (n = 80) and second-line (n = 182) has recently reported promising results in terms of OS, objective response and duration of response. This trial tested 48 patients in dose escalation and 214 in the dose expansion phase. The objective response rate was 20% (95% CI 15–26) in patients treated in the dose expansion phase (nivolumab 3 mg/kg), and median survival was close to 16 months in second-line patients. PD-L1 expression did not predict response and efficacy was similar across different aetiologies. The safety profile of nivolumab was manageable and consistent across patient cohorts and was similar to that observed in other tumour types. The most common symptoms are fatigue, pruritus, diarrhoea and elevated liver enzymes.[565] As a consequence of these results, the FDA granted nivolumab conditional approval in second-line therapy, with conventional approval pending phase III results comparing nivolumab with sorafenib in treatment-naive patients.

Cabozantinib
Cabozantinib is a MET, VEGFR2 and RET inhibitor approved for thyroid and renal cancer that showed clinical activity in a phase II discontinuation study in patients with advanced HCC in second- or third-line treatment.[597] The phase III CELESTIAL trial comparing cabozantinib (60 mg daily) with placebo in second-line treatment of advanced HCC (Child-Pugh A, ECOG PS 0/1) has been halted at the second interim analysis for efficacy. An improved overall survival from 8.0 months on placebo to 10.2 months was reported at ASCO GI in January 2018.[324]

Treatments that failed in second-line
Everolimus, an inhibitor of the mTOR pathway has been tested (7.5 mg OD) *vs.* placebo in a 2:1 ratio in a phase III trial, including 546 patients. The trial did not meet the primary endpoint of improved survival[573] (Table 5).

Brivanib was compared to placebo in a 2:1 ratio in 395 patients intolerant to (13%) or progressing (87%) on sorafenib. Most were PS 0, Child-Pugh A, 2/3 had extrahepatic metastases and less than one-third vascular invasion. The trial did not show differences in survival between brivanib and. placebo (Table 5), despite an improvement in mTTP and in objective response rate.[572]

Ramucirumab, a monoclonal antibody targeting VEGFR-2 was compared to placebo (ratio 1:1) in a randomised double-blind phase III trial including 565 patients progressing on sorafenib.[295] The study did not meet the primary endpoint (Table 5). The safety profile was as expected with an anti-angiogenic drug and was considered manageable. A pre-specified subgroup analysis of patients with high baseline alpha-fetoprotein (> 400 ng/ml), showed a significantly better survival with ramucirumab than placebo (7.8 months *vs.* 4.2 months; HR 0.67; 95% CI 0.51–0.90). To explore this concept, another phase III trial (REACH-2) is currently ongoing for this specific population. According to a press release on April 4th 2018 the REACH-2 study, investigating Ramucirumab in second line in patients with HCC and AFP ≥ 400, met its primary endpoint, demonstrating a statistically significant improvement in overall survival. This will add Ramucirumab to Regorafenib and Cabozantinib as second line treatment option in advanced stage HCC.

Tivantinib, a tubulin inhibitor, was tested in phase III after showing a signal of efficacy in a subgroup analysis of a randomised phase II study in second-line.[598] The phase III trial was the first biomarker-driven (MET-high tumours by immunostaining) study in HCC. The study was negative (Table 5).

Trials ongoing
Aside from the phase III trial comparing nivolumab *vs.* sorafenib in front-line therapy and pembrolizumab *vs.* placebo in second-line therapy, several controlled studies are currently ongoing. Phase II data on pembrolizumab (KEYNOTE-224) showed an objective response rate of 16.3%;[599] enrolment for the RCT (KEYNOTE-240) is ongoing.

Palliative and best supportive care

Recommendations

- In HCC on cirrhosis, acetaminophen (paracetamol) up to 3 g/day can be utilised for the management of pain of mild intensity. Non-steroidal anti-inflammatory drugs should be avoided whenever possible in patients with underlying cirrhosis. Opioids can be utilised for the management of pain of intermediate or severe intensity, paying attention to proactively avoid constipation (**evidence low; recommendation weak**).
- Bone metastases causing pain or at significant risk of spontaneous secondary fracture benefit from palliative radiotherapy (**evidence low**).
- In patients with advanced cirrhosis, the use of psychoactive drugs and particularly of benzodiazepines to treat psychological distress is associated with an increased risk of falls and injuries and altered mental status. Therefore, great caution should be adopted when using them in patients with HCC and cirrhotic liver dysfunction (**evidence low; recommendation strong**).
- Psycho-oncological support and adequate nutrition is recommended according to patients' condition (**evidence low; recommendation strong**).

Because of the dismal prognosis of patients with terminal HCC, as defined by the Barcelona Clinic Liver Cancer (BCLC) system, with life expectancy of about 3–4 months,[264] the management of end-stage disease is only symptomatic and no tumour directed treatment is indicated. These patients should receive palliative support including management of pain, nutrition and psychological support.[600]

Symptom management
Unrelieved symptoms have a negative effect on functional status, mood states, and quality of life.[601] Effective symptom management allows patients and their families to focus on maintaining hope, reaffirming important connections, and attaining a sense of completion.[600] The clinical picture of

patients with terminal HCC is particularly complex, resulting from a combination of symptoms deriving both from their end-stage cirrhotic liver disease and the effect of large tumour bulk.[602]

Pain has been reported as the most common symptom (65%),[601,603] originating from various aetiologies including inflammatory adhesions, liver capsular distension and musculoskeletal causes (immobility, metastasis). Since patients with HCC often suffer underlying liver cirrhosis, clinicians face peculiar problems in the prescription of analgesics, differing from most other oncological settings.

For pain of mild intensity, acetaminophen (paracetamol) is the preferred drug, by oral or intravenous administration up to a total dose of 3 g/day. In fact, non-steroidal anti-inflammatory drugs (NSAIDs) are associated with increased risk of gastrointestinal bleeding, decompensation of ascites and nephrotoxicity, particularly in patients with clinically significant portal hypertension and should be avoided.[600,604,605]

In case of moderate-to-severe pain, which usually is insufficiently controlled by acetaminophen, opioids are the drugs of choice. However, opioid metabolism may be deeply affected by liver cirrhosis and opioid-treated patients are at increased risk of constipation and consequently of hepatic encephalopathy.[606] Therefore, opioid prescription should be promptly associated with a purging programme, not waiting for severe constipation to occur.[600] In particular, pharmacologic treatments including osmotic laxatives may be helpful. To this end, the use of naltrexone might be of value. naltrexone is a pure opioid receptor antagonist, well absorbed orally, but subject to significant first pass metabolism, with oral bioavailability estimates ranging from 5 to 40%: this leads to greater activity at the level of the gastrointestinal tract rather than systemic.[607] It therefore appears as a convenient agent to be combined with opioids to limit constipation, as demonstrated in other populations critically vulnerable to opioid-induced constipation, such as Parkinson's disease and elderly patients.[608,609] However, adequate studies of naltrexone in patients with severe hepatic or renal impairment have not been conducted so far, which does not preclude cautious use.

When pain is generated by well identified (not diffuse) bone metastasis or when a lytic bone metastasis is considered at high risk of spontaneous fracture, especially due to the body weight load (*e.g.* in long bones of the lower limbs or in the spine), palliative radiotherapy is indicated.[610] A median radiation dose of 40 Gy (range, 20–66 Gy), with various fraction sizes (range, 2.0–6.0 Gy) was utilised in 91 patients with HCC and spine metastasis, providing pain response rates of 81%.[611] However, even a single palliative session of irradiation could be proposed in patients with the shortest expected prognosis. Such therapies do not interfere with liver function and might temporarily relief pain and reduce or delay the risk of spontaneous fractures.

Patients with decompensated cirrhosis commonly suffer weight loss and muscle wasting. These problems are multifactorial and their pathogenesis includes both poor caloric intake and alterations to absorption and metabolism of ingested nutrients. Nutritional status, assessed through psoas muscles mass for example,[612] has been found to be independently associated with overall survival in patients with advanced HCC[613] and its assessment is important for identifying the risk of deteriorating quality of life or functional status in patients.[614] Nutritional intervention should be considered in cases of low energy intake for a longer period of time. Since patients with terminal HCC may also have fluid retention and ascites and are highly subject to infections, oral supplementation should be preferred over intravenous administration.[600]

The assistance of a dietician experienced in liver disease could be highly valuable, although therapeutic interventions should consider the individual situation and needs of the patient.

Finally, the psychological burden should not be neglected or underestimated. In fact, patients with HCC were described to show the third highest reported level of psychological distress or depression among patients diagnosed with 14 other types of cancer.[615] Caring for dying patients can be a challenge for clinicians and can cause strong emotional reactions. A number of educational interventions focussing attention on clinicians' emotional response to their patients teach effective coping strategies.[616,617] Further research is needed to find ways to integrate these strategies into healthcare training and continuing medical education. However, it is worth repeating that benzodiazepines should be avoided whenever possible or utilised with extreme caution in patients with underlying advanced cirrhosis, given the risk of easier precipitation of altered mental status up to coma than in the non-cirrhotic population. Even when such effects remain apparently subclinical, a higher rate of falls was observed after adjustment for the contribution of encephalopathy with a triplicated risk of fall-related injuries.[618] The latter adverse event was also reported for other psychoactive drugs, possibly because of altered pharmacokinetics.[618]

Palliative Care Network

Palliative care (PC) has well-defined, supportive care goals related to optimising quality of life and addressing information needs regarding the illness and prognosis, alongside symptom control, psychosocial support, and spiritual care of the patient and their family.[619]

Despite an increasing number of people dying of end-stage hepatic diseases, little is reported on the challenge and practical implication of end-stage patients, as well as the difficulties faced by the patients, families and service providers.

The timing of activation of the PC network remains one the most undefined points. The National Comprehensive Cancer Network (NCCN) clinical guidelines support the incorporation of PC into the treatment of cancer at time of diagnosis regardless of stage.[620] Hospice care, which is a component of PC, is appropriate for those whose life expectancy is less than six months, which implies that the majority of patients progressing under the last possible line of therapy for advanced HCC should be evaluated for hospice care.

The "surprise question" is a simple and innovative tool to recognise patients who would benefit most from PC measures. The "surprise question" asks the primary and/or community care physician "Would you be surprised if the patient dies within a defined (short) time interval (*e.g.* seven days, thirty days or one year)?". A prospective study showed that clinicians could screen cancer patients for seven- or thirty-day survival using surprise questions with 90% or more sensitivity, although the positive predictive value was not very accurate. Therefore, if the answer to the surprise question is no, the provider is triggered to initiate primary palliative measures with the patient.[621]

In the largest study to date on terminal PC in HCC (performed in a Taiwanese population), Hwang and colleagues[622] compared 729 patients with terminal HCC receiving inpatient hospice care and 729 matched controls selected from 2,482 patients with HCC receiving usual care. Opioids were more frequently used in the hospice care group than in the usual care group (72.7%

Table 5. Phase III clinical trials testing molecular targeted therapies and devices in advanced HCC.

Trial	Drugs	n	Median OS (months)	Hazard Ratio (95% CI)	p-value
First-line					
SHARP[a]					
	Sorafenib	299	10.7	0.69	<0.001
	Placebo	303	7.9	(0.55–0.87)	
Asian-Pacific[a]					
	Sorafenib	150	6.5	0.68	0.01
	Placebo	76	4.2	(0.5–0.93)	
SUN1170[b]					
	Sunitinib	530	7.9	1.3	0.001
	Sorafenib	544	10.2	(1.13–1.5)	
BRISK-FL[b]					
	Brivanib	577	9.5	1.07	0.31
	Sorafenib	578	9.9	(0.94–1.23)	
LIGHT[b]					
	Linifanib	514	9.1	1.046	
	Sorafenib	521	9.8	(0.896–1.221)	
SEARCH[b]					
	Sorafenib + Erlotinib	362	9.5	0.92	0.2
	Sorafenib	358	8.5	(0.781–1.106)	
REFLECT/Study304[a]					
	Lenvatinib	478	13.6	0.92	
	Sorafenib	476	12.3	(0.79–1.06)	<0.05
ALLIANCE[b]					
	Sorafenib+ doxo	173	9.3	1.06	n.s.
	Sorafenib	173	10.5	(0.8–1.4)	
SILIUS[b]					
	Sorafenib+ HIAC	88	11.8	1	n.s.
	Sorafenib	102	11,8	(0.7–1.4)	
SARAH[b]					
	SIRT (Y-90)	Total 459	8	1.15	n.s.
	Sorafenib		9.9	(0.94–1.41)	
SIRveNIB[b]					
	SIRT (Y-90)	182	8.8	1.12	n.s.
	Sorafenib	178	10	(0.88–1.42)	
Second-line					
BRISK-PS[b]					
	Brivanib	263	9.4	0.89	0.33
	Placebo	132	8.2	(0.69–1.15)	
EVOLVE-1[b]					
	Everolimus	362	7.6	1.05	0.68
	Placebo	184	7.3	(0.86–1.27)	
REACH[b]					
	Ramucirumab	283	9.2	0.86	0.13
	Placebo	282	7.6	(0.72–1.05)	
RESORCE[a]					
	Regorafenib	379	10.6	0.63	<0.001
	Placebo	194	7.8	(0.50–0.79)	
METIV-HCC[b]					
	Tivantinib	226	8.4	0.97	n.s.
	Placebo	114	9.1	(0.75–1.25)	
CELESTIAL[a]					
	Cabozantinib	467	10.2	0.76	0.0049
	Placebo	237	8.0	(0.63–0.92)	

Superscript a and superscript b indicate positive and negative trials respectively. HCC, hepatocellular carcinoma; OS, overall survival. HCC, hepatocellular carcinoma.

vs. 25.5%, p <0.001), whereas the length of hospitalisation (8 ± 7.7 days *vs.* 14.1 ± 14.3 days, p <0.001), aggressive procedures (all p <0.005), and medical expenses (all p <0.001) were significantly less in the hospice care group.

However, PC still has a poor application in daily clinical practice. As shown in a retrospective study performed in an American tertiary care centre,[623] PC interventions for patients with advanced HCC were infrequent. Specifically, of 141 patients identified as having advanced HCC, only 15 (10.6%) had any PC intervention. Even more worrisomely, 70% of people with end-stage liver disease die in hospital, compared with 55% of the general population.[624]

For patients with end-stage HCC, a comprehensive assessment should be performed, which considers referral to

community PC and long-term conditions teams. Future studies that improve the identification of critical patients, and thus the integration of PC into the management of patients with HCC will be of great benefit to this frail and unfortunate population.

Trial design and endpoints

Recommendations

- For phase III clinical trials testing primary treatments (either loco-regional or systemic therapies) the primary endpoint should be OS, while for adjuvant therapies after resection/ablation it should be recurrence-free survival or time to response (**recommendation strong**).
- When testing neoadjuvant treatments for patients on the liver transplantation waiting list, OS, cancer-related deaths and waiting list drop-out rates are recommended as endpoints (**recommendation strong**).
- There are no optimal surrogate endpoints able to recapitulate OS in HCC. TTP and PFS are not suggested as primary endpoints (**evidence high; recommendation weak**).
- ORR, in particular complete response by mRECIST, correlate with OS in patients treated with thermal ablation and TACE (**evidence high**). For phase II trials testing TACE or thermal ablation, ORR and complete response may be considered as primary endpoints, respectively (**recommendation weak**). Conversely, ORR and disease control rate have not been robustly shown to correlate with OS in patients receiving systemic therapies.
- Phase II studies testing systemic therapies should be randomised and should target OS as a primary endpoint (**recommendation strong**). ORR, TTP and recurrence-free survival can be assessed as secondary endpoints.
- Use of RECIST1.1. and mRECIST is suggested for the assessment of response in HCC treated with systemic therapy (**recommendation weak**). Use of changes in serum biomarker levels for assessment of response (*i.e.* AFP levels) is under investigation.
- Selection of the target population for clinical trials should use BCLC staging system, Child-Pugh class and ECOG performance status (**recommendation strong**).
- Stratification for prognostic factors prior to randomisation is critical in randomised studies and is recommended (**evidence high; recommendation strong**).
- The control arm of randomised phase II and III studies should be the standard of care established in the current guidelines. When no standard of care is available (adjuvant trials, third-line setting) a placebo-control arm is recommended (**recommendation strong**).
- Upfront liver biopsy and blood sampling is recommended for clinical and diagnostic trials (**recommendation strong**).

Endpoints

Overall survival

Overall survival (OS) – which captures the time from random assignment until death - is the most important endpoint in oncology and HCC research, and is the one not subject to investigator bias. Regulatory agencies rely on OS as the primary endpoint for drug approval in oncology,[625] and it was recommended as the primary endpoint for HCC research in our previous guidelines.[1] The panel of experts recommends OS as the primary endpoint for phase III studies at intermediate and advanced stages in front-line and consecutive lines of treatment thereafter. In addition, this panel considers that OS can also be recommended as the primary endpoint in phase II studies in advanced cases, owing to the controversies currently unsolved regarding surrogate endpoints of OS in HCC, discussed later. Cancer-specific survival – where only deaths caused by cancer are considered for survival analysis and non-cancer-related deaths are censored – is a more complex endpoint to apply in the conventional trial design setting. Deaths due to competing risk factors, such as liver failure, require a subjective decision by the investigator, and thus are more prone to bias.

Surrogate endpoints

Overall survival has some limitations as a sole endpoint in cancer research: it might require a long follow-up to capture adequate numbers (*i.e.* median OS for transarterial chemoembolisation (TACE) is 26–30 months) and can be affected by sequential therapies. Thus, surrogate endpoints that are more practical for trial execution are needed. However, they are subject to interpretation by investigators and data on surrogates of OS are lacking in most instances.

Time to progression

Our former guidelines proposed time to progression (TTP), defined as the time between random assignment and radiological progression, as a less vulnerable surrogate endpoint of OS compared with progression-free survival (PFS). TTP has been assessed as a secondary endpoint in HCC in several randomised controlled trials.[295,320–322,566–569,572,573] Data correlating TTP and OS has been controversial and not fully supportive of our initial estimates. The sole meta-analysis, including nine RCTs, specifically assessing TTP as a surrogate endpoint of OS at advanced stages of HCC showed a medium strength correlation between treatment effects on TTP and OS ($r = 0.73$).[626] Discordant signals keep emerging in very recent randomised phase II trials at intermediate and advanced stages.[560] All these data support revisiting TTP as a reliable endpoint in HCC research. Whether TTP is failing because of the fact that it is capturing heterogeneous features (macrovascular invasion and extrahepatic spread *vs.* liver progression) needs to be further explored.[580,627] The panel of experts recommends capturing the type of progression in the setting of an RCT, in order to enable reassessment of TTP in pre-planned analyses.

Progression-free survival

Progression-free survival is a composite endpoint that includes two types of variables: death and evidence of radiological progression. It may capture (i) rapid progression before radiological confirmation, (ii) toxicity of therapy or (III) deterioration of liver function due to toxicity. Our former guidelines discourage this

composite endpoint because of the competitive risk effect of dying from the natural history of cirrhosis despite a relevant anti-tumoural benefit.[1] The likelihood of death as a result of liver decompensation (gastrointestinal bleeding, encephalopathy or infections) is 5% at one year.[255] Thus, a restrictive selection of patients with well-preserved liver function is recommended to minimise the impact of death unrelated to tumour progression if PFS is applied.

Time to recurrence and recurrence-free survival

In the former guidelines, time to recurrence was recommended as the primary endpoint for phase II and III studies assessing adjuvant therapies after resection or local ablation. Nonetheless, most phase III studies in the adjuvant setting, conducted under regulatory agreement, incorporated a composite endpoint of recurrence-free survival, where around 90% of events were recurrences.[394,628] Regulatory agencies endorse this composite endpoint because it can also indirectly capture treatment-related toxicities.

Response rate and response assessment tools

Tumour response in oncology trials is typically measured according to Response Evaluation Criteria In Solid Tumours (RECIST). The RECIST document acknowledges that amendments to the general guideline could be needed for the evaluation of other anticancer therapies, as well as for the assessment of tumours presenting unique complexities. The modified RECIST (mRECIST) for HCC[252] was adopted by the European Association for the Study of the Liver guidelines on the management of HCC.[1]

In the future the advent of immunotherapy might require modifications (iRECIST) of the basic structure of the RECIST model. As shown in the setting of melanoma patients treated with immunotherapies, standard RECIST may not provide a reliable assessment of the antitumour effect. *E.g.*, response to immunotherapy may take longer compared to other agents, and can manifest after imaging features that meet the current criteria for progression.

Objective response in loco-regional therapies

Several clinical investigations have shown that objective response (OR) measured by mRECIST predicts survival in patients receiving loco-regional therapies.[629] Overall median OR with TACE and with radioembolization with Y-90 have been reported to range from 40–80% with either therapy, depending mainly on whether treatment was applied to patients with early-stage or intermediate-stage disease.[630–633] A recent meta-analysis identified seven clinical trials assessing survival outcomes after loco-regional treatments according to mRECIST response.[634] Each individual study showed better survival for responders (complete response or partial response) compared to non-responders (stable disease or progressive disease). Overall, the meta-analysis included 1,357 patients. The hazard ratio for OS (responders *vs.* non-responders) was 0.39 (95% CI 0.26–0.61; p <0.0001). Thus, for phase II trials the panel endorses complete response (for ablation) and OR rate (ORR) (for TACE), as assessed by mRECIST, as primary endpoints.

Objective response in systemic therapies

Objective response by mRECIST has been shown to correlate with OS in two clinical trials, and thus additional data is needed to endorse this approach.[635,636] In these studies, OS was significantly better for responders, a fact that remained an independent prognostic factor. However, OR by RECIST has lower sensitivity for capturing response, as shown in several phase II and III investigations. Overall, both measurements are still suboptimal for identification of the maximum number of patients who benefit from treatment. Also, the advent of immunotherapy (and "pseudo-progression" patterns) must be properly captured by the above criteria. Investigation of this concept in HCC clinical trials is a top priority. The panel of experts recommends assessing tumour response according to mRECIST and conventional RECIST and correlating this with pathological studies and outcome prediction.

Trial design

Trial design should follow the recommendations posed in the previous guidelines.[1] Selection of patients should be based on Barcelona Clinic Liver Cancer staging, Child-Pugh class and Eastern Cooperative Oncology Group status, in order to minimise the competitive risk of death associated with liver failure. The control arm for clinical trials should be the standard of care stated in the current guidelines. Randomised 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. Thus, the panel recommends obtaining tissue biopsy and blood sampling from all patients included in clinical trials in HCC.

Future directions

Hepatocellular carcinoma (HCC) is the result of underlying and well-defined liver disease in most patients. Thus, it is preventable. The rising incidence of HCC in most European countries suggests an insufficient awareness of liver disease in general, calling for public health policies aiming to prevent, detect and treat liver disease – not only for HCC prevention. It is particularly frustrating to see most patients with HCC diagnosed at a stage no longer amenable to curative treatment, demonstrating again a neglect of liver disease and appropriate cancer surveillance.

To make surveillance cost-effective tools need to be developed to stratify patients at high, intermediate and low risk for hepatocellular carcinoma and to adjust surveillance strategies accordingly. Surveillance or secondary prevention needs to be complemented by primary prevention and the development and the utilization of chemo-preventive strategies is strongly encouraged.

Hepatocellular carcinomas are characterised by considerable phenotypic and molecular heterogeneity. During the last two decades, we have developed an increasing understanding of the most abundant molecular alterations in HCC which, however, has not translated into improved prognostic assessment or therapeutic decision making. This is at least in part the result of a lack of mandatory biopsies in the diagnosis of HCC in individual patients. Material is largely derived from subgroups of patients, *e.g.* after resection and thus the collective analyses are not fully comprehensive. Most trials have not linked molecular signatures with therapeutic response, explaining both the failure of some drugs in large phase III trials and the discrepancy with other tumours, such as breast or lung cancer, where molecular tumour boards are a clinical reality. All efforts should be undertaken to link molecular subclasses in clinical trials with

therapeutic response and outcome, thus paving the way for novel therapeutic strategies. It can be predicted that the advent of next-generation sequencing technologies will play an increasingly important role in clinical oncology. Molecular characterisation of genetic alterations within the tumour cell population, as well as the cellular composition of tumours and the corresponding tumour microenvironment, will enable the development of prognostic (predicting prognosis) and predictive (predicting therapeutic response) biomarkers that can be utilised in routine clinical practice.

Such markers (from tumour tissue, blood, urine *etc.*) are needed for early diagnosis and surveillance of patients at risk, to stratify patients for appropriate adjuvant and palliative treatments (including non-targeted therapies), to define mechanisms of escape and resistance and to allow early response prediction.

Thus, the panel suggests focussing on the following three goals:

1. ***Public health policies to prevent, detect, and treat chronic liver disease***

2. ***Appropriate cancer surveillance to detect HCC in a stage amenable to curative treatment***

3. ***Link molecular subclasses in clinical trials to therapeutic response and outcome***

In order to achieve these goals a variety of activities are required, including but not limited to those listed (Table 6).

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 U.S. Government.

Table 6. Unmet needs in HCC research. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; OS, overall survival; TKI, tyrosine kinase inhibitor.

• Major health policy interventions to secure a) universal vaccination against HBV, b) universal treatment of HCV if indicated and c) prevention of heavy alcohol intake and obesity
• Need for universal implementation of surveillance programs
• Need for new tools of early detection including assessment of liquid biopsy
• Transition to biopsy for HCC in all instances once a tissue biomarker predicting response is available
• Development of 3rd line therapies in advanced stage
• Need to define optimal sequencing of systemic therapy
• Need for surrogate markers recapitulating OS
• Translate molecular knowledge into precision medicine, linking response rates in trials to molecular subgroups
• Need to assess the role of prognostic and predictive markers in surgical and interventional therapies within prospective investigations
• Need to understand the impact of minimal invasive surgery on HCC recurrence and post-progression survival
• Need to define and evaluate reliable quality of life assement tools in HCC
• Need to stratify patients at risk for hepatocellular carcinoma and the utilisation of chemopreventive strategies

Conflict of interest

Peter R. Galle reports grant/research support from Bayer, Eli Lilly, BMS, MSD, SillaJen, Merck, Blueprint Medicines, Arqule, Gilead, AbbVie, WAKO; consultant/advisory roles with Bayer, Eli Lilly, BMS; sponsored lectures for Bayer, Lilly, WAKO. Fabio Piscaglia reports grant/research support from ESAOTE; consultant/advisory roles for Bayer, Eisai; sponsored lectures for Bayer, Bracco, Meda Pharma. Jean-Luc Raoul reports consultant/advisory roles for Bayer SP, BTG, MSD; sponsored lectures for Bayer SP. Josep Llovet reports grant/research support from Bayer, Blueprint Medicines, Boehringer-Ingelheim, BMS; consultant/advisory roles for Bayer, BMS, Boehringer-Ingelheim, Eli Lilly, Celsion, Biocompatibles, Novartis, GlaxoSmithKline, Blueprint Medicines, Eisai, Tiziana Therapeutic, Guerbert; sponsored lectures for AEEH, APASL, AACR, AASLD, EASL, ILCA, Bayer. Peter Schirmacher reports grant/research support for Novartis; consultant/advisory roles for Novartis, MSD, BMS. Valérie Vilgrain reports grant/research support from Sirtex; consultant/advisory roles for Guerbet; sponsored lectures for Supersonic, Bracco, Guerbet; Sirtex. Vincenzo Mazzaferro reports being on the advisory board of a BTG Inc. sponsored trial that failed recruitment; sponsored lectures for Bayer Italy; involvement in phase III RCTs for BMS and Arqule.

Please refer to the accompanying ICMJE disclosure forms for further details.

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