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EASL Clinical Practice Guidelines on the management of hepatocellular carcinoma☆

European Association for the Study of the Liver*

Summary

Liver cancer is the third leading cause of cancer-related deaths worldwide, with hepatocellular carcinoma (HCC) accounting for approximately 90% of primary liver cancers. Advances in diagnostic and therapeutic tools, along with improved understanding of their application, are transforming patient treatment. Integrating these innovations into clinical practice presents challenges and necessitates guidance. These clinical practice guidelines offer updated advice for managing patients with HCC and provide a comprehensive review of pertinent data. Key updates from the 2018 EASL guidelines include personalised surveillance based on individual risk assessment and the use of new tools, standardisation of liver imaging procedures and diagnostic criteria, use of minimally invasive surgery in complex cases together with updates on the integrated role of liver transplantation, transitions between surgical, locoregional, and systemic therapies, the role of radiation therapies, and the use of combination immunotherapies at various stages of disease. Above all, there is an absolute need for a multiparametric assessment of individual risks and benefits, considering the patient's perspective, by a multidisciplinary team encompassing various specialties.

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Introduction

Liver cancer is the sixth leading cause of cancer and the third leading cause of cancer-related deaths globally (GLOBOCAN).[1] Hepatocellular carcinoma (HCC) represents about 90% of primary liver cancers and constitutes a major global health problem. The management of patients with HCC is complex due the coexistence of a chronic liver disease, the multiplicity of diagnostic and therapeutic tools, and the relative lack of strong scientific evidence for some common practices, among other factors. Physicians or allied health-professionals, hospital managers and policy makers, and patients themselves are frequently confronted with difficult decisions. Providing the best possible care to patients requires updated information, deep understanding of the disease and access to multidisciplinary expertise. Over the last decade, the European Association for the Study of the Liver (EASL) has provided several guiding documents on the management of HCC, the last one in 2018.[2] Since then, we have gained significant knowledge that is transforming all aspects of HCC management, from personalised surveillance to improved diagnosis, from minimally invasive surgery to immune-based systemic therapy across tumour stages. Thus, updated EASL Clinical Practice Guidelines (CPGs) on the management of HCC were needed.

The present guidelines are intended for clinicians of all specialties who may deal with the management and care of patients with HCC. The main goal of this multidisciplinary effort has been to provide useful guidance that could help physicians, nurses and other allied health providers, health-policy makers and of course patients make individual or collective decisions that are based on scientific evidence and result in the delivery of optimal patient care. Optimal care includes the management of the underlying chronic liver disease present in most cases, and the EASL CPGs on HBV infection,[3] HCV infection,[4] alcohol-related liver disease,[5] non-invasive tests for evaluation of liver disease severity and prognosis,[6] decompensated cirrhosis,[7] acute-on-chronic liver failure,[8] as well as the Baveno VII consensus on portal hypertension[9] complement this CPG. While these guidelines do not specifically address the roles of nurses and palliative care specialists, the panel acknowledges their crucial and growing importance in the management of HCC and anticipates that their roles will continue to expand in the coming years. HCC is a global health problem that needs to be handled in very different social and health care environments. Readers should therefore adjust the recommendations made herein to their local context in terms of human and financial resources, technological availability, regulations, and team competence. Also, the 2018 EASL CPG recommendations should be followed in those scenarios that due to the constraints of a limited number of PICO questions have not been covered in this update. Owing to the rapid improvements in HCC management, the authors expect that frequent updates will be needed in the future.

* Corresponding author: European Association for the Study of the Liver (EASL). The EASL Building - Home of Hepatology, 7 rue Daubin, CH1203 Geneva, Switzerland. Tel +41(0)22 807 03 60. *E-mail address:* easloffice@easloffice.eu

☆ Clinical Practice Guideline Panel: Chair: Bruno Sangro; Secretary to the Chair: Josepmaria Argemi; Panel members: Maxime Ronot, Valerie Paradis, Tim Meyer, Vincenzo Mazzaferro, Peter Jepsen, Rita Golfieri†, Peter R. Galle, Laura A. Dawson; EASL Governing Board Representative: Maria Reig.

† Deceased

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Methods used to develop these guidelines

The EASL Governing Board selected a panel of experts to develop the current guidelines, according to a standard operating procedure set out by EASL that meets the international standards set out by the Guidelines International Network.[10]

The CPG panel drafted questions according to the PICO format (patient, problem, or population; intervention; comparison, control or comparator; outcome) on five main topics of prevention and early detection, diagnosis and staging, other locoregional therapies, and systemic therapies. Two or three experts were more directly involved in drafting the questions for each subtopic. PICO questions were submitted to the Delphi panel, composed of 30 experts, including patient representatives (Zorana Maravic, Digestive Cancers Europe; Teresa Casanovas, European Liver Patients' Association). Questions which received less than 75% agreement regarding their relevance and phrasing were revised and re-submitted for approval in a second round. An extensive literature search was then performed by panellists using PubMed, and expanding to other databases if needed, according to their expert judgement. Sometimes, when data from clinical trials of new therapeutic options had not yet been fully reported, the abstracts presented at international meetings were used as bibliographic references.

The quality of evidence was scored according to the Oxford Centre for Evidence-based Medicine (OCEBM) (adapted from The Oxford 2011 Levels of Evidence) (Table 1) and the strength of the recommendations was graded according to the OCEBM into two categories, strong or weak (Table 2).[11] For each PICO question, one or more recommendations were drafted by the same experts who formulated the questions and were agreed on by the panel in a process that involved extensive discussion and two virtual meetings. In addition, the panel chose to formulate general statements at the beginning of each section to provide a general conceptual framework. The Delphi panel voted on the recommendations, and consensus strength was defined as strong consensus (>95% agreement), consensus (>75-95% agreement), majority agreement (50-75% agreement) or no consensus (<50% agreement). As per the EASL methodology, there was no need to re-write the recommendations that found consensus (100% did) although corrections were often made to the document for fine tuning based on the comments from the Delphi panellists. During the process of elaborating the recommendations, the CPG panel identified some questions that could be added, merged or amended, and the agreement from the Delphi panel to these questions was sought at the time of consensus agreement. The final version of the CPGs was then finally sent to the EASL Governing Board for approval.

Prevention and surveillance

HCC is the most prevalent primary liver cancer, and it poses a significant global health challenge due to its increasing incidence and often dire prognosis. Most HCCs develop in a cirrhotic liver, so policy interventions to reduce the prevalence of cirrhosis will lead to significant reductions in the incidence of HCC. Complementary clinical efforts aim to 1) reduce the risk of HCC development among patients with cirrhosis through pharmacological treatments and lifestyle modifications, and to 2) use screening to diagnose HCC early if it develops anyway (Fig. 1). Thus, screening does not reduce the incidence of HCC, but it aims to reduce the risk of death from HCC by allowing the HCC to be diagnosed and treated at an earlier disease stage with better chances of cure. The term "HCC surveillance" refers to the repeated application of screening for HCC, *e.g.* every 6 months. The target population for HCC surveillance, the choice of screening test, and the practical implementation of HCC surveillance are subjects of constant debate and gradual improvement. Like all other cancer screening, HCC surveillance aims to reduce deaths from HCC without causing unnecessary harm from incorrect HCC diagnoses or overdiagnosis of HCC (a correct diagnosis of an HCC that would never have caused harm to the patient if left undiagnosed).

Should patients with chronic viral infection (HBV or HCV) receive antiviral therapy to reduce the risk of HCC?

Recommendations

- Patients with HBV infection should be treated with nucleoside or nucleotide analogues to reduce the risk of developing HCC (both *de novo* and recurrence) and the type and time of treatment should follow EASL guidelines on HBV infection **(LoE 2, strong recommendation, strong consensus)**
- Patients with HCV infection and liver fibrosis should be treated with direct-acting antivirals to reduce the risk of cirrhosis-related complications, including HCC **(LoE 2, strong recommendation, strong consensus).**
- Patients with HCV infection and a diagnosis of HCC under complete tumour response after surgical or locoregional therapies can be treated with antiviral therapy although the impact on the risk of HCC recurrence is inconclusive **(LoE 3, weak recommendation, strong consensus).**
- Patients with HBV and HCV co-infection can be treated following the same criteria as for mono-infected patients **(LoE 3, weak recommendation, strong consensus).**

Hepatitis B

The pivotal randomised-controlled trial (RCT) with lamivudine demonstrated that direct nucleoside or nucleotide analogues (NUCs) significantly decrease the risk of HCC development in patients with chronic hepatitis B virus (HBV) infection.[12] This information was validated in patients treated with NUCs other than lamivudine.[13,14] However, the risk is not eliminated.[13,15] In a recent meta-analysis, it was shown that NUC-treated patients have a significantly lower risk of HCC development in comparison to untreated ones (relative risk [RR] 0.48; 95% CI 0.30–0.75) although heterogeneity was very high (I^2 = 91%); it also showed that the incidence of HCC was significantly lower in patients treated with recommended NUCs (entecavir and tenofovir) than in those treated with non-first-line NUCs (lamivudine, adefovir, and telbivudine) (RR, 0.85; 95% CI 0.75–0.97, I^2 = 0%).[16]

Tenofovir and entecavir are most commonly used to treat chronic HBV infection. The impact of the choice of NUC on the development of HCC has not been studied in prospective studies. Both NUCs showed comparable antiviral efficacy and

Table 1. Level of evidence based on the Oxford Centre for Evidence-based Medicine.

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomised-controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	RCT or observational studies with dramatic effects; SR of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Non-randomised-controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than an individual study)	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
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

Table 2. Grades of recommendation.

Grade	Wording	Criteria
Strong	Shall, should, is recommended. Shall not, should not, is not recommended.	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested. May not, is not suggested.	

safety in randomised trials conducted mostly in patients without cirrhosis.[17,18] All but two systematic reviews and a meta-analysis showed a significantly lower risk of HCC or a trend towards lower risk in patients receiving tenofovir.[19–22] However, all studies included a limited number of patients with cirrhosis and showed high heterogeneity. In one study a trend towards lower risk of HCC was observed in patients with cirrhosis (adjusted hazard ratio [HR] 0.87, 95% CI 0.74–1.01) and not in patients without cirrhosis (adjusted HR 1.14, 95% CI 0.81–1.60).[23] An individual patient meta-analysis which included 42,939 patients (6,979 receiving tenofovir and 35,960 receiving entecavir) concluded that tenofovir was not associated with a lower risk of HCC compared with entecavir (HR 0.81, 95% CI 0.65-1.01).[24] Regarding HCC recurrence, a recent meta-analysis concluded that tenofovir reduces the risk of late recurrence compared to entecavir (adjusted HR 0.58, 95% CI 0.45–0.76, p = 0.0%) but not early recurrence (adjusted HR 0.88, 95% CI 0.76–1.02, p = 34.8%).[25]

Hepatitis C

No RCTs have evaluated the impact of direct-acting antivirals (DAAs) on HCC development, *de novo* or recurrent, in patients with chronic hepatitis C virus (HCV) infection. DAAs are recommended to reduce the risk of developing cirrhosis or cirrhosis complications. Several cohort studies (retrospective and prospective) or systematic reviews and aggregated meta-analyses have assessed the risk of HCC development after DAA treatment.[26–30] However, only one individual data meta-

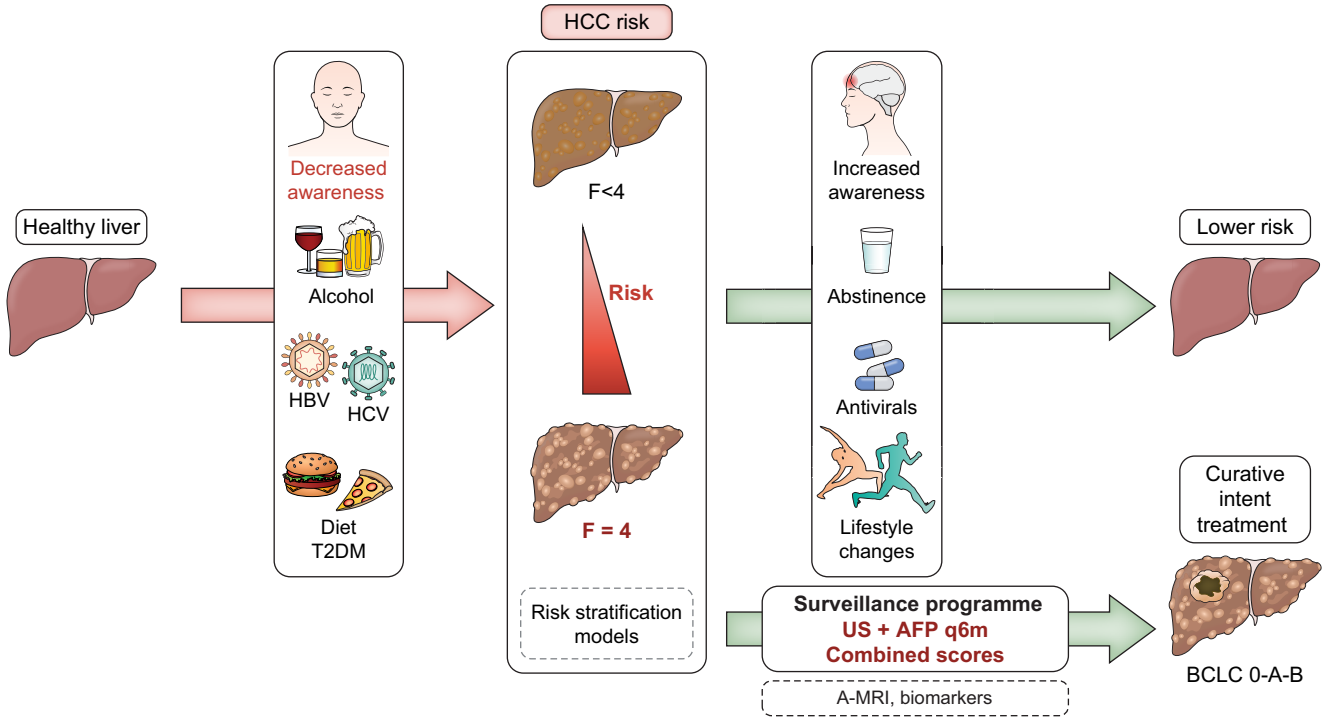

Fig. 1. Opportunities for the prevention of premature death related to HCC. AFP, alpha-fetoprotein; A-MRI, abbreviated magnetic resonance imaging; BCLC, Barcelona Clinic Liver Cancer; F, fibrosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; q6m, every six months; T2DM, type 2 diabetes mellitus; US, ultrasound. Dotted line boxes represent areas of ongoing research.

analysis has been published since the last version of the EASL guidelines.[30] All these cohort studies indicate that the risk of HCC after DAA treatment is multifactorial and that a key mechanism for the beneficial effect of DAAs on HCC development is their ability to reduce the risk of developing cirrhosis.[28,31–36]

Indeed, different scores have been proposed to stratify HCC risk among patients with advanced chronic liver disease treated with DAAs.[37–48] However, the study design significantly influences the results. In a meta-analysis assessing the impact of liver stiffness on HCC occurrence in patients with chronic HCV infection treated with DAAs, the pooled HRs of HCC occurrence in patients with high *vs.* normal liver stiffness measurement were different for the four retrospective studies (HR 2.29, 95% CI 0.96–5.45 and I^2 = 79.87%) and the four prospective studies (HR 4.61, 95% CI 2.44–8.71 and I^2 = 0%).[28] In brief, factors such as the absence of sustained virological response achievement, the presence of cirrhosis, low albumin, alpha-fetoprotein (AFP), low platelet count[45,49–51] or the presence of non-characterised liver nodules [52,53] before starting DAA therapy have been associated with a higher risk of HCC occurrence. Many of those factors reflect the degree of liver fibrosis and/or portal hypertension (*i.e.* presence/absence of cirrhosis, albumin, platelet count *etc.*).[54]

A multicentric and retrospective study in Spain initially reported that 27.6% of patients who achieved complete radiological response after HCC resection, ablation or chemoembolisation developed HCC recurrence after receiving treatment with DAAs.[55] Similar results were reported in Italy.[56] Later, many groups around the world analysed the topic and different meta-analyses have reported no differential risk of HCC occurrence or recurrence after DAAs.[26,27,29,57,58] In an individual patient data meta-analysis with pooled data from 21 studies including 977 patients, HCC recurrence after DAAs in patients with early HCC was 20 per 100 patient-years (95% CI 13.9–29.8), which was not statistically significantly lower than the recurrence rate in DAA-unexposed patients after propensity score-matched analysis (relative risk = 0.64, 95% CI 0.37–1.1; p = 0.1).[30] However, data heterogeneity was very high (I^2 = 74.6%) making results inconclusive and indicating the need to prospectively collect data on these specific patients. Although most patients have already been treated, the interferon-free DAA treatment rate was 52.3% and this data supports the need for continued research in this field. In brief, these data are inconclusive and might suggest that the risk of HCC recurrence persists even when the infection is eliminated by DAA treatment. However, the benefit of reduced risk of hepatic decompensation and improved overall survival (OS)[59,60] likely outweighs the potential increased risk of HCC occurrence or recurrence.

HCV and HBV co-infection

There is some concern about the risk of HBV reactivation in the context of HCV therapy with DAAs and the US FDA issued a specific warning note, but the impact on HCC development in this population is limited. Changes in hepatitis B surface or core antibodies did not predict HCC recurrence among 378 patients with HCC who achieved HCV clearance with DAAs.[61] Also, the incidence of HCC was not significantly different (p = 0.6366) between co-infected (n = 52) or HCV mono-infected (n = 8,549) patients treated with DAAs.[62]

Should lifestyle modifications be recommended for patients with cirrhosis to reduce their risk of HCC?

Recommendations

- Weight loss in patients with obesity, alcohol cessation, and tobacco cessation are recommended to reduce the risk of liver-related and other adverse outcomes and may be recommended to reduce the risk of HCC **(LoE 3, weak recommendation, strong consensus).**
- Coffee consumption may be recommended to reduce the risk of HCC **(LoE 3, weak recommendation, consensus).**

Many lifestyle factors are risk factors for HCC because they are risk factors for cirrhosis.[63] Here, we will focus our attention on risk factors for HCC among those who already have cirrhosis.

Alcohol consumption

Three studies have examined the effect of alcohol use on HCC risk in patients with alcohol-related cirrhosis.[64–66] A study published in 1993 followed Japanese patients with cirrhosis or chronic hepatitis and found that the risk of HCC was higher in former than in current daily drinkers.[65] A more recent study from Spain followed 727 patients with Child-Pugh class A or B alcohol-related cirrhosis and compared HCC incidence between 354 patients who maintained abstinence during a median follow-up of 5–6 years and 373 who were non-abstinent during follow-up. In the total cohort, abstinence during follow-up was not associated with a lower risk of HCC (HR 0.87, 95% CI 0.59–1.28). In the subset of patients without a history of decompensation, the risk of HCC was lower in patients who maintained abstinence, but only from around 6 years after inclusion. Three methodological points make this study difficult to interpret: First, 59 patients were lost to follow-up, adding uncertainty about the outcome. Second, patients were censored if they developed a severe comorbidity (n = 49) or transitioned to Child-Pugh class C and had contraindications for liver transplant(ation) (LT) (n = 9). An implication of this censoring is that the results of the analyses apply to a hypothetical world where the censoring events cannot occur, and that is not the clinical reality. Third, the classification as abstinent or non-abstinent was based on drinking patterns during the entire follow-up period, but in real life it is not possible to know whether your patient will or will not drink alcohol in the future, so it is difficult to convert the research findings into clinical practice. Finally, a recently published study concluded that hazardous alcohol use in patients with alcohol-related cirrhosis is associated with higher mortality and, consequently, a lower HCC risk.[66] The impact of alcohol consumption on HCC risk remains poorly defined. Nonetheless, there are many reasons to advise patients to abstain from alcohol.

Tobacco smoking

A 2009 meta-analysis of 38 cohort studies and 58 case-control studies found an overall association between tobacco smoking and HCC.[67] However, only few studies were restricted to patients with cirrhosis or chronic liver disease. Of those that were,

four were Japanese,[65,68–70] including one that reported a HR for current smokers *vs.* never-smokers of 2.30 (95% CI 0.90 to 5.86).[65] The one remaining study was from Germany and included 86 cases with HCC and the same number of controls; it reported no association between smoking and HCC.[71] A newer study from the US found a confounder-adjusted HR for current smokers *vs.* never-smokers of 1.63 (95% CI 1.01–2.63).[72] Thus, the effect of tobacco smoking on HCC risk among patients with cirrhosis is poorly defined, but there are multiple reasons to recommend smoking cessation to patients with cirrhosis.

Coffee

Two Japanese cohort studies examined the association between coffee consumption and HCC risk in patients with a 'history of liver disease' that was not further specified.[73,74] Compared with those who never drank coffee, patients who drank coffee occasionally had an incidence rate ratio of HCC of 0.51 (95% CI 0.27 to 0.97) in one study and 0.94 (95% CI 0.53 to 1.66) in the other. Those who drank coffee daily had incidence rate ratios of 0.52 (95% CI 0.25 to 1.07) and 0.44 (95% CI 0.22 to 0.88), respectively. A third Japanese cohort study of patients with current or previous chronic viral hepatitis found similar results,[75] so these studies suggest the presence of a dose-response protective effect of coffee on HCC risk. Other studies have found a lower HCC risk among coffee drinkers, but they were not restricted to patients with liver disease.[76–78] Studies of the effect of coffee on the development of liver disease have found similar results in European and Asian populations.[79] A US study found that coffee consumption reduced disease progression among patients with chronic HCV infection,[80] with 'disease progression' defined as progressive fibrosis or development of cirrhosis complications including HCC. The protective effect of coffee consumption was unchanged when HCC was excluded from the definition of disease progression, demonstrating that coffee had benefits other than protection from HCC development.[80] A study conducted in European patients on the LT waitlist reported that coffee consumption improved survival among those with alcohol-related liver disease or primary sclerosing cholangitis, but not among those with other chronic liver diseases. None of the included patients had HCC.[81] The evidence thus suggests that coffee reduces the risk of HCC, but observational studies of the effects of foods/drinks on HCC risk are difficult to interpret causally because people who drink coffee likely differ from non-drinkers of coffee in multiple ways, each of which may affect HCC risk. It thus remains uncertain whether the beneficial effects attributed to coffee are in fact caused by coffee, but at least there are no indications that coffee is harmful to patients with liver disease. Importantly, the potential effect of coffee is much less strong than that of alcohol and smoking cessation and does not apply to high-fat, high-sugar, latte type coffee. The effect of an active recommendation of coffee consumption in patients at high risk of HCC has not been prospectively evaluated.

Weight loss

The effect of weight loss on HCC risk among patients with cirrhosis has not been examined specifically, but weight loss has been associated with reduced disease activity among patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and overweight or obesity.[63,82] Therefore, weight loss could lead to a decreased risk of developing cirrhosis and HCC.

Should prescription drugs be recommended for patients with cirrhosis to reduce their risk of HCC?

Recommendation

- Owing to a lack of evidence, the use of statins, aspirin and metformin cannot currently be recommended to reduce the risk of HCC development **(LoE 3, weak recommendation, strong consensus).**

The benefits of using drugs to reduce the risk of HCC developing among patients with cirrhosis remain unclear. Although a recent meta-analysis[83] concluded that the use of statins prevents HCC development, the high heterogeneity precludes a robust conclusion. Heterogeneity is associated with several factors including that a) none of the studies were designed for that specific purpose; b) one study was focused on patients without cirrhosis[84]; c) another was a case-control study[85]; and d) the indication for statins was related to comorbidities. Indeed, statin users were older and had more comorbidities, including diabetes and cardiovascular disease, than non-users.[86] An observational study using an emulated trial design sought to eliminate confounding from these and other factors but concluded that only a true randomised trial can determine the causal effect of statins on HCC risk.[87] Thus, the current data on statin use does not allow for conclusive recommendations.

In several observational studies and a few RCTs, aspirin has been shown to have a chemopreventive effect on several cancers. The impact on HCC is still unclear despite the three prospective studies focused on this topic.[88–90] Their main limitations are related to the lack of information about HBV and HCV status of the participants and the fact that males represented the greatest proportion of aspirin users. An observational study restricted to patients with alcohol-related cirrhosis used an emulated trial design and concluded that aspirin does not affect HCC risk.[87]

Finally, in a meta-analysis that evaluated chemoprevention of HCC with statins, aspirin and metformin,[91] the authors observed a moderate to high degree of heterogeneity in all analyses for the association between statin use and HCC risk (except in the subgroup analysis for follow-up time <60 months); moderate to high degree of heterogeneity in all analyses for the association between aspirin use and HCC risk (except in the subgroup analyses for male sex and duration of follow-up); and high degree of heterogeneity in all analyses for the association between metformin use and HCC risk. In addition, the visual inspection of funnel plots suggests publication bias in the overall analysis for both statins and aspirin, while publication bias could not be assessed for metformin due to insufficient studies. Much caution is therefore needed when interpreting these data.

Should HBV vaccination be given to all high-risk seronegative people?

Recommendation

- High-risk seronegative people should be vaccinated against HBV to decrease HCC incidence and HCC-related death and improve overall survival **(LoE 3, strong recommendation, strong consensus).**

HBV vaccines effectively prevent infection and vaccination of all neonates is recommended by the World Health Organization.[92] In adults, vaccination of HBV seronegative persons is also recommended by the EASL clinical practice guidelines on HBV infection[3] and this recommendation includes high-risk seronegative people. According to the Centers for Disease Control and Prevention guidelines,[93,94] the following groups are at high risk of HBV infection: people whose sex partners have HBV infection; sexually active persons who are not in a long-term monogamous relationship; persons seeking evaluation or treatment for a sexually transmitted disease; men who have sexual contact with other men; people who share needles, syringes, or other drug-injection equipment; people who have household contact with someone infected with HBV; health care and public safety workers at risk of exposure to blood or body fluids; residents and staff of facilities for developmentally disabled persons; persons in correctional facilities; victims of sexual assault or abuse; travellers to regions with increased rates of HBV infection; people with chronic liver disease, kidney disease, HIV infection, or diabetes. There are no clinical trials or prospective studies focused on this topic.

Should patients with cirrhosis be offered surveillance for HCC?

Recommendation

- Patients with cirrhosis should be offered surveillance for HCC unless they have a relatively high risk of death from non-HCC causes, or they could not be offered a curative-intent treatment for HCC (*e.g.*, patients with Child-Pugh class C cirrhosis ineligible for liver transplantation) **(LoE 2, strong recommendation, strong consensus).**

The recommendation to offer surveillance for HCC to patients with cirrhosis is based on a strong rationale, one randomised trial from China[95] and evidence from non-randomised studies. No observational studies have compared survival from cirrhosis diagnosis to HCC diagnosis between patients under surveillance and those not under surveillance. The rationale for HCC surveillance is indeed strong. Roughly 80–90% of HCCs develop in patients with cirrhosis, and survival is improved when HCC is diagnosed at an early stage. HCC screening offered to patients with cirrhosis meets Dobrow's modernised criteria for a screening programme.[96] Screening should only be offered to patients who are candidates for curative-intent treatments.

A meta-analysis of 49 studies found that surveilled patients were more likely to have their HCC diagnosed at an early stage (relative risk 1.86, 95% CI 1.73–1.98).[97] Surveillance was also associated with increased survival from HCC diagnosis, including in studies which adjusted for lead-time bias (hazard ratio 0.67, 95% CI 0.61–0.72). The results of this meta-analysis favour HCC surveillance, but they do not quantify the benefit of surveillance in terms of clinical endpoints from the time surveillance is initiated. Furthermore, the meta-analysis did not examine the association between surveillance and HCC-related mortality. A US case-control study found that surveillance with ultrasound and/or AFP did not reduce HCC-related mortality.[98]

Studies comparing countries or eras with different surveillance strategies provide other pieces of evidence favouring surveillance. Survival from HCC diagnosis was markedly longer in Taiwan and Japan than in Europe and other countries where fewer patients with cirrhosis undergo HCC surveillance.[99] Similar evidence comes from a South Korean study that compared survival from HCC diagnosis between different eras and reported improved survival after surveillance was introduced.[100] These studies are consistent with a beneficial effect of HCC surveillance on survival time but do not rule out alternative explanations.

Simulation studies provide another line of evidence in favour of HCC surveillance.[101–106] They rely on assumptions about the rate of transition between modelled health states, the value of being in a particular health state, and other factors. A simulation study was the basis for the 1.5% per year threshold that has often been cited as the lower limit for cost-effective surveillance.[106,107]

Harms of surveillance remain an understudied issue.[108] They were reported in only four studies in the aforementioned meta-analysis and only physical harms were reported, not financial or psychological harms.[97] Up to 10% of patients experienced physical harm, often due to multiple follow-up computed tomography (CT) and/or magnetic resonance imaging (MRI) examinations, and rarely due to liver biopsy.

Not all patients with cirrhosis carry the same risk of developing HCC, and the net benefit of surveillance increases with increasing risk of HCC (assuming that overdiagnosis does not occur). The risk of HCC depends on the 'carcinogenicity' of the underlying disease and the patient's chances of living long enough to develop HCC. The incidence rate of HCC is higher in cirrhosis from chronic viral hepatitis than in cirrhosis from alcohol-related liver disease,[109,110] and highly variable in cirrhosis from MASLD.[111,112] Several models are emerging to stratify patients according to their risk of developing HCC.[41,113–117] This is a promising avenue of research, particularly if the models are validated in different settings, and their risk strata can be linked with differing surveillance strategies, *e.g.*, a no-surveillance strategy for a low-risk stratum and an 'intensified surveillance' strategy for a high-risk stratum. EASL endorses risk-based surveillance for HCC among patients with cirrhosis.[118]

Should patients with chronic liver disease and advanced fibrosis without cirrhosis be offered surveillance for HCC?

Recommendation

- Patients with chronic liver disease and advanced fibrosis without cirrhosis have a higher risk of HCC than the general population, but HCC surveillance cannot currently be recommended in this group owing to insufficient evidence **(LoE 3, weak recommendation, strong consensus).**

The risk of developing HCC and the benefit of surveillance among patients with advanced fibrosis have been studied mostly in patients with MASLD and in patients with HCV infection who have achieved a sustained virological response. Studies have examined the incidence rate of HCC but not the effect of HCC surveillance on patient survival or diagnosis at an early stage.

MASLD

HCC may occur at earlier stages in MASLD than in other chronic liver diseases. A meta-analysis of 61 studies showed that the prevalence of cirrhosis was lower in patients with HCC associated with non-alcoholic fatty liver disease (NAFLD) – hereafter referred to as MASLD according to the updated nomenclature – than in patients with HCC from other causes (61.5% *vs.* 85.4%). The degree of fibrosis defines the risk of HCC. A large US cohort study of 1,773 patients with MASLD reported an incidence rate of HCC in patients with advanced F3 fibrosis (0.34 per 100 person-years, based on six HCC cases among 369 patients) that was higher than the incidence rate in patients with F0–F2 fibrosis or cirrhosis.[112] Yet, it was not specified whether these patients were screened for HCC or not. Other studies have shown that patients with MASLD without cirrhosis had a markedly lower HCC incidence than those with cirrhosis, although not distinguishing between patients with F3 or F0–F2 fibrosis.[111,119]

Hepatitis C after eradication

Several studies have demonstrated that the risk of *de novo* HCC persists after successful cure of HCV infection in patients with advanced hepatic fibrosis without cirrhosis.[37,45,49,120] A meta-analysis including eight studies of patients with F3 fibrosis reported a pooled HCC incidence rate of 0.5 per 100 person-years.[121] The incidence rate was similar whether patients had achieved sustained virological response with interferon-based therapy (three studies, HCC incidence rate 0.4 per 100 person-years) or DAA therapy (five studies, HCC incidence rate 0.5 per 100 person-years).[121] Patients in these two studies were not surveilled for HCC after HCV eradication.

Studies in which patients with F3 fibrosis were offered surveillance after sustained virological response did not find a higher incidence rate of HCC. A prospective Spanish study surveilled a very well selected and homogeneous group of 63 patients with F3 fibrosis and 122 patients with cirrhosis after DAA cure who had non-characterised liver nodules at baseline.[122] No patient with F3 fibrosis developed HCC during follow-up, whereas the incidence rate among patients with cirrhosis was 2.24 per 100 person-years. Another Spanish study found that the incidence rate of HCC was 0.47 per 100 person-years among 506 patients with F3 fibrosis who were under HCC surveillance after HCV eradication with DAAs.[120] Finally, a French study showed an incidence rate of HCC of 0.52 per 100 person-years among 1,086 patients with advanced fibrosis with HCV infection eradicated with DAAs.[39]

In light of the available evidence, performing prospective studies on HCC surveillance in this population is encouraged to generate data for future guidelines. It should be noted that it is the assessment of fibrosis before and not after disease-modifying therapies like antivirals or abstinence from alcohol that should be used to establish the recommendation for HCC surveillance.

Which is the best test (or combination of tests) for HCC screening?

Recommendation

- An ultrasound examination of the liver every 6 months is recommended for screening of HCC. The combined use of ultrasound with AFP increases sensitivity while decreasing specificity and is a reasonable option. There is limited data to support the use of other promising imaging modalities such as abbreviated MR or serum biomarkers **(LoE 3, strong recommendation, consensus).**

Ultrasound

An RCT conducted in China established the basis for using ultrasound and AFP to survey patients at high risk of developing HCC.[95] However, a meta-analysis published in 2018 indicated that ultrasound exhibits low sensitivity in detecting small lesions. The sensitivity is notably impacted by studies conducted in the US (36%, 95% CI 27%–47%), as opposed to studies conducted elsewhere (47%, 95% CI 28%–67%).[123] An update of this meta-analysis reinforces the low sensitivity and a notable heterogeneity in all pooled estimates which reflects the need for further studies in the field.[97]

A recent study identified alcohol-related and non-alcohol-related fatty liver disease (odds ratio 6.1, 95% CI 1.7-21.3, $p = 0.005$) and ascites (odds ratio 3.9, 95% CI 1.2-12.6, $p = 0.021$) as independent factors associated with limited visualisation during ultrasound.[124] Similar data were reported in other studies and consequently the ultrasound LI-RADS (Liver Imaging Reporting and Data System) was introduced as a standardisation tool for ultrasound interpretation.[125] This algorithm incorporates both a detection score and visualisation scores. The visualisation score could serve as a means to identify patients who might not be ideal candidates for HCC screening with ultrasound. However, in a meta-analysis of 25,698 ultrasound examinations across 12 studies, the pooled proportions of visualisation scores A (no or minimal limitations), B (moderate limitations), and C (severe limitations) were 56.7% (I^2 = 99.2%), 30.3% (I^2 = 98.8%), and 6.9% (I^2 = 97.7%), respectively.[126] Studies that enrolled patients with cirrhosis and those focused on MASLD demonstrated significantly higher proportions of visualisation score C (p <0.05). Given that a considerable number of patients at risk exhibit cirrhosis, the utility of ultrasound LI-RADS in this context appears to be limited.[126] In addition, another study reported a limited agreement between primary and secondary sonographers and the primary sonographer and radiologist (weighted kappa of 0.73 and 0.48, respectively) for visualisation.[127] Thus, these data reflect that the sensitivity of ultrasound is operator-dependent and the incorporation of ultrasound LI-RADS does not solve it. Including the quality of liver

visualisation in the ultrasound report may help physicians decide whether to use other imaging tools in individual patients.

Regular and abbreviated magnetic resonance imaging

A prospective study from Korea demonstrated that the full MRI has higher sensitivity than ultrasound (84.8% *vs.* 27.3%) and a significantly higher positive predictive value than ultrasound for identifying single lesions <2 cm. It reported that MRI also showed a significantly lower rate of false-positive results.[128] A French study[129] also showed this result, but the main limitation of full MRI is the time and cost of the procedure and interpretation of results.[130] Although abbreviated MRI has been proposed as an alternative, most studies in this field are simulations or review a subset of sequences in patients who underwent a full MRI; or the study cohorts included patients who did not represent the screening population. In addition, no longitudinal study has directly compared the different abbreviated MRI approaches with each other or abbreviated MRI with ultrasound.[130] Thus, it is reasonable to wait for the results of the ongoing clinical trials (NCT05828446; NCT05716620; NCT05657249; NCT05486572; NCT05095714; NCT04455932; NCT04288323) before making a specific recommendation.

AFP and combined strategies

The most recent meta-analysis[131] showed that the sensitivity of AFP alone for the detection of early-stage HCC was poor (49.1%; 95% CI 40.7%–56.1%) with a specificity of 87.9% (95% CI 83.4%–92.5%). When AFP is combined with ultrasound, the sensitivity increases, but the specificity decreases. The sensitivity for early-stage HCC detection was 51.6% (95% CI 43.3%–60.5%) for ultrasound *vs.* 74.1% (95% CI 62.6%–82.4%) for ultrasound plus AFP, with a specificity of 87.9% for ultrasound *vs.* 83.9% for ultrasound plus AFP. In the same line, according to a 2018 meta-analysis,[123] the sensitivity of ultrasound to diagnose early-stage HCC increases from 45% to 63% when AFP is added, and the specificity falls from 92% to 84%. When only prospective studies were analysed (n = 6), the sensitivity for the detection of early-stage HCC was 60% (95% CI 45%–74%) for ultrasound plus AFP compared to 40% (22%–58%) for ultrasound alone. Despite the better performance of the combination strategy, it misses over one-third of HCCs at an early stage, with a pooled sensitivity of only 63%.[123] Thus, the decision to use AFP is a trade-off between false-negatives and false-positives. A recent survey of US patients with cirrhosis found that patients favoured sensitivity over specificity.[132]

Other blood tests have claimed to improve the performance of AFP, including des-gamma carboxy-prothrombin (DCP) and lectin-bound AFP (AFP-L3).[133,134] A meta-analysis of studies focused on AFP-L3 for early HCC diagnosis showed a significant heterogeneity in sensitivity, specificity, and diagnostic ratio (I^2 values of 83.5%, 89.4%, and 68.4%, respectively) that limits the interpretability of the results.[135] There are also proposals to combine AFP with both clinical and serum biomarkers in different models such as VA,[136] ASAP,[137] male-ABCD,[138] HEB,[139] HES[140] or GALAD. GALAD is the most accepted one and includes AFP, AFP-L3, DCP, age, and gender. The performance of the GALAD score in identifying Barcelona-Clínic Liver Cancer (BCLC) stage 0/A HCC and detecting early HCC in patients with cirrhosis was analysed in a meta-analysis that included 19,021 patients.[141] A high or unclear patient selection bias was observed in 16 study cohorts, primarily attributed to the retrospective case-control design. GALAD showed a sensitivity of 0.73 (95% CI 0.66–0.79), specificity of 0.87 (95% CI 0.81–0.91), and false-positive rates ranging from 4.2% to 27.2% for the detection of early HCC. These results change only slightly when the analysis is restricted to identifying HCC within BCLC 0/A stages in the population of patients with cirrhosis, where GALAD demonstrated a pooled sensitivity, pooled specificity, and estimated AUC of 0.78 (95% CI 0.66–0.87), 0.80 (95% CI 0.72–0.87), and 0.86 (95% CI 0.83–0.89), respectively. Additionally, better performance was observed in retrospective studies than in prospective studies, which also reflects the selection bias in retrospective studies.

Thus, despite the promising performance of GALAD and those models which included DCP and AFP, their main limitations for implementation in clinical practice are the selection bias and the threshold values of these models for detecting early-stage HCC. Consequently, these scores should be further validated by more high-quality studies before being recommended as routine screening tools.

Diagnosis and staging

Diagnosis

Accurate diagnosis and staging are pivotal for guiding effective therapeutic decisions in oncology, influencing treatment strategies and patient outcomes. Histopathology plays a crucial role not only by providing true confirmation of the malignant nature of a given liver tumour, but also by providing essential insights into tissue characteristics such as cellular differentiation, vascular and lymphatic invasion, and metastatic potential. HCC most commonly develops in a liver that suffers from chronic tissue damage, and a model of stepwise carcinogenesis is widely accepted, where premalignant lesions occur. In the pathway from benign to dysplastic to malignant liver nodules, changes in vascularisation occur that can be captured by contrast-enhanced imaging and are the basis of the non-invasive diagnosis of HCC. In patients with cirrhosis, HBV infection or a previous diagnosis of HCC, a liver nodule can be diagnosed non-invasively as HCC when major features are observed with dynamic contrast-enhanced CT, MRI or ultrasound (CEUS) (Fig. 2). The terminology and criteria used to describe liver nodules should follow the LI-RADS v2018 recommendations. Non-invasive diagnosis can be sufficient in clinical scenarios where the additional information provided by histopathology will not influence a therapeutic decision. HCC diagnosis should be confirmed by tumour biopsy when the non-invasive imaging-based diagnostic criteria are not met. Non-invasive criteria have not been pathologically validated in advanced stage tumours.

For the non-invasive diagnosis of HCC, should LI-RADS criteria be used to define contrast-enhanced imaging techniques (CT, MRI or ultrasound)?

Recommendations

- The LI-RADS should be used to favour standardisation in the acquisition, description and reporting of liver imaging examinations **(LoE 3, strong recommendation, strong consensus).**
- Non-invasive diagnosis of HCC should be based on the LI-RADS CT/MR v2018 or the LI-RADS CEUS v2017 criteria. With CT/MRI, the following major imaging features are combined to reach the diagnosis: tumour size, rim and non-rim arterial hyperenhancement, peripheral and non-peripheral washout (in the portal venous or delayed phases on CT and MRI using extracellular contrast agents or gadobenate dimeglumine, or in the portal venous phase only with MRI using gadoxetic acid), enhancing capsule and threshold growth. With CEUS, non-rim arterial hyperenhancement with late-onset (>60 s) and washout of mild intensity are combined to reach the diagnosis **(LoE 1, strong recommendation, strong consensus).**

Imaging is essential to HCC diagnosis, contributing to primary liver tumour characterisation and HCC staging. Historically, pathologists have shown that HCC is subject to significant neo-angiogenesis. Its occurrence is the turning point in hepatocarcinogenesis in the context of chronic liver disease. It is visible as contrast uptake on contrast-enhanced imaging during the arterial phase. In 2001, experts introduced the concept of non-invasive imaging-based diagnosis based on the presence of arterial phase hyperenhancement (APHE) on two different imaging modalities (CT, MRI, angiography or ultrasound) in patients with cirrhosis with nodules >20 mm.[142] The very high pre-test probability of HCC was the reason why such non-invasive criteria were initially restricted to patients with cirrhosis. The main problem was that numerous other lesions and pseudo-lesions might cause focal APHE in patients with cirrhosis. For instance, in one study of 61 nodules showing APHE on CT before LT, only 17 (28%) were HCCs.[143] Other nodules were mostly benign regenerative or dysplastic nodules. Therefore, APHE lacked specificity. In 2005, a new radiological hallmark (*i.e.*, washout on the portal venous and/or delayed phase) was introduced to gain specificity.[144] For 10-20 mm nodules, hallmarks had to be depicted on two imaging modalities (CT, MRI, or CEUS). Since then, numerous radiological-pathological correlation studies have challenged these criteria and led to substantial updates and modifications.

Regarding the challenging group of 10-20 mm nodules, a study addressing the diagnostic accuracy of MRI in a series of transplanted patients reported a false-positive rate of more than 10% when using only one imaging technique.[145] Prospective studies have shown that combining two imaging modalities resulted in high specificity at the cost of very low sensitivity (around 30%). The consequence was that more than two-thirds of nodules would still require pathological examination.[146] Furthermore, a prospective study reported a false-positive rate above 10% with either one or two imaging techniques, with a specificity of 81% and 85%, respectively.[147] 2012 EASL guidelines advocated the use of two coincidental techniques in non-expert centres and only one in expert centres for 10-20 mm nodules.[148] However, this statement was not evaluated, and expert centres were not defined.

In 2010, a study suggested that a sequential algorithm would maintain excellent specificity with increased sensitivity, avoiding a significant number of biopsies for 10-20 mm nodules.[149] This elegant approach also considered the respective value of different imaging techniques (MRI, CT or CEUS). The performance was confirmed by a prospective multicentric study including 381 patients with 544 nodules which reported a sensitivity and specificity in 10-20 mm nodules of 70.6% and 83.2% for MRI using extracellular contrast agents and 67.9% and 76.8% for CT.[150] Again, the concurrent use of CT and MRI had a specificity of 100% but a sensitivity of 55.1%. Interestingly, a very high specificity was reached when CEUS was used as a second-line test after a first inconclusive CT or MRI.[150] This became possible only because other studies had refined and identified the typical hallmarks for HCC at CEUS (*i.e.*, APHE and late [>60 s] and mild washout).[151,152] This perspective justified the two-step 2018 EASL non-invasive diagnostic algorithm.[2]

In 2011 the American College of Radiology introduced the LI-RADS to standardise the terminology, acquisition technique, interpretation, reporting and data collection of liver imaging exams and characterise liver observations in patients at high risk of HCC.[153] LI-RADS includes four parts, screening and surveillance, diagnosis, staging and decision-making, and treatment response assessment.

Two diagnostic LI-RADS algorithms have been developed, one for CT/MRI and another one for CEUS. These algorithms are categorical and algorithmic systems where liver observations are assigned a category corresponding to the estimated probability of HCC or malignancy. The LI-RADS has undergone several updates to clarify definitions and concepts, address limitations, and incorporate new evidence, and has gained worldwide acceptance, at least in academic centres and scientific studies. The latest version (released in 2018) is aligned with the Organ Procurement and Transplant Network.

The LI-RADS CT/MR diagnostic algorithm can be used in patients with cirrhosis or chronic HBV infection or current or prior HCC, regardless of lesion size. It cannot be applied to patients <18 years old, patients with cirrhosis due to congenital hepatic fibrosis vascular disorders such as hereditary haemorrhagic telangiectasia, Budd-Chiari syndrome, chronic portal vein occlusion, cardiac congestion, or diffuse nodular regenerative hyperplasia. It cannot be applied either to pathologically proven tumours. The CT/MR algorithm combines five major features, *i.e.*, tumour size, APHE, washout, an enhancing capsule, and tumour growth. APHE is further categorised into rim (confined to the observation's periphery) or non-rim APHE. Similarly, washout is further categorised into peripheral and non-peripheral washout (not mainly in the observation's periphery). The capsule corresponds to a smooth, uniform, sharp border on CT or MRI around most or all of the observation, and the threshold for growth is a ≥50% increase in size in ≤6 months. A definite HCC (*i.e.*, LR-5) is present if a lesion ≥20 mm shows non-rim APHE and at least one additional major feature among a non-peripheral washout, an enhancing capsule, and threshold growth. The LR-5 category also applies to lesions 10-19 mm in size showing non-rim APHE

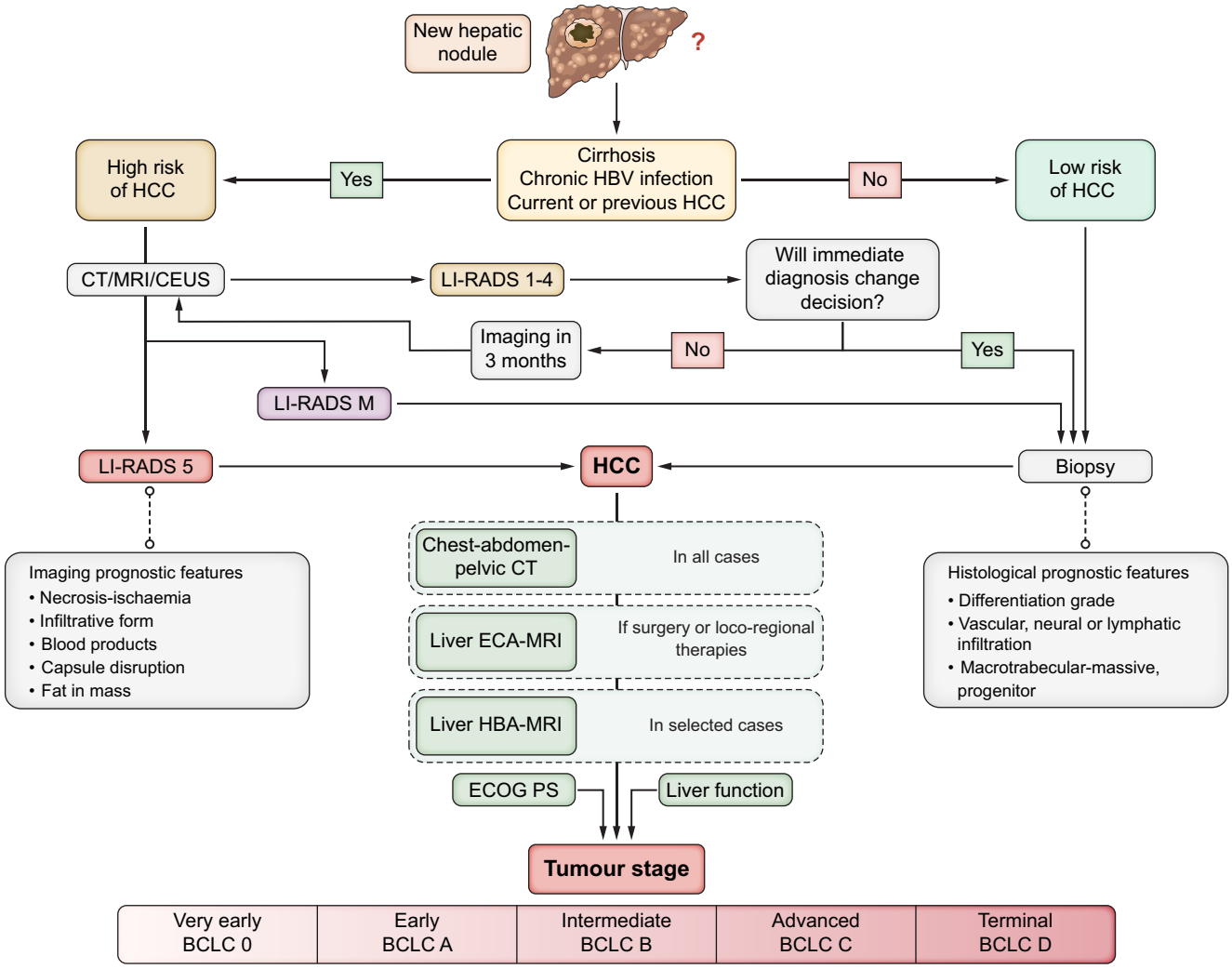

Fig. 2. A framework for the diagnosis and staging of patients with HCC. BCLC, Barcelona Clinic Liver Cancer; CEUS, contrast-enhanced ultrasound; CT, computed tomography; ECA, extracellular contrast agent; ECOG PS, Eastern Cooperative Oncology Group performance status; HBA, hepatobiliary agent; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LI-RADS, liver reporting and data system; MRI, magnetic resonance imaging.

and either non-peripheral washout or threshold growth. Notably, LI-RADS also considers the presence of unequivocal enhancing soft tissue in a vein, regardless of visualisation of a parenchymal mass, as highly specific of HCC, and reports it as 'tumour-in-vein' (LR-TIV). The LI-RADS TIV category has only moderate sensitivity but excellent specificity for diagnosing macroscopic vascular invasion. In a retrospective study including 1,322 patients with (n = 101) or without (n = 1,221) macroscopic vascular invasion at pathology, the sensitivity and specificity of TIV on imaging were 62% and 99% for CT and 64% and 99% for MRI.[154] Finally, the LR-M category (probably or definitely malignant but not necessarily HCC) is introduced, mainly for lesions displaying a target-like morphology, *i.e.* concentric arrangement of internal components that likely reflects peripheral hypercellularity and central stromal fibrosis or ischaemia.

The CEUS diagnostic algorithm can be used in the same high-risk patients as the CT/MR algorithm. It can only be applied to lesions visible at pre-contrast ultrasound. It applies to CEUS examinations performed with pure blood-pool agents (Lumason® in the US, SonoVue® outside the US; Definity® in the US and Canada, Luminity® outside the US or Canada), but not to CEUS exams performed with combined blood-pool and Kupffer-cell agents such as Sonazoid®. The same categories of the CT/MR algorithm are used, but the major imaging features differ and include size, rim, APHE (non-rim and not peripheral discontinuous), and washout (refined into early [<60 s] or late [≥60 s] and into marked or mild). The rim APHE is also applied for LR-M categorisation. A definite HCC (LR-5) is present if a lesion ≥10 mm shows non-rim and non-peripheral discontinuous globular APHE plus late and mild washout. The algorithm also considers the LR-TIV and LR-M categories. This CPG endorses the use of the LI-RADS CT/MR and CEUS criteria for the non-invasive diagnosis of HCC.

If the criteria for the non-invasive diagnosis of HCC are not met, a tumour biopsy is mandatory. When performed, the aim of a tumour biopsy should be to reach an accurate diagnosis and determine relevant prognostic factors. Accordingly, its adequacy is critical, and several recommendations should be followed: (i) it should be obtained using percutaneous access under CT or ultrasound guidance,[155] (ii) it should provide

sufficient tissue material from the target nodule and eventually from the background liver when sampled, (iii) extensive sampling of the tumour biopsy through serial sections and routine staining should be performed to explore cytological aspects (H&E) and architectural patterns (reticulin),[156,157] while additional immunostainings may be useful to differentiate dysplastic nodules from early HCC.[158,159] While the specificity and positive predictive value of biopsy are excellent (100%) for hepatocellular nodules <2 cm, it has a variable sensitivity (66%-93%), which depends on tumour size, experience of the operator and pathologist, and needle size.[155] Repeated biopsies may be necessary for patients with imaging features that raise suspicion of malignancy and negative tumour biopsy.[160] However, such an invasive strategy should be nuanced by well-known limits of biopsy, including low risks of complications (track seeding and bleeding), sampling error, and the various likelihoods of malignancy for indeterminate liver nodules.[161,162] These limitations are mostly driven by tumour location.

Is the LI-RADS more accurate than the 2018 EASL algorithm for the non-invasive diagnosis of HCC?

Recommendation

- The LR-5 category and the 2018 EASL algorithm have similar performance for the non-invasive diagnosis of HCC. However, LI-RADS should be preferred because it introduces valuable refinements (*e.g.*, LR-M and LR-TIV categories) and allows for an estimation of the probability of HCC in nodules that do not meet the LR-5 category **(LoE 3, strong recommendation, strong consensus).**

One of the main benefits of LI-RADS over pre-existing systems is that it categorises liver observations according to the risk of HCC or malignancy and endorses management suggestions. To be valid, this approach requires that this risk be known for each LI-RADS category. Since 2018, more than 20 systematic reviews and meta-analyses have been published to assess LI-RADS performance. All have consistently validated the excellent specificity of the LR-5 category (definitely HCC) and the value of the LR-TIV (macrovascular venous invasion) and LR-M (malignancy but not specific for HCC) categories.[163–165] Notably, the proportion of HCC and malignancy across categories was shown not to be affected by the imaging modality (*i.e.*, CT or MRI) or contrast agent used (*i.e.*, extracellular or liver-specific).[164]

Of course, the system is not perfect. While systematic reviews have confirmed that the likelihood of an observation being an HCC corresponds to the ordinal LI-RADS category,[163–165] a recent meta-analysis (49 studies, 9,620 patients with 11,562 observations, comprising 7,921 HCCs, 1,132 non-HCC malignancies, and 2,509 benign entities) reported a relative range of proportions of HCC for LR-2 (probably benign, HCC in 2% to 18%), LR-3 (intermediate probability of malignancy, HCC in 32% to 60%), and LR-4 (probably HCC, HCC in 67% to 93%), which calls for improvements.[164] In this meta-analysis, 97% of LR-5 cases were confirmed as HCC by pathology or imaging follow-up. Additionally, the agreement for LI-RADS categorisation remains moderate[166] despite recent updates and clarification in the LI-RADS lexicon.[167,168]

A direct comparison of EASL v2018 and LI-RADS v2018 is challenging because these systems do not share the same definition of high-risk patients. Therefore, a proper comparison should be performed in populations considered by both systems (*i.e.* only in patients with cirrhosis). Most comparative studies include Asian populations with a predominance of patients with chronic HBV infection[169] and show similar performance of the LR-5 and EASL criteria for diagnosing HCC. A systematic review assessed the adherence to LI-RADS and EASL high-risk population criteria in 219 original studies (215 used LI-RADS only, 4 EASL only, and 15 LI-RADS and EASL).[170] Inadequate adherence to high-risk population criteria was observed in 8.4% of LI-RADS and 42.1% of EASL studies, regardless of imaging modality. This shows that EASL criteria are often misused and applied to patients with chronic HBV infection without evidence of cirrhosis or patients without cirrhosis with different aetiologies of chronic liver disease.

Broadening the definition of the high-risk population, especially by including HBV patients without cirrhosis, is a matter of debate. The 2018 EASL guidelines limited non-invasive diagnosis to patients with cirrhosis, but patients with HBV and cirrhosis at intermediate or high risk of HCC according to PAGE-B classes are candidates for surveillance. Using platelets, age and gender, PAGE-B classifies individuals with HBV infection into three classes according to their risk of developing HCC (at 5 years, low risk, almost 0%; intermediate risk, 3%; high risk, 17%).[171] The performance of EASL and LI-RADS criteria for diagnosing HCC in patients with HBV without cirrhosis has recently been analysed. Among 280 patients with 338 observations (76% HCC, 12% non-HCC malignant lesions, and 12% benign lesions), when the pre-test probability of HCC was >70% (estimated as a PAGE-B score ≥10), EASL or LR-5/LR-TIV criteria were associated with a >90% probability of HCC.[172] In populations at lower risk, the probability of HCC was lower, between 80% and 85%. Altogether, EASL and LR-5/TIV seem to offer the same diagnostic specificity. Nevertheless, LI-RADS diagnostic algorithms provide a more granular assessment of liver nodules, introduce valuable refinements (*e.g.*, non-rim APHE, LR-M) and standardise definitions and features. Future studies are needed to quantify the clinical benefit of adopting LI-RADS in clinical practice.

Should contrast-enhanced MRI be preferred to contrast-enhanced CT for the non-invasive diagnosis of HCC?

Recommendation

- Multiphasic CT or dynamic contrast-enhanced MRI are recommended, without preference, for the non-invasive diagnosis of HCC **(LoE 1, strong recommendation, consensus).**

A prospective study evaluated the diagnostic accuracy of CEUS, CT and MRI performed in the assessment of liver nodules detected in every consecutive patient with compensated cirrhosis under surveillance with ultrasound. Among 64 patients with 67 *de novo* liver nodules (44 HCC, 34 HCC 1-2 cm), the sensitivity of CEUS, CT and MRI for 1-2 cm HCC was 26%,

44% and 44%, with 100% specificity.[149] More recently, a multicentre prospective trial investigated patients with 1-3 cm nodules who had CEUS, CT and MRI using extracellular contrast agents performed within a month.[150] Among 381 patients with 544 nodules (342 HCC, 187 HCC 1-2 cm), the sensitivity and specificity for the diagnosis of HCC were 71% and 85% for MRI, 70% and 81% for CT, and 46% and 93% for CEUS. For 10-20 mm nodules, the sensitivity and specificity were 71% and 83% for MRI, 68% and 77% for CT and 40% and 93% for CEUS.

Is hepatospecific contrast-enhanced MRI more accurate than extracellular contrast-enhanced MRI for the non-invasive diagnosis of HCC?

Recommendation

- Extracellular contrast agents should be favoured over gadoxetic acid for the non-invasive diagnosis of HCC using MRI **(LoE 1, strong recommendation, consensus).**

A significant development in liver imaging was the introduction of liver-specific MR contrast agents, also called hepatobiliary agents (HBAs). These agents are gadolinium chelates that, contrary to extracellular contrast agents (ECAs), are taken up by functioning hepatocytes. Radiological-pathological studies have shown that their internalisation is mediated by organic anion transporting polypeptides (OATP) expressed on the sinusoidal membrane of functional hepatocytes.[173] The level of expression of OATP is significantly decreased in impaired hepatocytes. Consequently, these contrast agents are accurate markers of such hepatocellular function. On dedicated T1-weighted images obtained when the liver and bile ducts are markedly enhanced (in the so-called 'hepatobiliary [HB] phase'), non-hepatocellular tumours, tumours containing impaired hepatocytes (such as most HCC), vessels and cysts appear hypointense. Loss of hepatocellular function occurs early during hepatocarcinogenesis, even before neoangiogenesis. This is why 80% to 90% of HCC are hypointense on the HB phase, while most non-HCC, cirrhosis–associated regenerative or dysplastic nodules appear iso- or hyperintense. Therefore, liver-specific agent-enhanced MRI has a higher sensitivity for detecting nodules. A meta-analysis focusing on the diagnostic performance of MRI for diagnosing HCC up to 2 cm showed that HBA-MRI had significantly increased sensitivity compared to ECA-MRI (92% and 67%, respectively).[174] It may be tempting to consider hypointensity on HB phase as a new imaging hallmark of HCC and to expect an improvement in diagnostic performance, the same way the criterion of washout did. In a study including 420 nodules >1 cm in 228 patients,[175] the authors developed a classification and regression tree using three MRI findings independently associated with HCC (*i.e.*, HB phase hypointensity, arterial hyperintensity, and diffusion restriction). This algorithm demonstrated, both in the entire study population and for nodules ≤2 cm, higher sensitivity but slightly lower specificity than classical criteria. However, the algorithm was not externally validated.[176] The significance of hypointensity on the transitional phase and/or the HB phase is not the same as that of washout. This is why other studies have shown that hypointensity on HB phase used as an alternative to washout led to a significant increase in sensitivity for the diagnosis of HCC but at the cost of an unacceptable decrease in specificity.[177,178]

Several meta-analyses have studied the sensitivity of ECA- and HBA-MRI.[177,179] All have found that HBA-MRI is associated with higher sensitivity than ECA-MRI, particularly in small HCC. On the other hand, several head-to-head studies consistently showed the superiority of ECA-MRI over HBA-MRI for diagnosing HCC. Among 91 patients with chronic liver disease who underwent ECA-MRI and HBA-MRI within a 1-month interval for a first detected hepatic nodule on ultrasound, 117 observations (95 HCCs, 19 benign lesions, and 3 other malignancies; median size, 18 mm) were identified after surgical resection. ECA-MRI had higher sensitivity (77.9% *vs.* 66.3%) and accuracy (82.1% *vs.* 72.6%) than HBA-MRI in the LR-5 category v2017.[180] In a multicentric prospective study of 171 patients with cirrhosis who underwent ECA-MRI and HBA-MRI within a month, 225 observations were made (153 HCCs), each with 1 to 3 nodules measuring 1-3 cm. The sensitivities of both MRI techniques were similar, but specificity was 83.3% (95% CI 72.7-91.1) for ECA-MRI and 68.1% (95% CI 56.0-78.6) for HBA-MRI.[181]

Another prospective study included 125 patients with chronic liver disease (163 observations, 124 HCCs, 13 non-HCC malignancies, and 26 benign lesions; mean size, 20.7 mm) who underwent CT, ECA-MRI, or HBA-MRI (with gadoxetic acid) before surgery for a nodule initially detected by ultrasound. ECA-MRI detected HCC with 83.1% sensitivity and 86.6% accuracy, compared to 64.4% sensitivity and 71.8% accuracy for CT (p <0.001) and 71.2% sensitivity (p = 0.005) and 76.5% accuracy for HBA-MRI (p = 0.005).[182] Interestingly, adding CT to either ECA-MRI (89.2% sensitivity, 91.4% accuracy; both p <0.05) or HBA-MRI (82.8% sensitivity, 86.5% accuracy; both p <0.05) significantly increased its diagnostic performance in the detection of HCC compared with MRI alone. The same group compared ECA-MRI and HBA-MRI in 179 participants with cirrhosis (n = 105) or HBV infection without cirrhosis (n = 74) using LI-RADS v2018 as a reference. LR-5 with ECA-MRI provided the highest sensitivity (80.7%), followed by EASL v2018 with ECA-MRI (76.2%), LR-5 with HBA-MRI (67.3%), and EASL v2018 with HBA-MRI (63.0%, all p <0.05). The specificities were comparable (89.4% to 91.5%). When the analysis was limited to participants with pathological cirrhosis (123 observations), the sensitivity of LR-5 with ECA-MRI was similar to that of EASL v2018 with ECA-MRI (82.7% *vs.* 80.2%, p = 0.156) but higher than LR-5 with HBA-MRI (65.1%) or EASL v2018 with HBA-MRI (62.8%, both p <0.001), with comparable specificities (87.5% to 91.7%).[183] Finally, in a study that assessed and compared the reliability of LI-RADS v2018 and EASL v2018 criteria for diagnosing HCC using ECA-MRI of HBA-MRI, the inter-reader agreement for definite HCC diagnosis was substantial and similar between ECA-MRI and HBA-MRI for EASL and LI-RADS criteria.[166]

Specific issues with gadoxetic-enhanced MRI

Biokinetics of gadoxetic acid, with half the dose excreted into the bile ducts and the other half excreted by the kidneys, has several diagnostic consequences. First, hypointensity on the

transitional or the HB phase should be regarded as ancillary findings favouring malignancy (not specifically HCC), not as equivalent to washout. As most HCCs (80%–90%) are hypointense on the HB phase, this feature may contribute to the differentiation between HCC and benign nodules developed on chronic liver diseases[184] but not as a major feature. Second, hypointensity on the transitional phase appears before APHE. As a result, non-hyperenhancing but HB phase hypointense nodules are depicted, which correspond mainly to early HCC or dysplastic nodules. These nodules have a higher risk of progression to typical HCC than iso- or hyperintense nodules on HB phase.[185] Third, injecting gadoxetic acid is associated with an increased risk of transient respiratory motion artefacts in the arterial phase (occurring in 2.4% to 18% of cases) that could reduce image quality.[186,187] Whether these artefacts hamper the detection of lesion hyperenhancement on the arterial phase remains debated. Nevertheless, ECA-MRI identified APHE in a significantly higher proportion of patients than CT (97.6% *vs.* 81.5%; p <0.001) or HBA-MRI (89.5%; p = 0.002).[182] In another study, ECA-MRI and HBA-MRI identified APHE in 90% and 78% of cases, respectively.[181]

Should CEUS be used as a first-line examination for the non-invasive diagnosis of HCC?

Recommendations

- CT or MRI should be preferred over CEUS as a first-line examination for the non-invasive diagnosis of HCC because of their higher sensitivity and their utility for analysis of the whole liver **(LoE 3, strong recommendation, consensus).**
- When used for the non-invasive diagnosis of HCC, CEUS should be performed according to the LI-RADS technical recommendations **(LoE 4, strong recommendation, strong consensus).**

As mentioned above, the use of CEUS for the non-invasive diagnosis of HCC has been debated because of a theoretical risk of misdiagnosis, especially with intrahepatic cholangiocarcinoma, which appeared to occur at a rate of 2–5% of all new nodules in cirrhosis.[188,189] Indeed, APHE followed by washout at CEUS is not specific for HCC and occurs in about 50% of mass-forming intrahepatic cholangiocarcinomas in cirrhosis.[188,189] However, the onset of washout takes place earlier than 60 s after contrast injection in 50% to 85% of intrahepatic cholangiocarcinomas,[190,191] while this is rarely observed in HCC. Also, the intensity of washout in the portal phase is more marked in intrahepatic cholangiocarcinoma than in HCC.[192] Hence, the main imaging features for HCC at CEUS are APHE followed by late (>60 s) washout of mild intensity.[151,152]

Using these criteria, a large retrospective study of more than 1,000 lesions in cirrhosis reported a positive predictive value for HCC of almost 99% and a positive likelihood ratio of 15.5, with no case of misdiagnosis with intrahepatic cholangiocarcinoma.[193] Such improved diagnostic capacity was associated with only a slight decrease in sensitivity compared to the EASL and AASLD criteria (from 67% to 62%).[193] Furthermore, in a prospective multicentric study, CEUS had a specificity of 92.9% *vs.* 76.8% for CT and 83.2% for MRI in 10–20 mm nodules.[150] 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 a washout than with CT or MRI.[146,194] CEUS can be used when CT or MRI are inconclusive. When the diagnosis of HCC is based on CEUS, disease staging should include chest CT and abdominal CT or MRI.

Should imaging-based non-invasive criteria for the diagnosis of HCC be used in patients without cirrhosis?

Recommendation

- The non-invasive criteria should only be applied to patients with cirrhosis, chronic HBV infection or a history of HCC. In other patients, the diagnosis of HCC should be confirmed by biopsy **(LoE 1, strong recommendation, consensus).**

Evidence suggests that the imaging appearance of HCC is similar in patients with or without cirrhosis. However, knowledge of imaging presentations of HCC in patients without cirrhosis is limited. The main reason is that very few studies, all including small series of patients, have described the clinical, pathological, and imaging features of HCCs developing on non-cirrhotic livers. Interestingly, these studies consistently reported that the main imaging features of HCC are present in most patients. However, these studies did not differentiate between HCCs developing in the context of advanced fibrosis and those developing in non-fibrotic livers, and did not specifically categorise patients by aetiologies of chronic liver disease, *e.g.*, MASLD from metabolic dysfunction-associated steatohepatitis (MASH) or MASLD from other causes of liver disease.

A critical (and often overlooked) factor is that the non-invasive diagnosis of HCC can only be applied to patients who are considered at high risk of developing HCC. The definition of high-risk patients is needed to maintain a high specificity for diagnosing HCC due to several HCC mimickers in patients without risk factors. Indeed, the accuracy of a diagnostic test (*e.g.*, imaging) is affected by the pre-test probability of the disease. In a population that does not have a sufficiently high pre-test probability of having HCC, typical imaging features can be observed in other benign and malignant non-HCC lesions, leading to an unacceptable number of false-positive diagnoses and a reduced specificity for HCC. The non-invasive diagnosis of HCC cannot be made in patients without cirrhosis or chronic HBV infection and with no history of HCC (*e.g.*, in patients with MASLD without cirrhosis). In these patients, a biopsy is required. Indeed, despite an unequivocally increased risk of HCC in patients with MASLD without cirrhosis, the pre-test probability in these populations has not yet been precisely established.

Data regarding the performance of the non-invasive diagnosis in MASLD patients without cirrhosis is scarce because

most studies addressing the performance of the non-invasive diagnosis of HCC adhere to the definition of high-risk populations. One study has specifically focused on the performance and reliability of LI-RADS for distinguishing HCC from non-HCC primary liver carcinomas in patients who did not meet strict LI-RADS high-risk criteria.[195] It studied 131 patients, including 19% with steatosis without fibrosis, 7% with steatosis and fibrosis, 6% with MASH but without fibrosis, and 25% with MASH and fibrosis. In the entire cohort, the specificity of LR-5 as a predictor of HCC was 97%-100%, and the combination of LR-5 or LR-TIV as a predictor of HCC did not change the specificity. However, the authors did not provide the result for the subgroup of patients with MASLD. The same group published another study focusing on non-HCC malignancies.[196] They suggested that non-HCC malignancies were more likely to mimic HCCs on CT and MRI in the LI-RADS target population than in patients without LI-RADS-defined HCC risk factors. However, again, no subgroup analysis in patients with MASLD was provided. Other studies have also focused on patients without LI-RADS-defined HCC risk factors, but no patients with MASLD were included.[197]

Specifics of patients with MASLD without cirrhosis

Most HCCs developing in patients with MASLD without cirrhosis present as solitary lesions or as a dominant mass with satellite nodules. Infiltrating forms are anecdotal. The vast majority of HCCs present with non-rim APHE and non-peripheral washout. No evidence suggests any differences between patients with and without cirrhosis, except for larger tumour size in patients without cirrhosis, probably due to surveillance programmes. A systematic review and meta-analysis of five studies including 170 patients with MASLD and 193 HCCs showed that the pooled percentages of APHE, washout, and enhancing capsule were 94.0% (95% CI 89.1–96.7%), 72.7% (95% CI 63.3–80.4%), and 57.5% (95% CI 45.1–69.1%), respectively.[197] The percentages of these three major features did not significantly differ between MASLD and MASH. MRI showed similar pooled percentages of APHE (94.3% *vs.* 93.4%, $p = 0.82$) and washout (70.4% *vs.* 77.2%, $p = 0.38$) to CT, but a higher pooled percentage of enhancing capsule (67.1% *vs.* 44.7%, $p = 0.02$). The better ability of MRI to depict an enhancing capsule was also shown in another study.[198]

The detection and characterisation of focal liver lesions are modified by steatosis. It may lead to underestimation of the tumour burden, particularly with CT. It can also make the characterisation of the lesion more difficult. MRI is the most appropriate imaging examination to address this limitation. In a study that assessed the effect of hepatic steatosis on major features of HCC at MRI in patients with MASLD, an 18% and 22% increase in the odds of absent washout and capsule appearance was reported for every 1% increase in hepatic fat fraction.[199]

Steatohepatitic HCC

Steatohepatitic HCC (sh-HCC) is one of the many variants of HCC listed in the WHO classification. It was described in 2010 as an HCC presenting histological features of steatohepatitis (*i.e.*, ballooning, steatosis, fibrosis, inflammatory infiltrates, Mallory-Denk bodies).[200] It is one of the most frequent subtypes, accounting for about 20% of HCCs. It was initially described in patients with HCV and alcohol aetiologies, but its association with the metabolic syndrome and MASLD is now well established. The diagnosis relies on depicting a steatohepatitic component in ≥50% of the total viable tumour area on pathology. A less than 50% component will classify the tumour as classic HCC (non-otherwise specified HCC) with a steatohepatitic component.[201]

There are still few radiological descriptions of sh-HCC. They are usually smaller than other HCCs and classically develop on a background of hepatic steatosis. Therefore, tumours may be difficult to distinguish from the surrounding liver parenchyma in patients with severe hepatic steatosis. On CT and MRI, fat in mass is significantly more frequent in sh-HCCs than in other subtypes. This is depicted as a diffuse or low focal attenuation on CT and intralesional signal loss on opposed-phase MR images.[202–204] However, the presence of fat in mass is insufficient to reliably predict the sh-HCC subtype because this feature is also observed in other HCC subtypes, in early HCC and other fat-containing liver lesions. In high-risk patients, most sh-HCCs are categorised as LR-5 since most tumours show APHE, washout, and a capsule.[204] The majority of tumours also show hypointensity in the HB phase. Steatohepatitic HCC uncommonly exhibits TIV. Notably, the possible non-invasive diagnosis of sh-HCC should be considered only in the appropriate clinical context (*e.g.*, HCC showing fat in mass in patients with steatosis, metabolic syndrome).

If a biopsy is obtained, should HCC subtyping be performed on biopsy material, including immunostainings with hepatocellular and cholangiocellular markers?

Recommendations

- Pathological diagnosis of HCC should be based on the International Consensus recommendations using the required histological and immunohistochemical analyses **(LoE 1, strong recommendation, strong consensus).**
- If a biopsy is obtained, relevant prognostic features should be reported, including tumour differentiation and HCC subtyping per the WHO classification **(LoE 1, strong recommendation, strong consensus).**

HCC is histologically defined by the malignant proliferation of tumour cells that may present varying degrees of hepatocellular differentiation (*i.e.*, resembling more or less normal hepatocytes). Based on the arrangement of tumour proliferation, three main architectural patterns are described (i) a trabecular pattern where malignant hepatocytes are arranged in plates with variable thickness (from 2 to over 20 cells); (ii) a compact or solid pattern when tumour plates are closely aligned and sinusoids become compressed and unapparent; and (iii) an acinar or pseudoglandular pattern where tumour cells are arranged in glandular structures that may contain bile. The large majority of HCC do not display significant fibrous stroma. The recent WHO classification identifies HCC with no morphological particularity as 'not otherwise specified HCC'

(NOS-HCC). Additionally, eight different morphological subtypes are recognised (*i.e.*, fibrolamellar, scirrhous, clear cell, steatohepatitic, macrotrabecular/massive, chromophobe, neutrophil-rich and lymphocytic-rich).

Integrative molecular analysis based on genomic, transcriptomic and epigenomic screening has enabled refinement of the molecular landscape of HCC and the identification of distinct molecular classes associated with specific biological behaviours.[205] By correlating molecular and morphological features, a pathomolecular classification of HCC has been proposed.[206] According to this classification, some histotypes (*e.g.*, the macrotrabecular/massive and progenitor phenotypes) are associated with a poor prognosis, while others (*e.g.*, the lymphocyte-rich subtype) have a better prognosis. Beyond subtyping, the histological grading of differentiation (well/moderately/poor) is commonly used in practice and has been shown to bear prognostic value in surgical and transplantation series.

Differential diagnosis

Hepatocellular nodules <2 cm in size encompass a broad spectrum of lesions from regenerative to dysplastic nodules (*i.e.*, low grade and high-grade dysplastic nodules) and early HCC.[156] Discriminating premalignant high-grade dysplastic nodules from malignant well-differentiated HCC is the main challenge. Differential diagnosis relies on cytological and architectural features.[157] The most informative features include the presence of unpaired arteries, increased sinusoidal capillarisation, stromal invasion and reticulin loss.[157] As these features can be missed in biopsy specimens, further immunohistochemical analysis is helpful to demonstrate markers associated with malignancy. A panel of three immunohistochemical markers (glypican-3, glutamine synthetase and heat shock protein 70) was shown to have 100% specificity and 72% sensitivity for the diagnosis of HCC when all three markers are positive, while the use of single markers can be misleading.[158,159] Notably, such a panel does not significantly improve the performance of tumour biopsy for diagnosing HCC in an expert setting.[159] In malignant nodules <2 cm, two distinct subtypes are defined, early HCC and progressed HCC, based on their growth development (vaguely nodular *vs.* distinctly nodular), and histological differentiation (well *vs.* moderately to poorly differentiated).[207] Fatty change is a common feature observed in around 40% of early HCC, and its prevalence decreases as size increases.[208] Compared to early HCC, progressed HCC is associated with vascular invasion and intrahepatic metastasis.[207]

Among primary liver cancers, differential diagnosis includes intrahepatic cholangiocarcinoma and combined tumours (*i.e.*, tumours showing both hepatocellular and cholangiocellular components within the same nodule). Both types of tumours may arise in patients with or without cirrhosis. Morphological analysis is always supported by immunohistochemical markers indicative of hepatocellular differentiation (HepPar-1, Arginase-1, CD10, pCEA, glypican 3 and BSEP) or cholangiocytic differentiation (cytokeratin 7 and 19). A higher performance for HCC diagnosis in terms of specificity and sensitivity has been reported for CD10, pCEA, and BSEP,[209] compared to HepPar-1 and glypican 3. In addition, markers of progenitor phenotype (cytokeratin 19, EpCAM, NCAM, CD133, SALL4, and nestin) may be helpful to support the diagnosis of a subtype of combined tumours (with stem cell features).

Beyond the diagnosis of HCC, histological analysis of the tumour biopsy offers an exhaustive characterisation of HCC through its pathomolecular subtyping, highlighting the significant heterogeneity of HCC between patients and nodules within a given nodule. Such intratumoral heterogeneity, which is a frequent observation, may consequently hamper the reliability of the biopsy, especially in large tumours.[210–212] Nevertheless, an excellent inter-observer agreement between three pathologists (Cohen kappa 0.82) has been reported for identifying the macrotrabecular/massive subtype from a tumour biopsy, supporting its significant performance and usefulness in clinical practice.[213] Interestingly, endothelial-specific molecule 1 or ESM1 has been identified as a reliable surrogate marker of the macrotrabecular/massive subtype, with 93% sensitivity and 91% specificity as well as a good interobserver agreement (Cohen Kappa 0.76) in a validation set.[214] While the prognostic value of the tumour biopsy has not yet been fully recognised, the recognition of the worst prognostic subtypes (*i.e.*, macrotrabecular/massive and progenitor subtypes) and poorly differentiated tumour areas should be reported. They may be considered in patient management, at least for LT candidates[215] or after hepatic resection or ablation.

Should the non-tumoural liver parenchyma be systematically sampled in patients undergoing biopsy for the diagnosis of HCC?

Recommendation

- In patients undergoing tumour biopsy for the diagnosis of HCC, it is suggested to simultaneously obtain a sample of the non-tumoural liver parenchyma to facilitate the diagnosis **(LoE 3, weak recommendation, consensus).**

In patients with suspected or even confirmed HCC, a biopsy of the non-tumoural liver allows for a comparative histological analysis of the tumour nodule and the background liver, which can be very helpful for differential diagnosis between early HCC (malignant) and high-grade dysplastic nodules (pre-malignant).[216] It will further provide an exhaustive assessment of non-tumoural damage (severity of the disease based on fibrosis stage and activity grade) and the potential presence of comorbid factors. This may be particularly informative in patients with MASLD, where non-invasive tests for fibrosis evaluation are less performant. A meta-analysis including 82 studies and 14,609 patients with MASLD showed that the sensitivity and specificity of transient elastography for detecting any degree of fibrosis were 78% and 72%, respectively (80% and 77% for advanced fibrosis).[217]

Should biopsy sampling systematically include material for further molecular biology techniques?

Recommendation

- Until therapeutic decisions can be reliably informed by molecular analysis of tumours, routine molecular analysis is not recommended **(LoE 3, strong recommendation, strong consensus).**

No evidence supports the need for systematic molecular analysis for predicting clinical outcomes. However, despite the absence of clinically validated specific molecular theranostic signatures, future progress in HCC patient management towards precision medicine will require the integration of molecular analysis, as already performed in various cancers (*e.g.*, melanoma, lung, breast cancers). This is expected to be particularly relevant for patients in adjuvant settings, even though the number of targetable drivers in HCC remains limited. As technology evolves, routine biopsies (formalin-fixed and paraffin-embedded archival tissue samples) may be used for molecular testing, avoiding collecting additional frozen tissue samples. In addition, with the development of targeted therapies, increasing indications for molecular profiling are expected. In any case, performing tumour biopsy for research purposes is an absolute need to advance the field.

Staging

Once a definitive diagnosis of HCC has been obtained by non-invasive criteria (irrespective of the imaging procedure used for this purpose) or histological confirmation, tumour burden inside and outside the liver must be mapped in order to make sound therapeutic decisions. Initial tumour staging should always include contrast-enhanced chest, abdominal and pelvic scans and CT offers advantages over MRI in terms of time and availability. Bone scintigraphy and brain MRI are not necessary in the absence of organ-related symptoms. When surgical, thermal or radiation-based ablation is considered, MRI sometimes provides valuable additional information that helps in accurately determining tumour number, size, location and relation to vessels and bile ducts. After mapping the tumour burden, tumour stage should be defined since this helps in establishing the prognosis and providing the best treatment recommendation.

Should HBA contrast-enhanced MRI be performed for initial tumour staging?

Recommendation

- Gadoxetic acid-enhanced MRI is suggested in patients who are candidates for curative-intent treatments (*i.e.*, transplantation, liver resection, thermal or radiation ablation) as it may improve local tumour staging **(LoE 3, weak recommendation, consensus).**

The importance of specificity in the non-invasive diagnosis of HCC is matched by the importance of sensitivity in staging. In patients who are candidates for curative-intent treatments (*i.e.*, BCLC stage 0 or A and subgroups of BCLC stage B), accurate tumour staging is mandatory to improve patient selection and treatment planning. While ECAs were shown to be superior to HBAs for the non-invasive diagnosis of HCC, evidence shows that MRI using HBAs is associated with higher sensitivity than with extracellular agents, particularly in small HCC, which may lead to better local tumour staging. A meta-analysis including 29 studies and 2,696 HCCs has shown that the sensitivity of HBA-MRI with HB phase in detecting HCC ≤3 cm was significantly higher than that without HB phase (84% *vs.* 68%, $p = 0.01$).[218] In a retrospective analysis of 700 patients with a single nodule HCC on dynamic CT, 323 underwent additional evaluation with HBA-MRI and 74 additional HCC nodules were detected in 53 patients (16.4%).[219] These additional nodules resulted in BCLC upstaging and modified treatment plans in 43 patients (13.3%). On multivariable analyses, the group explored with HBA-MRI had a significantly lower rate of HCC recurrence (HR 0.72; 95% CI 0.54–0.96) and lower overall mortality (HR 0.65; 95% CI 0.44–0.96) than the group explored by CT only. In an analysis of 285 pairs of patients matched based on the propensity score, the HBA-MRI group had significantly lower overall mortality (HR 0.66; 95% CI 0.44-0.99). In a group of 63 LT candidates, adding HB phase images improved the detection of 1-2 cm HCC and HBA-MRI showed 92.1% accuracy in patient allocation based on the Milan criteria (*i.e.*, single nodule of HCC ≤5 cm in diameter or multiple, up to 3, nodules of HCC, each ≤3 cm in diameter, without evidence of macroscopic vascular tumour invasion, in patients with chronic liver diseases) and UNOS (United Network for Organ Sharing) guidelines.[220] HBA-MRI also enables detection of premalignant dysplastic nodules or early HCC that appear hypointense on HB phase images without APHE. These nodules are independent predictors of recurrence after ablation or resection[221,222] and independent risk factors for *de novo* HCC.[223,224] Finally, when the cost-effectiveness of the two strategies (dynamic CT *vs.* dynamic CT followed by HBA-MRI) was compared for the initial workup of patients with early-stage HCC, who were candidates for curative-intent treatment other than LT, the latter was cost-effective for detecting additional HCC.[225]

Current algorithmic systems provide an accurate non-invasive diagnosis of HCC using composite features applied to high-risk patients, but these systems do not include imaging features that may predict outcomes. Many studies have focused on imaging features that predict the important pathological factors of tumour grade, subtype and invasiveness. Larger size, disrupted capsule, peritumoral APHE, low apparent diffusion coefficient (ADC), and HB phase hypointensity correlate with worse tumour grade.[226,227] Substantial necrosis, low ADC, and larger size may indicate macrotrabecular/massive HCC.[204,228] Macrotrabecular/massive HCC and vessel encapsulating tumour clusters (or VETC) patterns share common imaging features, and a larger tumour size and necrosis are associated with a VETC pattern.[229] Little is known about the imaging appearance of other subtypes, like scirrhous, neutrophil-rich or progenitor-type HCC. These subtypes may have distinctive features, with a higher incidence of targetoid dynamic enhancement pattern (LR-M), more marked HB phase hypointensity, lower ADC, and non-smooth tumour margin.[204,228]

Much attention has been paid to predicting microscopic vascular invasion in HCC. Associated imaging features include

non-smooth tumour margin,[230] capsule disruption,[231] low ADC, large size, peritumoral APHE and HB phase hypointensity.[232] Various prognostic nomograms or feature clusters for predicting microscopic vascular invasion have been proposed.[233–235] Unfortunately, considerable interobserver variability in assessing these features using MRI seems present even for experienced readers.[236] Not all imaging features are associated with a poor prognosis. For example, hyperintensity on HB phase has been associated with a better prognosis, possibly related to upregulation of *OATP1B3* by activating mutations in the *CTNNB1* gene, which encodes for β-catenin.[237]

Strict rules for incorporating prognostic or predictive markers into clinical practice have been published.[238] According to these rules, acceptable biomarkers should be obtained from randomised investigations. In particularly compelling circumstances, prognostic or predictive markers tested in cohort studies can be adopted in clinical practice. A panel of experts recommends that the following requirements should be met to incorporate biomarkers into the management of HCC: i) demonstration of prognostic prediction in adequately powered randomised studies or training and validation sets from cohort studies; ii) demonstration of independent prognostic value in multivariable analysis including known clinicopathological predictive variables; iii) confirmation of the results using the same technology in an external cohort reported by independent investigators. None of the imaging features tested so far fulfil these criteria in HCC. There is room for further refinement of prognostic evaluation. Therefore, the panel encourages the reporting of prognostic imaging features but acknowledges that more evidence is needed before they can be confidently implemented into recommendations.

Should 18F-FDG-PET/CT be performed for prognostication at initial tumour staging?

Recommendation

- 18F-FDG and 18F–FCH PET/CT are not recommended for tumour staging **(LoE 3, strong recommendation, strong consensus).**

[^{18}F]Fluorodeoxyglucose (18F-FDG) uptake is observed in less than 40% of HCCs,[239] and most well-differentiated HCCs are 18F-FDG-PET negative. [^{18}F]Fluorocholine (18F–FCH), which uses a precursor of phospholipid synthesis, is taken up by well-differentiated HCCs. The overall detection rate of PET-CT using these tracers cannot be compared to that of contrast-enhanced CT or MRI.[240] However, 18F-FDG uptake is associated with poor prognosis, increased serum AFP[241] and microscopic vascular invasion.[242] Therefore, authors have suggested that 18F-FDG-PET may facilitate the selection of patients for liver resection or transplantation. Most published series include a single modality with a single radioactive tracer (most often 18F-FDG) and have been conducted in Asian countries. Some demonstrated a limited contribution of 18F-FDG to staging (less than 2.5% changes in tumour stage) or predicting the risk of tumour recurrence after curative treatment.[243] Others have shown a potential benefit in patients with an unexplained increase in serum AFP (18F-FDG uptake in 71%) or for the identification of extrahepatic disease that was not detected on conventional imaging (6% of patients with HCC).[244,245] The usefulness of 18F–FCH PET-CT in HCC has been tested individually or in combination with 18F-FDG PET-CT in small retrospective series mixing benign liver tumours on healthy liver and malignant tumours in patients with cirrhosis. Studies have suggested that 18F–FCH PET-CT has better sensitivity for detecting HCC (78–88% positivity) than 18F-FDG PET-CT.[239,246] A small retrospective study suggested that 18F–FCH PET-CT identified 50% additional tumour lesions leading to treatment modification in 52% of patients.[247] In a retrospective study of 192 patients with HCC assessed by 18F-FDG plus 118F–FCH, dual-tracer PET-CT identified new tumours in 21% of patients, resulting in tumour stage modification in 11% and treatment modification in 15%.[248] Half of the new lesions detected by dual-tracer PET-CT were extrahepatic metastases, mainly in bone, while the other new lesions detected were either intrahepatic or tumour portal thrombosis. No significant change was observed in BCLC 0 stages. However, this retrospective study may carry selection bias and calls for prospective validation.

Should serum biomarker (AFP, PIVKA-II, others) levels be systematically measured at diagnosis?

Recommendation

- Measurement of AFP once a definitive HCC diagnosis has been made is recommended as it may provide useful prognostic information **(LoE 3, strong recommendation, strong consensus).**

High serum levels of AFP, AFP-L3 and DCP are associated with biologically aggressive HCC and correlated with histo-prognostic factors, including microscopic vascular invasion and poor differentiation.[249] Such increased levels are associated with worse prognosis and predict tumour recurrence following liver resection[250] and transplantation.[251] They also predict worse survival after locoregional therapies like radiofrequency ablation (RFA) (*111*) and transarterial chemoembolisation (TACE) (*116*) and after all systemic therapies included those approved as first-line treatments.[252–255] Other serum tumour biomarkers have been proposed (v.g., osteopontin, vascular endothelial growth factor [VEGF], angiopoietin-2, glypican 3) but less well studied. Technical limitations should be stressed concerning DCP, which cannot be accurately quantified in several settings, such as in patients with vitamin K deficiency, those using oral anticoagulants, or those with a poor nutritional status associated with alcohol abuse. Several HCC staging systems and many phase III clinical trials have considered AFP as a stratification factor. Indeed, worse survival has been shown for patients with AFP ≥400 ng/dl in all pivotal trials of agents or combinations approved for the systemic

treatment of HCC.[252,253,256,257] However, the presence of normal levels of AFP or other serum biomarkers does not rule out HCC aggressiveness or worse outcomes.

Among patients who progressed or were intolerant to sorafenib, ramucirumab only improved survival in patients with AFP ≥400 ng/dl.[258] However, increased AFP by itself does not define a subgroup of patients who would benefit from ramucirumab better than other options and the benefit of ramucirumab is unknown among patients previously treated with immunotherapy combinations. Early changes in AFP levels during treatment with atezolizumab plus bevacizumab also provide prognostic information.[254]

Should the BCLC classification be used for tumour staging?

Recommendation

- The BCLC classification is recommended for tumour staging and provides important prognostic information **(LoE 1, strong recommendation, consensus).**

Once the diagnosis of HCC is established, prognostic assessment is critical in managing HCC. Cancer classification is intended to establish the prognosis and enable the selection of adequate treatment for the best candidates. In addition, it helps researchers 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, complicates prognostic assessments. In addition, cancer-related symptoms have consistently been shown to impact survival. Finally, any system aimed at being clinically meaningful should link prognostic prediction to treatment indication.

Some staging systems for HCC have integrated data from two sources. Prognostic variables were obtained from studies describing the natural history of cancer and cirrhosis. Treatment-dependent variables were obtained from evidence-based studies that provide the rationale for assigning a given therapy to patients in each subclass. The main clinical prognostic factors in patients with HCC are tumour burden (defined by the number and size of nodules and the presence of vascular invasion or extrahepatic spread), liver function (defined by Child-Pugh class, bilirubin, albumin, clinically relevant portal hypertension or ascites) and general HCC-related health status (v.g. the Eastern Cooperative Oncology Group [ECOG] classification or presence of symptoms). Aetiology has not been identified as an independent prognostic factor.[259]

Several staging systems have been proposed for a clinical classification of HCC. In oncology, the standard is TNM staging. In HCC, the 8th TNM edition[260] has several limitations. It requires pathological information to assess microvascular invasion, only universally available in surgical patients; considers only tumour burden but not liver function or health status; and has limited prognostic value in non-early tumours. Six more comprehensive staging systems have been broadly tested (*i.e.*, French,[261] CLIP [Cancer of the Liver Italian Program],[262] BCLC,[263] CUPI [Chinese University Prognostic Index],[264] Hong-Kong Liver Cancer [HKLC],[265] and JIS [Japan Integrated Staging][266]). Most of them have been externally validated. Three include the three types of prognostic variables mentioned above (BCLC, CUPI, and HKLC), and two assign treatment options to every stage (BCLC and HKLC).

BCLC has been externally validated in different regions and clinical settings and has evolved over the years.[267–270] The most recent version has introduced several significant changes, including a refinement of the intermediate (BCLC B) stage with the definition of three subgroups that differ in terms of tumour burden and recommended treatment.[263] As a treatment allocation tool besides its staging aim, BCLC includes a clinical decision-making section where the characterisation of the non-liver profile and the concepts of treatment stage migration and untreatable progression are described.[263]

A multidisciplinary approach to treatment

HCC is a complex disease, often lacking a direct link between stage and a specific therapy. Such complexity is captured in recent proposals for therapeutic decision-making.[271,272] However, the tumour stage serves as the foundation for determining the initial treatment approach, which is then contextualised on the basis of liver function and other determinants in an often-demanding exercise of clinical decision-making (Fig. 3). Different therapies must be considered based on individual patient scenarios, and therapeutic options frequently overlap. Therefore, optimal management of HCC requires the opinion and expertise of various specialists, making a coordinated multidisciplinary team (MDT) essential. MDTs should include at least a hepatobiliary and/or transplant surgeon, a medical oncologist or hepatologist specialised in liver cancer, a radiation oncologist, an interventional radiologist, a diagnostic radiologist, a pathologist, and a dedicated nurse, when available. Every patient with HCC should be assessed by an expert MDT at the time of initial presentation and whenever a change in treatment objectives is anticipated. All decisions should be documented to ensure cohesive care. Patient preferences ought to be an essential part of the decision-making process. During MDT meetings, clinicians should be aware of potential biases that may play a role in decision-making as illustrated in Table 3. To avoid these biases, the responsibilities of individual participants in MDT

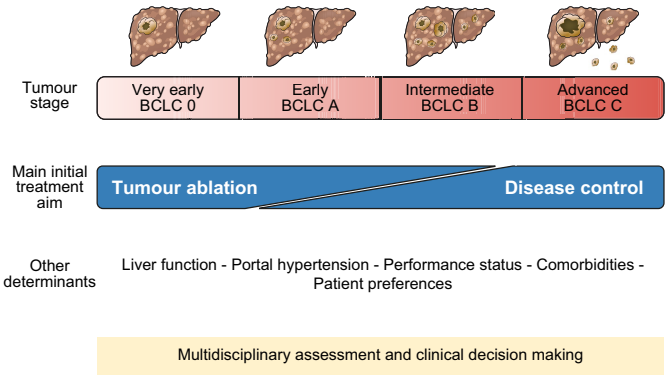

Fig. 3. Main determinants of the process of clinical decision-making. BCLC, Barcelona Clinic Liver Cancer.

Table 3. Potential biases in multidisciplinary meetings.

Bias	Definition	Example
Excessive empiricism	Too much weight is given to the clinicians' personal experiences and viewpoints	"My last patient with similar characteristics received *X* treatment and had adverse events resulting in death, thus this patient should not receive *X*"
Excessive rationalism	Too much weight is given to a parameter that can be quantified in a straightforward way	"Patients with max tumour diameter of 5.1 cm cannot be considered for the same treatment as patients with tumours ≤5 cm in diameter"
Uneven perception of gain and loss (or loss aversion)	The risk of adverse events is weighted more than the probability of clinical benefit	"This patient has a 20% chance of serious adverse events with treatment *X*, so treatment *X* should be avoided even though it has a 30% of increasing the patient's survival"
Lack of clustered principle	A treatment is considered only on its own and not as part of a multi-step process	"Treatment *X* has low chances of increasing the patient's survival, so it should not be offered even though it may lead to conversion to treatment *Y*, which has high chances of increasing the patient's survival."

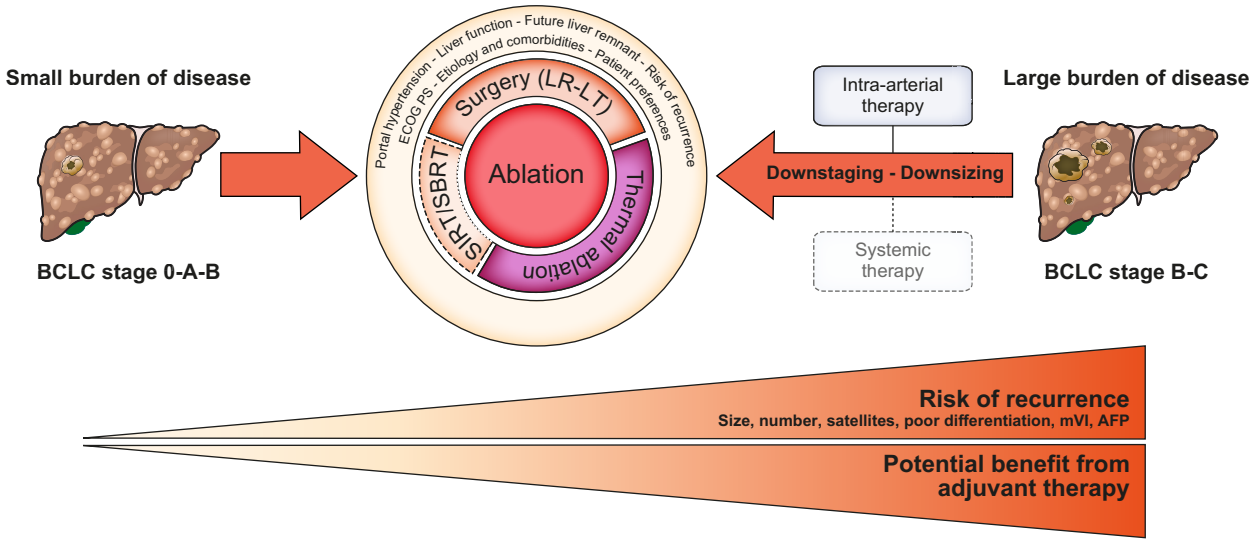

Fig. 4. Therapeutic approach of patients with the aim of tumour ablation. AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; LR, liver resection; LT, liver transplantation; mVI, microscopic vascular invasion; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy. Dotted-line boxes represent options with lower levels of supporting evidence.

meetings should be clearly delineated, and feedback on each treatment-related decision should be obtained on a regular basis.

Surgery

Surgical interventions for HCC are liver resection (LR) and LT, which are both performed with curative intent (Fig. 4). Indeed, LT is the only single therapy that can cure both HCC and the underlying chronic and carcinogenic hepatic damage. Liver surgery is a demanding technical procedure that requires a significant level of expertise and should be conducted in specialised centres with experience and proficiency in hepatobiliary surgery. All patients with HCC free from distant metastasis should be considered for surgical interventions by the MDT. As mentioned, such MDT should at least include a hepatobiliary and/or transplant surgeon, plus the other specialists. MDTs taking care of patients with HCC in centres without a transplant service should have an established network with a transplant centre to facilitate prompt referral of any potential candidate.

Preoperative assessment of surgical candidacy for liver resection

Should eligibility for liver resection be based on a comprehensive multi-parametric pre-operative assessment of liver function, portal hypertension, remnant liver volume and function and prediction of early post-operative patient outcome?

Recommendation

- 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 patient's comorbidities to ensure perioperative mortality is lower than 3% and morbidity is lower than 20% **(LoE 2, strong recommendation, strong consensus).**

Great progress has been made in the past decades in lowering the risk of postoperative mortality after LR, thanks to a combination of better surgical technique, perioperative management, and risk stratification. Large series from Europe,[273] Asia,[274,275] and North America[276] have demonstrated that surgery in patients with HCC and cirrhosis can be safely performed with mortality under 3%. Accurate preoperative risk stratification and patient selection are key for maintaining good perioperative outcomes. Postoperative liver function is driven by a simple principle, *i.e.*, the liver remnant must have enough residual volume/function and be of sufficient quality to sustain the body's demands after surgery. Many risk assessment tools are available, as summarised in Table 4. We recommend including at least volumetry, indocyanine green liver retention test and one laboratory value-based test (*e.g.* Child-Pugh, model for end-stage liver disease [MELD], albumin-bilirubin [ALBI], aspartate aminotransferase-to-platelet ratio index) for risk assessment in all LR candidates. In case a major hepatectomy is planned, scintigraphy should also be added.

In patients with otherwise resectable HCC according to multi-parametric assessment, are clinically significant portal hypertension (defined as HVPG >10 mmHg) or Child-Pugh class B absolute contraindications to liver resection?

Recommendations

- Clinically significant portal hypertension (HVPG >10 mmHg) and Child-Pugh class B cirrhosis are not absolute contraindications for limited resections approached with minimally invasive techniques. However, the risks and benefits of resection should be weighed against those of alternative options such as LT or locoregional therapies. **(LoE 3, weak recommendation, strong consensus).**
- Clinically significant portal hypertension and Child-Pugh class B cirrhosis should be regarded as an absolute contraindication to major resections (*i.e.*, >2 segments) **(LoE 3, strong recommendation, strong consensus).**

Portal hypertension is a major predictor of post-hepatectomy liver failure (PHLF), perioperative mortality,[295,306] and long-term survival.[296,307] Caution should be exercised when recommending LR to a patient with clinically significant portal hypertension. However, portal hypertension should be considered an important element of a broader risk assessment and not a stand-alone absolute contraindication. Overall, a precise hierarchic interaction of three main factors determines the risk of PHLF,[295] with portal hypertension exerting the highest decisional influence, followed by extent of LR and grade of liver function (Fig. 5). Indeed, postoperative mortality increases and 1-year survival decreases in parallel with portal hypertension in patients with cirrhosis undergoing elective extrahepatic surgery[308]

A major advance in LR of the cirrhotic liver is the implementation of minimally invasive liver surgery (MILS) through laparoscopic/robotic approaches. Several authors have reported acceptable rates of PHLF, perioperative morbidity and mortality in patients with clinically significant portal hypertension,[309–312] especially in those with Child-Pugh A cirrhosis,[309,311,313] undergoing limited resections[311,312] performed with MILS.[314,315]

It must be noted that the definition of portal hypertension varies among studies and often does not rely on hepatic venous pressure gradient (HVPG) but on indirect radiological signs. A prospective study assessed portal hypertension through transjugular HVPG measurement in 40 patients with cirrhosis before LR for HCC and found that HVPG correlated with PHLF and mortality, while commonly used indirect signs (presence of oesophageal varices or splenomegaly with platelet count <100,000/mm^3) did not.[297] These findings indicate a relevant caveat of indirect assessment of portal hypertension. Transvenous HVPG measurement carries a known risk that should be considered when accurate measurement of HVPG is mandatory, particularly in patients with other relative contraindications to LR, such as Child-Pugh A6-B cirrhosis, or those who require extended LRs. Overall, portal hypertension remains a limiting factor for major surgical resection while not being an absolute contraindication in trained centres with full availability of MILS and access to LT.

Some evidence suggests that appropriately selected patients with Child-Pugh B cirrhosis may achieve good postoperative results after LR, especially those with Child-Pugh B7 undergoing MILS.[316–318] In a retrospective Asian study on 119 patients with Child-Pugh B cirrhosis who underwent LR for HCC,[319] bilirubin ≥1.5 mg/dl, AFP ≥400 ng/ml, presence of ascites and non-curative hepatectomy were identified as adverse prognostic factors. Survival in patients with no or one adverse prognostic factor was 45.8% at 5 years, *vs.* 7% for patients with at least two adverse prognostic factors. These findings highlight the interplay between liver function and HCC prognosis on long-term survival. While Child-Pugh class B should not be considered an absolute contraindication to LR, the decision to recommend LR should be balanced against possible therapeutic alternatives. Patients with Child-Pugh B cirrhosis, HCC within LT criteria and no other contraindications to LT should strongly be considered for LT, as they may not have another window for LT in case of cirrhosis progression or HCC recurrence. For patients who are not LT candidates, a therapeutic alternative to LR is locoregional therapy. Large retrospective studies offer contradictory results regarding the survival benefit of LR *vs.* locoregional therapy in patients with Child-Pugh B cirrhosis.[320] Recently, a nomogram to predict perioperative morbidity, OS and disease-free survival in patients with Child-Pugh B cirrhosis undergoing LR was derived from large retrospective series.[316] According to the hierarchic approach to decision-making on LR in cirrhosis,[295] marginal liver function, as in Child-Pugh B cirrhosis, can be managed in patients without portal hypertension undergoing minor LR with MILS.

Should prediction of years of life lost with respect to the general population be an additional parameter to assess in elderly (>70 years old) candidates for liver resection after multi-parametric assessment?

Recommendation

- Advanced age should not be considered as an absolute contraindication to liver resection **(LoE 3, strong recommendation, consensus).**

Table 4. Risk assessment tools for liver function and post-hepatectomy liver failure.

Instrument	Description	Invasive grade	Parameters	Evidence
Liver function				
ALBI grade	Laboratory values	–	(Log_{10} total bilirubin × 0.66) – (albumin × 0.085)	Simple method that can identify different subcategories of patients with HCC with different prognoses and PHLF[277–279]
APRI	Laboratory values	–	(AST/the upper limit of normal value) × 100 ÷ platelet (10^9/L)	Predictor of PHLF[280]
Breitenstein score	Algorithm	–	One point for ASA III and IV, two points for major (extensive) liver resection, three points for AST ≥ 40 U/L, four points for extrahepatic procedures	Predictor of post-hepatectomy serious complications (Clavien-Dindo grade III, IV or V)[281,282]
ICG-R15	ICG clearance	+	% of ICG clearance measured via spectrophotometry after IV ICG infusion	Can be used as marker of portal hypertension in compensated cirrhosis.[283,284] Correlates with PHLF,[285] perioperative mortality,[286] and maximum extent of resection in Makuuchi criteria.[287,288]
Heidelberg score	Algorithm	–	One point for age ≥ 60 years, right trisectionectomy, preoperative INR ≥ 1.1, preoperative GGT ≥ 60 U/L, intrahepatic cholangiocarcinoma, ASA III. Two points for preoperative platelet count ≤ 120/nl, and perihilar cholangiocarcinoma. Three points for preoperative creatinine value ≥ 2 mg/dl. Five points for ASA IV	Predictor of perioperative mortality[289]
Child-Pugh	Algorithm	–	Serum bilirubin, albumin, INR, ascites, encephalopathy	Good predictor of short- and long-term outcomes after liver resection,[290,291] but subject to "floor effect" (poor discrimination in Child-Pugh 5-6)
MELD	Laboratory values	–	3.78 × ln[serum bilirubin (mg/dl)] + 11.2 × ln[INR] + 9.57 × ln [serum creatinine (mg/dl)] + 6.43	Predictor of perioperative mortality[292]
FIB-4	Algorithm	–	Age × AST/platelet count [$\times 10^3$/μl] × ALT1/2	Simple predictor of postoperative outcomes when combined to future liver remnant volume[293]
Transient elastography	Imaging	–	Combination of ultrasound and low-frequency elastic waves to assess liver fibrosis	Predictor of PHLF.[294] Requires dedicated equipment. Operator dependent.
HVPG	Interventional radiology	++	Measurement of portal hypertension	Portal hypertension is a major predictor of PHLF and perioperative outcomes[295–297]
Makuuchi criteria	Algorithm	+ (requires ICG-R15)	Ascites Total bilirubin ICG-R15	Simple algorithm with good correlation to PHLF[298]
Hierarchic interaction	Algorithm	–	Portal hypertension Extent of hepatectomy MELD score	Simple algorithm with risk stratification for low-, intermediate- and high-risk of PHLF[295]
Volume, extent of resection				
CT volumetry	Imaging	–	Liver remnant volume calculated on CT scan with dedicated software	Reliable predictor of post-hepatectomy remnant liver volume.[287] Easily available.
3D reconstruction	Imaging	–	Three-dimensional CT scan	Better correlation of future remnant liver volume than conventional volumetry.[299,300] Useful for planning complex resections and LDLT surgery.[301] Needs dedicated software
Function plus extent of resection				
Liver scintigraphy	Nuclear imaging	+	Assessment of liver function per liver segment	Predictor of PHLF. May be more informative than CT volumetry,[302,303] but requires presence of nuclear imaging and dedicated expertise.
Liver MRI with hepatobiliary contrast agents	Imaging	+	Assessment of liver function per liver volume	Predictor of PHLF. May be more informative than ICG clearance but results are heterogenous[304,305]

Invasiveness: - none or requiring routine laboratory values; + mildly invasive, requiring procedures that are not otherwise performed.
ALBI, albumin-bilirubin; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; INR, international normalised ratio; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; PHLF, post-hepatectomy liver failure.

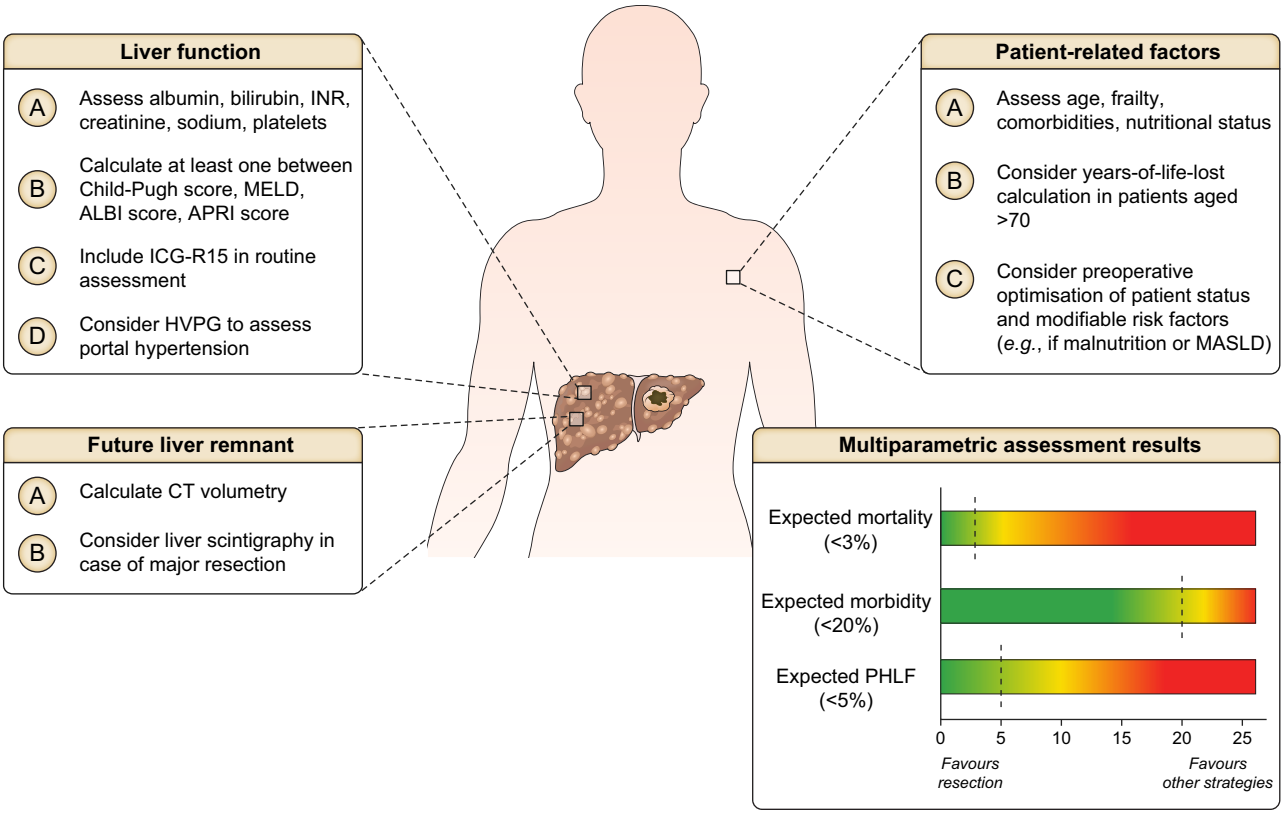

Fig. 5. Multiparametric preoperative assessment for patients eligible for liver resection. ALBI, albumin-bilirubin; APRI, aspartate aminotransferase-to-platelet ratio index; CT, computed tomography; HVPG, hepatic venous pressure gradient; ICG-R15, indocyanine green retention test; INR, international normalised ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; PHLF, post-hepatectomy liver failure.

Whether increasing age is associated with higher perioperative morbidity and mortality is controversial. The National Surgical Quality Improvement Program (NSQIP) of the American College of Surgeons collects 135 clinical variables including preoperative risk factors, intraoperative variables, and 30-day postoperative mortality and morbidity outcomes for patients undergoing major surgical procedures. An analysis of 7,621 patients (11.7% aged ≥75) found a higher rate of major complications and perioperative mortality in older patients.[321] Similarly, an analysis of over 27,000 patients undergoing hepatectomy for HCC in Japan showed that mortality and morbidity were higher in patients older than 70 years compared to younger patients but plateaued in octogenarians and nonagenarians.[322] PHLF after right hepatectomy was more frequent in patients aged ≥75 years, while the incidence of major morbidity was higher in patients aged >70 years.[323] Conversely, several smaller studies and two meta-analyses found no difference in perioperative outcomes between elderly and younger patients,[324–329] even after major hepatectomies[330] .[331] Age should thus not be considered an absolute contraindication to LR, nor should arbitrary age cut-offs be applied. In a retrospective study of 803 patients undergoing LR, ischaemic heart disease, major hepatectomy, cirrhosis, and transfusion with ≥3 units of red blood cells were predictors of mortality while age was not, although elderly patients with more than two of these risk factors had higher mortality than younger patients.[332] The importance of comorbidities and blood loss has also been highlighted in other studies.[333,334] Regarding surgical approach, elderly patients seem to benefit from MILS just as much as, if not more than, younger patients.[325,331,335]

HCC recurrence does not seem to occur more frequently in elderly patients.[330,336,337] Some authors have reported worse OS in elderly patients compared to younger patients; however, this may be due to death from other causes and is not necessarily associated with cancer-related outcomes.[337,338] Prediction of years of life lost is a measure of premature death that considers age-specific life expectancy[339](briefly, if life expectancy in a particular patient cohort is 85 years, a patient aged 60 and a patient aged 80 who survive for three years after LR will have, respectively, (85-83) = 2 and (85-63) = 22 years of life lost). Years of life lost may help determine whether the predicted difference in life expectancy after LR is enough to overcome the potential risks of surgery, as demonstrated in competing risk analysis-based studies.[340,341]

Should patients with resectable HCC arising in MASLD and/or metabolic syndrome be assessed with additional parameters?

Recommendation

- Since patients with MASLD and HCC may experience better long-term survival outcomes but higher perioperative morbidity compared to those with viral aetiologies, a thorough pre-operative assessment of metabolic-related conditions should be performed in such patients and pre-operative optimisation of modifiable metabolic-related risk factors is recommended **(LoE 3, strong recommendation, strong consensus).**

The rising incidence of MASLD worldwide implies that an increasingly high percentage of patients undergoing LR will have MASLD or the metabolic syndrome. Patients with MASLD or the metabolic syndrome undergoing LR for HCC have a higher rate of perioperative morbidity[342,343] and mortality.[344,345] A NSQIP analysis of 2,927 major hepatectomies (30% with MASLD) reported a major morbidity rate of 32% in patients with MASLD *vs.* 24% in those without MASLD after propensity score matching.[346] Similarly, another study from the US on 13,898 patients undergoing hepatectomy found more frequent complications, readmissions and perioperative deaths in patients with the metabolic syndrome, who were also less likely to achieve a textbook outcome.[345] However, long-term survival outcomes appear to be comparable or even superior in MASLD compared to non-MASLD aetiologies,[342,343,347–349] although there are some inconsistent reports. These findings were further confirmed by a recent meta-analysis of 15 retrospective studies,[350] which found higher morbidity but similar survival outcomes in patients with metabolic syndrome compared to other aetiologies. The largest published series of resected HCC in patients with MASLD confirms the benefit of optimising those metabolic-related risk factors that are modifiable before surgery.[351]

The good long-term survival of patients with MASLD or the metabolic syndrome in the face of worse perioperative outcomes calls for greater efforts to optimise these patients in the preoperative period. Modifiable risk factors should be addressed with targeted and evidence-based interventions, including nutritional prehabilitation, balanced weight loss, smoking and alcohol cessation, preoperative physical rehabilitation, and optimisation of pre-existing comorbidities. Since patients with HCC do not routinely receive neoadjuvant treatment outside clinical trials, they have a limited window of intervention. However, studies have demonstrated that a reduction in liver steatosis can be achieved with lifestyle changes and therapy in as little as 2 weeks.[352–354]

Liver resection in the non-cirrhotic liver

Should liver resection be the preferred therapeutic option in a patient with single HCC arising in non-cirrhotic liver?

Recommendation

- Liver resection is recommended as the preferred therapeutic option in patients with single HCC (with or without satellites) arising on a non-cirrhotic liver **(LoE 3, strong recommendation, consensus).**

Should liver resection be the preferred therapeutic option in a patient with multiple, unilobar HCC arising in non-cirrhotic liver?

Recommendation

- Multifocal tumours involving multiple segments require bridging or downstaging therapies to allow a positive test of time before considering surgical resection **(LoE 3, weak recommendation, consensus).**

Should patients without cirrhosis exceeding the tumour burden-related eligibility criteria for resection and transplantation used in the cirrhotic setting (e.g. Milan criteria for transplantation) be treated with resection or transplantation?

Recommendation

- Liver transplantation is not recommended in patients without cirrhosis who have unresectable HCC that is beyond the Milan criteria. Exceptions should be based on sustained response to non-surgical therapies and assessment of transplant benefit **(LoE 4, weak recommendation, strong consensus).**

Less than 20% of HCCs develop in patients without cirrhosis[355] and although reported as arising in "healthy liver" these tumours are frequently associated with some form of chronic inflammation or underlying fibrosis. LR is the mainstay of the treatment of resectable HCC in patients without cirrhosis regardless of tumour size and number.[356–358] Thanks to preserved liver function and lower risk of PHLF, surgical treatment can be more aggressive than in patients with cirrhosis and in fact more extensive parenchymal resections are common in patients without cirrhosis. In case of curative LR with clean margins and in the absence of tumour vascular invasion, post-surgical prognosis is usually more favourable than in patients with cirrhosis [359–361] and is mainly related to tumour characteristics rather than the underlying liver disease.[362,363] While satellite nodules do not represent a contraindication to

resection of single tumours in the non-cirrhotic liver, true multifocal tumours involving multiple segments of a liver lobe require a positive test of time with bridging or downstaging therapies before they are considered for LR. In HCCs meeting the Milan criteria, long-term survival of patients without cirrhosis undergoing LR is comparable to that of patients with cirrhosis undergoing LT.[359,361,364–366] Patients who experience intrahepatic recurrence should be considered for further LR[357,365,367] if liver function and remnant liver volume allow, even though LT may be proposed.

The role of LT in these patients is debated; it is more often proposed in younger patients and as a salvage option in patients with unresectable disease or unresectable intrahepatic recurrence. An analysis of the UNOS database on 4,373 patients without cirrhosis undergoing first-time LT for HCC showed similar post-transplant survival as reported for patients with cirrhosis.[368] However, patients without cirrhosis represent a less favoured population than those with cirrhosis since the former usually bear unresectable, large tumours or multifocal recurrence.[369] These considerations justify LT as salvage treatment in patients without cirrhosis, especially in the absence of adverse prognostic factors such as macrovascular invasion, lymph node involvement, and early post-resection recurrence.[369]

Liver resection in the cirrhotic liver

Should liver resection be preferred to ablation as initial treatment in well-compensated patients with cirrhosis and a solitary HCC ≤2 cm located in unfavourable anatomical sites?

Recommendation

- Liver resection, particularly by minimally invasive means, and thermal ablation are recommended, without preference, in compensated patients with cirrhosis and a solitary HCC ≤2 cm who are otherwise not candidates for liver transplantation. Ablation should be preferred when a major hepatectomy is needed **(LoE 2, strong recommendation, strong consensus).**

Should one thermal ablation technique be recommended over the others?

Recommendation

- No one thermal ablation technique (radiofrequency or microwave) is recommended over the others **(LoE 2, strong recommendation, strong consensus).**

Several pieces of evidence show that LR competes with thermal ablation with respect to cancer-related outcomes in patients with early HCC.[370–375] In particular, patients with peripherally located, single HCC ≤2 cm are ideal candidates for minimally invasive LR.[373] However, LR is associated with higher morbidity than thermal ablation[372,373,375] and this must be considered when dealing with patients with a high-risk surgical profile, poor hepatic function, or centrally located tumours which would require extensive LR. In such cases, thermal ablation is preferable to both LR and intra-arterial therapies. No thermal ablation strategy has been demonstrated to be significantly superior to the others.[376,377] The decision on which ablation strategy to use should be based upon technology and device availability, expertise, and patient and tumour characteristics.

Should resection be preferred to other locoregional therapies in patients with cirrhosis and HCC within or beyond Milan criteria if multi-parametric assessment predicts a favourable patient outcome?

Recommendations

- Liver resection is recommended for single HCC >2 cm in patients with cirrhosis when hepatic function is preserved and sufficient remnant liver volume can be maintained **(LoE 2, strong recommendation, consensus).**
- Owing to insufficient evidence, resection cannot currently be recommended over locoregional therapies or vice versa for patients with cirrhosis and multiple tumours when resection is feasible after multiparametric assessment **(LoE 2, weak recommendation, strong consensus).**

Despite advances in both locoregional and systemic therapies, complete tumour removal remains a pillar of any potentially curative strategy in HCC. Therefore, if an acceptable surgical risk is predicted, LR or LT should be considered within any strategy aimed at curing HCC in chronic liver diseases. In retrospective series, LR offers better survival outcomes than locoregional treatment for both patients within[378,379] and beyond Milan criteria[380–382] or both,[383] including in a meta-analysis of 18 high-quality studies including 5,986 patients.[381] In a single-centre trial, 173 patients with resectable HCC outside Milan criteria (90% had 2 or 3 tumours) were randomised to LR or TACE and OS was superior in the LR arm (median OS 41 *vs.* 14 months).[384] However, the small sample size and the suboptimal survival performance of TACE are important limitations of this trial. Therefore, prospective studies on this group of patients are encouraged.

Surgical technique in liver resection and multimodal treatment

Should minimally invasive liver surgery for HCC conducted via a laparoscopic-robotic approach be favoured over open laparotomic resections whenever feasible?

Recommendation

- In properly trained centres, liver resection should be performed via laparoscopic or minimally invasive approaches whenever feasible, especially for tumours in anterolateral and superficial locations **(LoE 3, strong recommendation, strong consensus).**

The advantages of minimally invasive surgery on early postoperative outcomes have been demonstrated in several fields of abdominal surgery, with LR being no exception.

Laparoscopic LR has been associated with improved early postoperative outcomes,[385–387] including reduced morbidity,[386–388] blood loss,[386–388] length of hospital stay,[386–388] and perioperative mortality [388] compared to open surgery. Similar findings have been shown for major hepatectomies[386,389] and in elderly patients.[390] The only advantage of open surgery seems to be reduced operative time,[385,386,389] especially in major resections. Long-term survival outcomes appear to be similar,[385,388,391] or slightly superior in MILS *vs.* open surgery.[392,393] Given the improved early outcomes and comparable long-term outcomes, centres should strive to perform LR for HCC with a minimally invasive approach, especially for small tumours in favourable locations. No definitive advantage of robotic over laparoscopic LR has been established.[394] Currently, the choice of MILS approach should be based on availability of techniques and surgical expertise.

A controversial aspect of MILS is the contention that it is associated with less anatomical resection compared to open surgery and that it may also be associated with reduced tumour-free margins.[395] However, reports are inconsistent.[396] The advance of dye-guided techniques[397] and 3D reconstruction[398] has, however, increased the number of anatomical resections performed using precise segmental anatomy.[399] Anatomical MILS resections are feasible, and they seem to be non-inferior to open anatomical LR.[400] MILS also seems to induce a lower postoperative inflammatory response compared to open LR.[401] This may be beneficial in the early postoperative recovery and may also have a positive influence on the tumour microenvironment,[402] potentially reducing the risk of perioperative tumour cell engraftment. For this reason, MILS may potentially reduce cancer recurrence although definitive demonstration of such an effect is lacking.

Should patients with resectable HCC receive preoperative locoregional and/or systemic neoadjuvant treatment prior to resection?

Recommendation

- Neoadjuvant therapies should only be considered in the context of prospective studies, as evidence of a survival advantage with pre-surgical treatments is lacking **(LoE 3, strong recommendation, strong consensus).**

The rationale for perioperative or preoperative neoadjuvant therapy is to increase the resectability of a tumour and reduce postoperative recurrence, and consequently improve long-term survival. This strategy has shown significant benefit in the pre-transplant setting in patients with intermediate to advanced HCC beyond conventional criteria and a similar hypothesis could be proposed for LR. However, no neoadjuvant strategy has proven any recurrence-free survival (RFS) or OS benefit so far. Current developments in systemic treatments for HCC are reaching the neoadjuvant setting. A single-arm trial of neoadjuvant cemiplimab,[403] a programmed cell death protein 1 (PD-1) blocker, in resectable HCC showed tumour necrosis in 4 out of 20 (20%) resected patients, giving hope for future breakthroughs. In a randomised phase II trial comparing perioperative nivolumab (up to 3 doses before surgery and up to 2 years after surgery) with or without ipilimumab (one dose before surgery and up to four doses after surgery) in 27 patients with resectable HCC, no patients in either group had their surgery cancelled due to treatment-related adverse events, a major pathological response (*i.e.*, ≥70% necrosis) was observed in 33% of patients with nivolumab monotherapy *vs.* 27% of those with nivolumab plus ipilimumab, and median RFS was 9.4 and 19.5 months, respectively (HR 0.99).[404] In a phase Ib study of neoadjuvant cabozantinib and nivolumab, 5 out of 12 (42%) resected patients had major pathologic responses, responding tumours being enriched in T effector cells, tertiary lymphoid structures and plasma cells.[405] Reported and ongoing trials vary widely in terms of the drugs or combinations used and exposure to systemic therapy before and eventually after resection. Patient enrolment in prospective trials assessing the combination of locoregional and systemic therapies prior to LR is encouraged.

Should patients who achieve downsizing/downstaging after locoregional and/or systemic treatment be considered for liver resection or transplantation?

Recommendations

- Patients who achieve downsizing/downstaging after locoregional treatment should be considered for liver resection or transplantation **(LoE 2, strong recommendation, strong consensus).**
- Patients who achieve downsizing/downstaging after systemic treatment may also be considered for liver resection or transplantation, preferably in prospective studies **(LoE 3, weak recommendation, strong consensus).**

High-quality evidence demonstrates that patients who undergo surgical treatment after downstaging have better outcomes than with any other treatment modality,[406–412] and can achieve outcomes that compare well with those of patients who received upfront surgery (resection or transplantation)[413–417] (Fig. 6). While downstaging with locoregional therapy is well established, more evidence is needed to confirm immunotherapy as a successful downstaging modality, although preliminary studies suggest that patients who achieve downstaging with immunotherapy can safely undergo resection or transplantation with good early outcomes.[418–420]

Should patients with HCC treated with successful resection or ablation receive adjuvant treatment after resection or ablation?

Recommendation

- Adjuvant treatment after resection or ablation is not recommended **(LoE 2, strong recommendation, strong consensus).**

The use of adjuvant therapy after LR or ablation aims at eradicating any residual microscopic disease to reduce recurrence rates and improve disease-free and OS. Different pharmaceutical agents have been tested as adjuvant treatments in

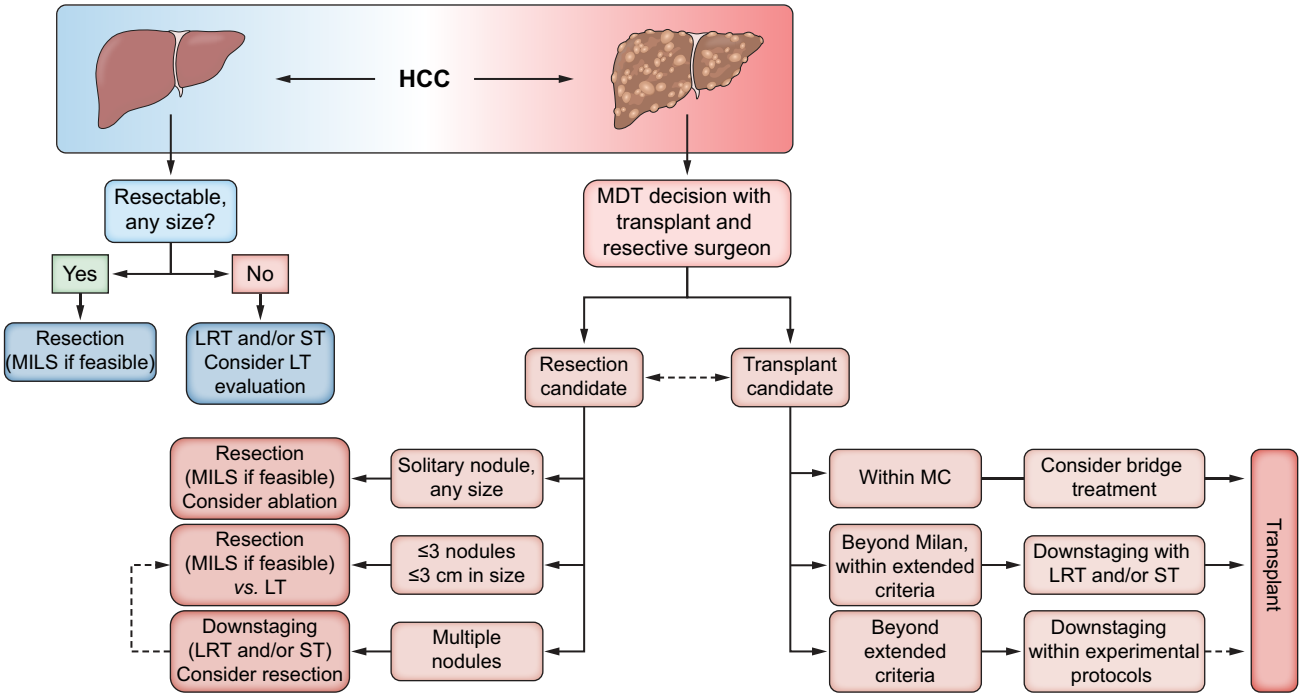

Fig. 6. Decision-making pathway in patients with HCC who are surgical candidates. HCC, hepatocellular carcinoma; LRT, loco-regional therapy; ST, systemic therapy; LT, liver transplantation; MC, Milan criteria; MDT, multidisciplinary team; MILS, minimally invasive liver surgery.

RCTs, including interferon,[421,422] vitamin K,[423] preretinoid[424] and sorafenib,[425] but none has demonstrated a significant survival advantage.

Most data on adjuvant locoregional treatments come from Eastern countries, limiting the generalizability of their results. An RCT from China on adjuvant radioactive iodine (131I)-labelled metuximab[426] met its primary endpoint of improved 5-year RFS (43.4% *vs.* 21.7% in the control group). However, we lack data on Western patients. A meta-analysis of 9 RCTs and 15 non-randomised studies including 6,912 patients who underwent either surgery alone or surgery followed by TACE showed improved OS (HR 0.67, 95% CI 0.60–0.76) and disease-free survival (HR 0.71, 95% CI 0.61–0.84) with adjuvant TACE.[427] A network meta-analysis on eight adjuvant treatments from 23 RCTs found improved survival with hepatic artery infusion chemotherapy (HR 0.44, 95% CI 0.21–0.87), internal radiotherapy (HR 0.54, 95% CI 0.36–0.81), and TACE (HR 0.62, 95% CI 0.44–0.88) compared to observation alone.[428] Trials recruiting a significant proportion of Western patients are needed to shed light on the efficacy of these adjuvant locoregional treatments for the European population.

Lymphokine activated killer cells are autologous lymphocytes activated *in vitro* with recombinant interleukin-2 and antibody to CD3. In an RCT including 150 patients after curative LR,[429] this form of adoptive immunotherapy significantly lowered the risks of overall recurrence by 41% compared to no adjuvant treatment. The difference in OS was not significant ($p = 0.09$) although the estimated 3-year survival rates were 88% and 74%, respectively.

The role of immunotherapy in the treatment of HCC is growing and several ongoing trials are evaluating immunotherapy in the adjuvant setting, including Checkmate-9DX (nivolumab *vs.* placebo, NCT03383458), KEYNOTE-937 (pembrolizumab *vs.* placebo, NCT03867084), and EMERALD-2 (adjuvant durvalumab with or without bevacizumab *vs.* placebo, NCT03847428).

In an open-label phase II trial in China, 198 resected patients with microscopic vascular invasion were randomised to receive sintilimab (a PD1 inhibitor) or active surveillance.[430] RFS was significantly prolonged with sintilimab (median RFS 27.7 *vs.* 15.5 months; HR 0.534, 95% CI 0.36–0.79) while OS was not reported.

At the pre-specified interim analysis, the phase III IMbrave 050 trial reported having met its primary endpoint of improved RFS in patients with HCC at high risk of recurrence treated with atezolizumab plus bevacizumab for 1 year after surgery.[431] High risk of recurrence after surgery was defined as i) ≤3 tumours with the largest tumour >5 cm irrespective of vascular invasion or poor differentiation, ii) ≥4 tumours with largest tumour ≤5 cm irrespective of vascular invasion or poor differentiation, or iii) ≤3 tumours with largest tumour ≤5 cm with vascular invasion and/or poor differentiation. Patients in the control arm were allowed to switch to atezolizumab plus bevacizumab upon recurrence. After a median follow-up of 17.4 months, the HR for RFS was 0.72 (95% CI 0.56-0.93) with median RFS not reached for any of the two arms. Since the trial met its primary endpoint earlier than expected, the data were not mature enough to analyse secondary endpoints, including OS. However, in a further analysis with a median follow-up of 35.1 months, the initial RFS benefit was not sustained.[432] The updated RFS HR was 0.90 (95% CI 0.72–1.12) and median RFS was 33.2 months (95% CI 24.3–NE) with atezolizumab plus

bevacizumab and 36.0 (95% CI 22.7, NE) with active surveillance. At the second interim analysis, OS remained immature (HR 1.26; 95% CI 0.85–1.87).

Should resected patients at high-risk of recurrence based on pathological findings (i.e., satellites, microvascular invasion, poor differentiation) be considered for liver transplantation?

Recommendation

- Resected patients with pathological findings associated with a high risk of recurrence other than Milan criteria (*i.e.*, satellites, microvascular invasion, poor differentiation) may be considered for liver transplantation if a predicted transplant benefit in survival can be shown and adequate observation time (>6 months) has elapsed **(LoE 4, weak recommendation, consensus).**

HCC recurrence after resection (defined as early or late if detected before or after 2 years from surgery, respectively) is strongly related to tumour biology and pathological characteristics assessed in the resected tumour. Patients with high-risk pathology findings after LR may benefit from "pre-emptive" or *ab initio* LT, *i.e.* LT before HCC recurrence. The concept of pre-emptive LT has been tested in multiple studies. The BCLC group [433] reported excellent survival in patients who underwent pre-emptive LT after discovery of high-risk features of HCC at final pathology, such as microvascular invasion and detection of additional nodules.[434] Similarly, in a study evaluating 121 patients listed for LT after LR for HCC, better 5-year survival was observed in patients undergoing pre-emptive *vs.* salvage LT.[435] Patients who would most benefit from pre-emptive LT are those at high risk of recurrence beyond Milan criteria, *i.e.* those who would not be eligible for salvage LT in case of recurrence. Recurrence beyond Milan is associated with microvascular invasion,[436,437] poor differentiation,[437] AFP >400 ng/ml,[438] lympho-vascular invasion,[438] extent of disease [436] and tumour burden score.[438,439] Two prediction models for recurrence beyond Milan criteria are available[436,438] on top of several models predicting survival after LT.[440] Those models may help in determining the difference in survival with transplant *vs.* no-transplant strategies, since a predicted durable benefit in survival achieved with LT is required to justify the use of donated organs. Accordingly, pre-emptive LT should not be used as a strategy to enlist patients who would otherwise be outside transplant criteria. To avoid this, an observation period of at least 3 to 6 months should elapse before listing a patient for LT is considered, to exclude early post-transplant HCC recurrences and therefore futile LT.

Should liver resection be applied to downstage HCC to liver transplantation eligibility criteria?

Recommendation

- Liver resection should not be considered as a downstaging procedure for HCC beyond Milan criteria to meet liver transplantation eligibility criteria **(LoE 4, strong recommendation, consensus).**

LR should not be considered as a standalone bridge-to-transplant treatment. While resection of some nodules can certainly diminish the tumour burden to within Milan criteria, such a strategy of surgical downsizing does not consider tumour biology. True tumour downstaging should treat intra- and eventually extrahepatic micrometastases, increase margins of resection and achieve tumour response as a surrogate of risk of recurrence. Therefore, only in patients who have achieved partial response after locoregional or systemic therapy can LR be employed to reach complete response before LT.[406]

As mentioned previously, HCC beyond Milan criteria is not an absolute contraindication to LR in patients with a favourable surgical risk profile. Patients beyond Milan can achieve good survival outcomes if successfully downstaged,[402,441] especially if they have a low tumour burden score.[442] In transplant candidates who are also good LR candidates with tumours beyond Milan criteria, a downstaging attempt with locoregional or systemic therapy is worthwhile. In this way, the final decision between resection *vs.* transplant strategies could incorporate response to therapy and effective downstaging as prognostic criteria.[406]

Patient selection for liver transplantation and tumour downstaging strategies

Should liver transplantation be the preferred therapeutic option for a patient with HCC within Milan criteria unsuitable for resection?

Recommendation

- Patients with HCC within Milan criteria who are unsuitable for resection (due to tumour location, marginal liver function or other liver-related contraindications) should be considered for liver transplantation. An ablate-and-wait strategy can be recommended for solitary HCC ≤2 cm **(LoE 2, strong recommendation, strong consensus).**

LT is the only solid organ transplant widely accepted to treat solid forms of cancers and the success of LT in treating HCC has generated a new field named transplant oncology. Survival rates after LT for patients with HCC within Milan criteria approach 80% at 5 years,[443] justifying the use of cadaveric organs in this patient population. All patients with HCC within Milan criteria who are unsuitable for resection (either due to tumour location, marginal liver function or other kinds of contraindications) should therefore be considered for LT and eventually listed if contraindications to transplant and better hepato-oncology alternatives are not found (Fig. 7).

The decision is more complex in patients within Milan criteria who are also potential candidates for LR. Overall, large series and a meta-analysis have demonstrated that the potential for cure is significantly lower for locoregional alternatives compared to LT.[444] The main limitation of LT is the limited number of donated organs. When different strategies are feasible, the choice between LT, LR and other locoregional or systemic therapies depends not only on the predicted absolute post-transplant survival but also on the predicted gain in life-years after LT compared to the other

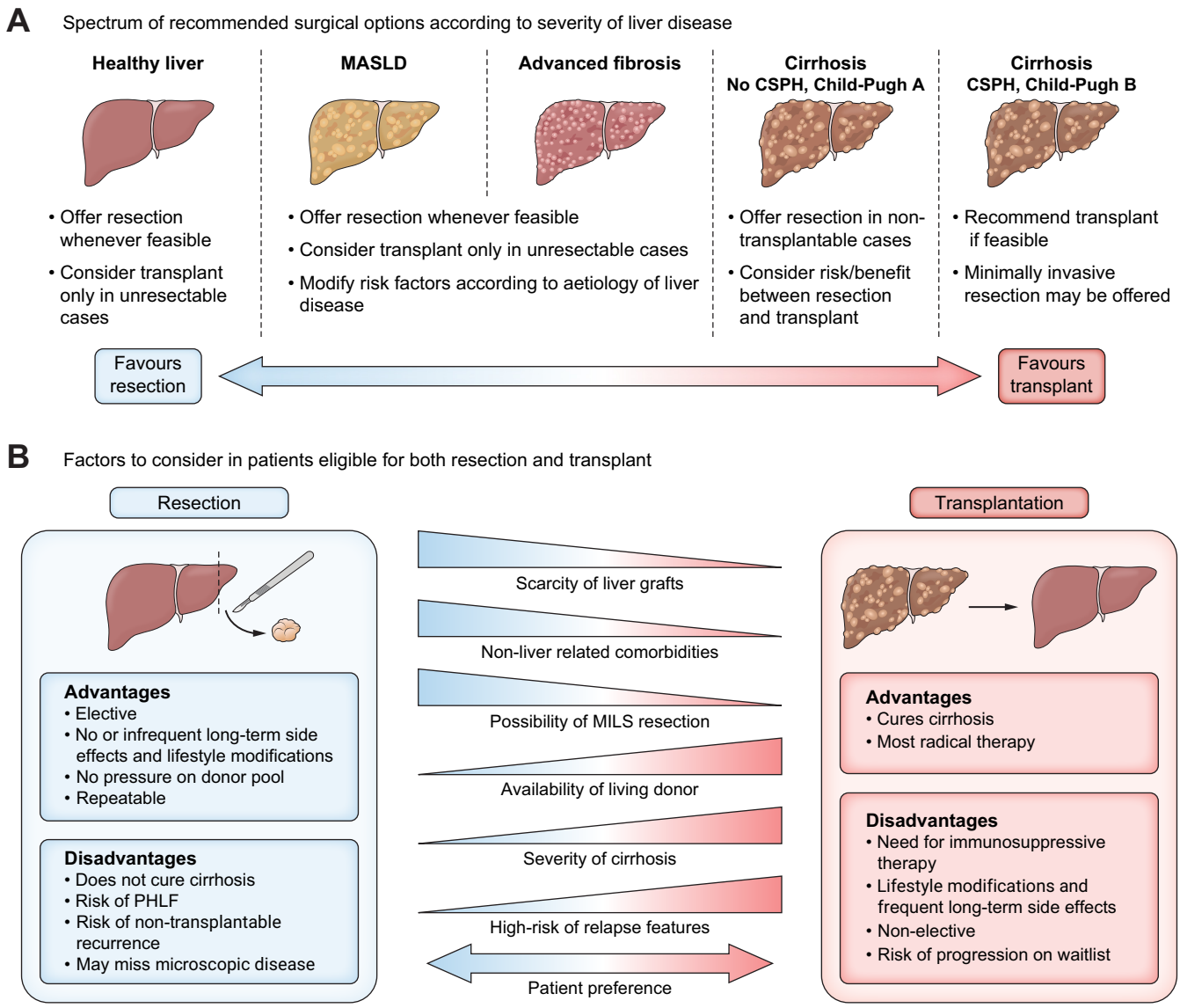

Fig. 7. Surgical decision-making framework for patients with HCC who are surgical candidates. CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MILS, minimally invasive liver surgery; PHLF, post-hepatectomy liver failure.

therapies. LT should be the first option to pursue when a substantial transplant benefit is achievable. This might not be the case for potential LR candidates.[445] Very early HCC (single tumour not larger than 2 cm) can be cured by LR or ablation and LT in such instances could be futile from a transplant benefit perspective, especially in patients with good liver function.[446] When resectable tumours within Milan criteria occur in patients with good liver function, principles of LR should be scrutinised (see recommendations on LR) and the potential for rescue LT in case of recurrence after LR (*i.e.*, salvage LT) should be considered.[435] In patients with resectable HCC, the choice of upfront LT is therefore multifactorial and must also consider patient's age, tumour characteristics and biology, AFP level and variations, tumour response to locoregional and systemic treatment, as well as the conditions of the local donor pool and waitlist composition. Transplant allocation based on an exclusive approach to one of the principles guiding the optimal use of the limited resource of organs (*i.e.*, urgency, utility and benefit) may lead to miscalibration of the survival prediction with and without transplant and to the unintended consequence of frequent adjustments of the adopted models.[447]

Should patients with HCC meeting expanded criteria with/out downstaging be treated with liver transplantation (considering tumour-related, patient-related, donor-related as well as non-cancer waitlist-related conditions, also including the principles of utility, cancer-related urgency and transplant benefit)?

Recommendations

- Patients with HCC beyond the transplant criteria adopted by each centre should be considered for liver transplantation after successful downstaging to within Milan criteria. Patients who do not achieve downstaging are poor candidates for liver transplantation **(LoE 2, strong recommendation, strong consensus).**
- The choice of downstaging strategies should be based on patient and tumour characteristics and no single locoregional procedure is recommended over the others. There is insufficient evidence to recommend systemic therapy as a downstaging treatment **(LoE 3, strong recommendation, strong consensus).**

Should patients reaching Milan criteria and AFP <1,000 ng/ml for at least 3 months at the end of preoperative downstaging treatment be listed for liver transplantation?

Recommendation

- AFP >1,000 ng/ml should be considered an absolute contraindication to liver transplantation regardless of tumour burden. Patients downstaged to within Milan criteria should have an AFP level ≤1,000 ng/ml for at least 3 months before they are listed **(LoE 3, strong recommendation, strong consensus).**

High-quality evidence supports transplant listing for patients with HCC beyond Milan and UCSF (University of California, San Francisco) criteria (*i.e.*, 1 tumour ≤6.5 cm or ≤3 tumours with the largest tumour diameter ≤4.5 cm and total tumour diameter ≤8 cm) if they achieve downstaging to within Milan,[406,417] as such patients have comparable outcomes to patients within Milan at presentation[413–415,448–450] and better outcomes than with any other treatments.[441] Aggressive downstaging protocols are thus recommended for patients with HCC beyond Milan.

Success of downstaging strategies has changed the conventional paradigm of patient eligibility for LT. Rather than expanding the LT indication *per se* – an effort that has continued without consensus for decades – LT beyond conventional criteria is increasingly proposed once other therapies (locoregional or systemic, alone or in combinations or sequences) has achieved the target of valuable tumour response, sufficient to predict a positive post-transplant outcome.[406,448,451] Several models have been published that assess the prognosis of downstaged HCC listed for LT.[452–455] In a network meta-analysis of validated prognostic calculators, Metroticket 2.0 and the AFP-French models offered the best prediction of post-transplant outcomes.[456]

No single locoregional or systemic therapy has been unequivocally associated with higher pre-transplant downstaging efficacy. The downstaging strategy should be tailored to each patient and a multimodal, sequential approach is recommended when downstaging is not achieved with a single treatment option.[457] When a properly delivered downstaging therapy results in partial tumour response according to modified RECIST (mRECIST) criteria,[458] patients can still be considered for transplant, although at a higher risk of list-dropout due to tumour progression compared to post-downstaging complete tumour responses.[459,460] According to the transplant benefit principle, those patients in partial response after downstaging with a good post-transplant prediction of survival should receive additional waitlist priority with respect to those with complete tumour response.[461–464]

Assessment of downstaging efficacy should include both morphometric and tumour biology parameters, particularly AFP. An AFP level >1,000 ng/ml may be considered a surrogate marker for vascular invasion and poor tumour differentiation and is unequivocally associated with high post-LT HCC recurrence.[412,465,466] Thus, an AFP level >1,000 ng/ml should be considered an absolute contraindication to transplant listing, and a level >400 ng/ml a strong relative contraindication.[467,468] Indeed, the true single AFP level that appears to be prognostic is the last one measured before transplant, although initial AFP and AFP dynamics should be considered.[468,469] Conversely, successful downstaging with sustained response lasting for more than 3 months from treatment completion and a parallel and equally sustained drop in AFP is associated with good post-transplant outcomes, making these patients eligible for LT.

If the patient cannot receive tumour downstaging because of concomitant end-stage liver disease, transplant listing based on biologic MELD and MELD adjustments[470–472] may be considered for HCC within or slightly beyond Milan criteria, providing a 5-year predicted HCC-specific survival above a given threshold for minimum accepted survival.[473] If so, prognostication tools[440,452–455,474] may help determine the transplant benefit by estimating survival without cancer treatment and comparing it with the expected survival based on liver decompensation status. This approach may help in the multifactorial determination of transplant eligibility. However, it should be considered with caution in such a borderline indication, as advanced cirrhosis in patients with HCC is associated with higher waitlist dropout and post-transplant recurrence, especially if increased levels of AFP are detected.[412]

Overall, failure of tumour downstaging after multimodal treatment is associated with poor post-transplant outcomes, and therefore listing of such patients is not recommended.[414,475]

Should neoadjuvant locoregional therapy be prescribed in patients who will likely remain on the waitlist for >6 months?

Recommendation

- Pre-transplant locoregional therapies should be considered, if not contraindicated due to liver dysfunction, in patients who will likely remain on the waitlist for >6 months **(LoE 4, strong recommendation, strong consensus).**

Patients with HCC eligible for LT upfront or after successful downstaging are at risk of waitlist dropout, mainly because of cancer progression. The European Hepatocellular Cancer Liver Transplant Study Group assessed the risk of HCC-dependent LT failure (defined as pretransplant tumour-related delisting or post-transplant recurrence) in patients within Milan criteria according to pre-transplant therapy using inverse probability of treatment weighting.[476] A significant reduction in treatment failure was observed in patients who received up to three locoregional treatments while on the waitlist, while the benefit was lost if more locoregional treatments were required. Although such studies are at high risk of selection bias as highlighted in a meta-analysis,[477] it is unlikely that risks related to locoregional treatments outweigh the potential benefits of therapy while on the waitlist. Therefore, although randomised evidence is lacking, offering locoregional treatments to patients awaiting LT is recommended whenever feasible, with the aim of sustaining disease stability and reducing the risk of dropout. While little can be said at the moment regarding the role of systemic therapy in waitlisted patients, anecdotal case series suggest that LT may also be feasible in those patients who experience tumour response to immunotherapy with immune checkpoint inhibitors (ICIs).[418,419,478] Such strategies need to be explored in auditable prospective studies.

List priority, living donation, marginal graft and dynamic preservation techniques in liver transplantation for HCC

Should patients with HCC on the liver transplant waitlist be prioritised according to the differential post-treatment response, with the aim of balancing the transplant offer in cancer vs. non-cancer indications?

Recommendations

- Prioritising a cadaveric graft allocation for patients with or without HCC within a common waitlist is complex, and no system can serve all regions. Prioritisation criteria for HCC should at least include tumour burden, AFP, waiting time and response to tumour treatment **(LoE 4, strong recommendation, strong consensus).**
- Transplant benefit for patients with HCC should be considered in combination with the conventional transplant principles of urgency and utility in the allocation policies of donated organs in each region **(LoE 4, strong recommendation, strong consensus).**

In the context of limited graft availability, policies for organ allocation must ensure that the allocation system is equitable and fair, with the aim of maximising graft and patient outcomes while avoiding futility, defined as unacceptable post-transplant outcomes (*i.e.*, 5-year survival <60% or survival lower than non-cancer indications) and non-competitive transplant benefit with respect to other therapies (see previous sections). It is recommended that patients with HCC be listed and maintained on the list only if their predicted post-transplant survival exceeds the minimum accepted survival.[473] After listing, organ allocation should consider and balance the principles listed in Table 5, namely utility (*i.e.*, allocation to the patient with the best predicted post-transplant survival); urgency (*i.e.*, allocation to the patient with the highest predicted waitlist mortality); and benefit (*i.e.*, allocation to the patient with the highest predicted difference in survival considering transplant *vs.* other therapies).[462] Transplant benefit combined with post-transplant absolute survival has been shown to reduce waitlist mortality in HCC while maximising the cumulative survival of the waitlisted population.[479,480] The ultimate aim of LT allocation is to ensure, within a common waitlist, a fair distribution between patients with cancer *vs.* non-cancer indications.[481]

Should living donor LT for HCC be considered an alternative to deceased donor LT?

Recommendation

- Living donor liver transplantation should be considered for selected patients with HCC, if performed in experienced centres according to the local context of waitlist time and providing adherence to donor-recipient double equipoise principles **(LoE 3, strong recommendation, strong consensus).**

Extensive experiences from Eastern and selected Western centres have shown that living donor LT is safe for donors and can be safely and effectively offered as an alternative when the availability of grafts from deceased donors is scarce[482,483] since living donor LT decreases the waitlist dropout rate.[484] Patients with HCC have comparable post-transplant outcomes after LT with living or deceased donors,[485] particularly in intention-to-treat analysis considering waitlist dropout.[486,487] Living donation should thus be considered an alternative to deceased donation for patients with HCC if the chances of LT with a deceased donor are low due to graft shortages and

Table 5. Principles of equitable organ allocation.

Principle	Definition	Measure	Objective
Urgency	The organ should go to the patient with the highest predicted waitlist mortality (*i.e.*, the sicker patient first)	Waitlist mortality	Minimise waitlist dropout/mortality
Utility	The organ should go to the patient with the best predicted post-transplant outcome	Post-transplant survival	Maximise outcomes
Transplant benefit*	The organ should go to the patient with the highest predicted gain in life-years after transplant.	Post-transplant survival minus survival achieved with non-transplant therapies	Maximise outcomes while considering alternative treatment and waitlist dropout
Justice	Patients with the same predicted post-transplant outcomes should have the same chance of receiving an organ.		Ensure equity

*Transplant benefit principle considers post-transplant life expectancy minus waitlist life expectancy/life expectancy with alternative treatments. For example, if patient A has a predicted survival of 10 years with transplant and 8 years with an alternative treatment (waitlist life expectancy), while patient B has a survival of 8 years with transplant and 2 years with the alternative treatment, allocation to patient A has higher utility (10 *vs*. 8 years) but lower transplant benefit (2 *vs*. 6 years). Notably, transplant benefit should be considered only when a predetermined minimal threshold in absolute post-transplant survival is determined, to avoid futility.

waitlist competition. In many contexts, living donor LT is frequently offered to patients with HCC outside the conventional criteria for deceased donor LT together with less stringent tumour biology and downstaging assessment. Even in such conditions the principle of donor-recipient double equipoise is strongly recommended, as living donation should only be considered if the transplant benefit in the recipient is substantially higher than the potential risk to the donor.[488]

Should liver transplantation in HCC be investigated in the context of marginal grafts and advanced graft reconditioning/preservation techniques?

Recommendation

- Any approach aimed at widening the availability of liver grafts (*e.g.* marginal cadaveric grafts from donation after brain death or cardiac death, the use of machine perfusion and dynamic preservation techniques) should be considered in patients with HCC **(LoE 3, strong recommendation, strong consensus).**

Increasing the donor pool remains a priority in LT. Several efforts have been undertaken during the last years, such as increasing organ utilisation rates by expanding criteria for acceptable donors and using machine perfusion and dynamic preservation techniques to either evaluate or recondition organs.[489,490] The use of grafts under extended criteria requires careful recipient selection, as the lower functional reserve of a marginal donated organ should be compensated for by a non-end-stage functional reserve in the recipient. Patients with HCC, who often have low MELD scores and compensated cirrhosis, are generally good candidates for extended criteria grafts,[491–493] while such grafts are contraindicated in patients with severely compromised liver function. In fact, adequate post-transplant outcomes for patients with HCC have been observed with elderly donors,[491] donation after cardiac death[493] and other expanded criteria donors.[492] Use of machine perfusion and dynamic preservation techniques represents a breakthrough in LT. The most common strategies to increase the donor pool and use perfusion machines are illustrated in Table 6. Other less commonly utilised strategies such as controlled oxygenated rewarming of mixed perfusion strategies (*e.g.* sequential perfusion, with hypothermic perfusion followed by normothermic perfusion) can also be selectively performed. Normothermic regional perfusion is used to decrease organ discard rates and improve the quality of grafts from donation after circulatory death. Normothermic machine perfusion and HOPE (hypothermic oxygenated machine perfusion) can be used to both assess and recondition the grafts and have been associated with improved early post-transplant outcomes.[494,495] Some retrospective evidence suggests that HOPE may reduce post-transplant HCC recurrence.[496] The underlying mechanism may be linked to the reduction of ischaemia/reperfusion injury and subsequently activated cascades that favour circulating tumour cell escape and engraftment.[497] Prospective trials investigating the role of machine perfusion in HCC beyond conventional transplant criteria are warranted.

Table 6. Strategies to increase the donor pool.

Strategy	Method/definition
Use of extended criteria donors	Donor age >65; organ dysfunction at procurement; graft steatosis >40%; BMI >30 kg/m^2; HCV/HBV positivity; cold ischaemia time >12 hours; non-trauma related cause of death; donation after cardiac death; split liver graft for two recipients
Normothermic regional perfusion (NRP)	Dynamic preservation technique that consists in the regional perfusion of abdominal organs in the donor after circulatory death, thus allowing for viability assessment during organ procurement as well as mitigation of warm and cold ischaemic injury during procurement
Normothermic machine perfusion (NMP)	*Ex situ* graft perfusion with warm oxygenated perfusate, allowing for near-physiological metabolic activity and viability assessment during preservation
Hypothermic oxygenated machine perfusion (HOPE)	*Ex situ* graft perfusion with hypothermic oxygenated perfusate, which reduces post-transplant ischaemia/reperfusion injury by restoring the levels of oxygen before full metabolic reactivation.

Other locoregional therapies

Non-surgical locoregional therapies include percutaneous ablation, intraarterial embolising therapies and external beam radiation therapy (EBRT). Thermal percutaneous ablation is usually performed using radiofrequency and microwave as the source of heating energy. Embolising techniques rely on the predominantly arterial vascularisation of HCC and include bland transarterial embolisation (TAE), conventional TACE (cTACE), drug-eluting beads TACE (DEB-TACE) and selective internal radiation therapy (SIRT), also called transarterial radioembolisation. TAE results in ischaemic damage of tumour cells after the occlusion of tumour-feeding arteries. The rationale for TACE lies in further enhancing tumour cell killing through the local delivery of chemotherapeutic agents that are emulsified with lipiodol in cTACE or loaded inside the embolising beads in DEB-TACE. Microspheres used in SIRT are made of resin, glass or polylactic acid, carry radioactive isotopes (yttrium 90, a pure beta emitter, or holmium 166, a beta and gamma emitter) and act as internal sources of radiation with minimal ischaemic effect. The amount and distribution of radiation depends on the amount of activity used, the place from where beads are released into the bloodstream and the local haemodynamics; they can be simulated prior to treatment using macroaggregated albumin or a scout amount of polylactic acid beads. EBRT is delivered from a linear accelerator that delivers multiple beams of ionizing radiation to deposit high dose to the tumor, with rapid dose fall off to the surrounding normal tissues. EBRT may be delivered using photon RT, that is often delivered in five or fewer highly focused treatments, referred to as stereotactic body radiation therapy (SBRT), or proton RT, which is associated with more dose sparing to non-tumour tissues. SBRT and proton RT have been used to treat HCC in case series, propensity-matched studies and RCTs. In EBRT, the amount and distribution of radiation in tumour and non-tumour tissues is accurately planned prior to treatment.

Complete tumour ablation may be the aim of locoregional therapies in the presence of limited disease and they may therefore be considered as an alternative to surgery in certain clinical scenarios. Technical success in this setting should be

assessed at the local level, in terms of local failure. In other scenarios, locoregional therapies aim to reduce the tumour burden, delay tumour progression and, in this way, prolong survival. Consequently, they can be applied to a wide population of patients across tumour stages, either as an alternative or in preference to surgery or systemic therapies or integrated in multidisciplinary strategies that aim to combine or sequence individual treatments to improve patient outcomes. Multidisciplinary team discussion is mandatory (Fig. 8). Selective delivery of the tumour cell-killing effect is essential to achieve treatment success while preserving liver function for all locoregional therapies. Response evaluation criteria that specifically assess tumour necrosis, such as mRECIST, are recommended for locoregional therapies.

In candidates for TACE, should DEB-TACE be preferred to cTACE?

Recommendation

- In candidates for TACE, DEB-TACE and cTACE should be considered equivalent **(LoE 2, strong recommendation, strong consensus).**

As mentioned, embolising techniques include TAE, cTACE and DEB-TACE. cTACE improved OS compared to best supportive care in two RCTs.[498,499] A meta-analysis including seven trials with a supportive care control arm and either TAE or cTACE as the experimental arm demonstrated a 2-year benefit for intervention.[500] Supported by this evidence, cTACE has since been considered the standard treatment of patients in the intermediate stage and of those in earlier stages who were not candidates for surgery or thermal ablation. DEB-TACE allows for better standardisation of the technique, and lower peak plasma concentrations of doxorubicin may reduce its toxic effects.[501] However, two retrospective studies have reported a higher risk of hepatic and biliary injury after DEB-TACE compared to cTACE.[502,503] Despite the differences between techniques, RCTs have not demonstrated superiority of DEB-TACE *vs.* cTACE.[504–507] This effect was not explained by suboptimal performance or patient selection. For instance, in one trial complete response occurred in 70.6% of patients with cTACE *vs.* 51.5% with DEB-TACE.[504] In another, median OS was 19.6 months with cTACE *vs.* 20.8 months with DEB-TACE (HR 1.11; p = 0.64).[505] The results of individual studies have been confirmed in a meta-analysis including 1,449 patients from four randomised and eight observational studies, which confirms the absence of superiority of DEB-TACE over cTACE in terms of tumour response and survival.[508] A pharmacoeconomic analysis indicates that the higher cost of DEB-TACE compared to cTACE can be offset by a shorter hospital stay and better quality of life.[509]

In candidates for TACE, is bland TAE an acceptable alternative to cTACE and DEB-TACE?

Recommendation

- In candidates for TACE, bland TAE should be considered an alternative to cTACE or DEB-TACE **(LoE 1, strong recommendation, consensus).**

No RCTs have demonstrated superiority of TACE or DEB-TACE compared to TAE. Furthermore, five meta-analyses of trials comparing TACE to TAE have shown no difference in OS.[510–514] Importantly, no evidence of heterogeneity was found at any time points evaluated, no publication bias was detected and restricting the analysis to high-quality studies or excluding each article once per time did not change the results. Propensity score analyses have also failed to show a difference in outcomes between TAE and TACE (cTACE or DEB-TACE) in terms of response rate, OS, progression-free survival (PFS) or transplantation-free survival.[515,516] Additionally, a RCT of DEB-TACE *vs.* TAE using the same particles (loaded or unloaded with doxorubicin) showed no difference in the rate of adverse events (38% for TAE *vs.* 40% for DEB-TACE), PFS (median 6.2 *vs.* 2.8 months, HR 1.36; p = 0.11), and OS (19.6 *vs.* 20.8 months; HR 1.11; p = 0.64).[517] That said, cTACE and DEB-TACE add cost and complexity and a meta-analysis of five trials showed increased risk of severe adverse events with TACE (cTACE or DEB-TACE) *vs.* TAE (RR = 1.33, 1.03–1.73, p = 0.03) and no difference in 2-year survival rate (RR 0.88, 0.74–1.06, p = 0.18).[514]

Is SIRT an acceptable alternative to percutaneous ablation for patients with single tumours within Milan criteria that are unsuitable for resection or transplantation?

Recommendation

- Radiation segmentectomy can be considered an alternative to percutaneous ablation for single tumours within Milan criteria that are unsuitable for resection or transplantation, when there is a significant risk of post-ablation recurrence based on size (>3 cm) or location (v.g. in contact with large vessels) **(LoE 3, weak recommendation, strong consensus).**

There are many single-institution series and trials describing the use of SIRT for the treatment of single HCC within Milan criteria that are unsuitable for resection of transplantation, with high local control and long-term survival.[518] However, there are no RCTs comparing SIRT to local ablation.

Selective injection of a high number of microspheres into a tumour-feeding or segmental artery results in the delivery of exceedingly high doses of radiation (in excess of 400 Gy) to the tumour and the non-tumour surrounding liver tissue in what is called radiation segmentectomy.[519] Performed in this way, SIRT aims at complete tumour ablation since it allows for delivery of tumoricidal doses to both the tumours and the potential microsatellites, thus maximising the antitumor effect.[520] In the initial report among patients with tumours <5 cm not suitable for ablation, an 86% EASL response rate at 6 months and a median time-to-progression (TTP) of 2.4 years were reported after radiation segmentectomy.[520] More recently, the LEGACY study included 162 patients with single nodules ≤8 cm, Child-Pugh A and ECOG performance status 0/1 undergoing radiation segmentectomy.[521] Median tumour size was 2.6 cm (range 0.9–8.1) and >90% of patients had one 3-5 cm nodule. Objective response rate by mRECIST for patients with BCLC A HCC was 90% (95% CI 82.4-92.4), and response lasted for ≥6 months in 66% of patients. At 2 years, the local progression rate was 0, similar to ablation, and the local PFS rate was 93.9%.

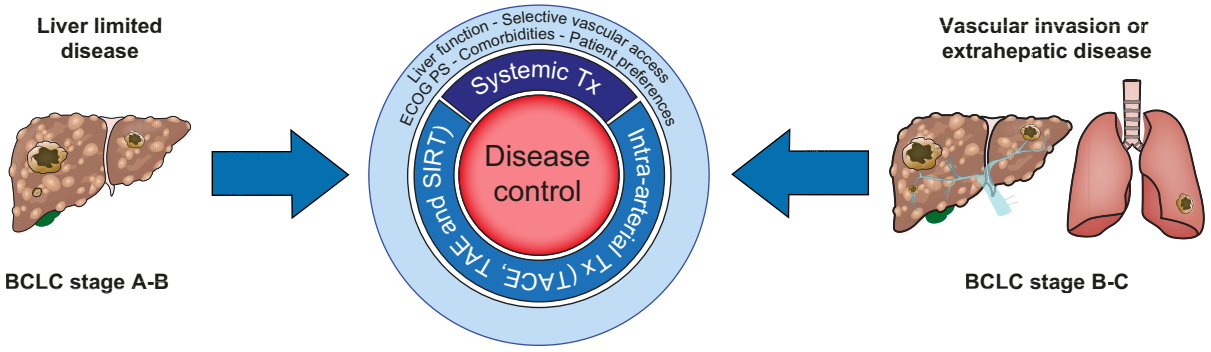

Fig. 8. Therapeutic approach of with the aim of disease control. BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation; TAE, transarterial embolization; TX, therapy.

Dosimetry is key in achieving good outcomes. In a radiology-pathology correlation of 33 patients transplanted after radiation segmentectomy of single tumours ≤5 cm not amenable to RFA, complete pathological necrosis was observed in 17 (52%) and extensive 50-99% necrosis in 16 (48%).[522] When the dose of radiation absorbed by the targeted segment was >190 Gy, complete pathological necrosis occurred in 67% *vs.* 25% with lower doses. In a confirmatory analysis of 45 patients bridged to LT or LR, 86% of patients who had a dose >190 Gy achieved complete pathological necrosis compared to 65% of those who had <190 Gy ($p = 0.001$); all 11 patients with ≥400 Gy had complete pathological necrosis.[523] Recent recommendations for glass[524] or resin microspheres[525] should be followed to personalise dosimetry targeting and thereby maximise the ablative effect of SIRT.

Is EBRT an acceptable alternative to percutaneous ablation for patients with single tumours within Milan criteria that are unsuitable for resection or transplantation?

Recommendation

- EBRT can be considered an alternative to percutaneous ablation for single tumours within Milan criteria unsuitable for resection or transplantation, when there is a significant risk of post-ablation recurrence based on size (>3 cm) or location (v.g. in contact with large vessels) **(LoE 4, weak recommendation, consensus).**

SBRT and proton RT have been used to treat HCC in case series, propensity-matched studies and RCTs. One RCT and many case series have studied EBRT for HCC within Milan criteria. A phase III non-inferiority RCT of proton RT *vs.* RFA was conducted in 154 patients with recurrent, small HCCs <2.5 cm (median 1.2 cm). Patients were heavily pre-treated, with 45% of patients having received prior TACE. This study met its primary endpoint of superior 2-year local PFS with EBRT (93% after EBRT and 83% after RFA), and no difference in survival (2- and 4-year survival rates of 91% and 76%, respectively).[526]

There are no RCTs of SBRT *vs.* thermal ablation for patients with HCC within Milan criteria. A pooled analysis of 297 patients without macroscopic vascular invasion from two American centres revealed a 3-year local control rate of 87%. The median HCC diameter was 2.7 cm, and 23% of patients had tumours >5 cm. The median survival was 25.6 months.[527] A systematic review and meta-analysis has studied 32 observational studies involving 1,950 patients with HCC (82.3% Child-Pugh class A) treated with SBRT.[526] Four studies included at least 30% of patients with macroscopic vascular invasion and the median tumour size was 3.3 cm (range: 1.6 to 8.6 cm). Three-year OS following SBRT was 48.3% and 3-year local control rate was 83.9%. Pooled hepatic and gastrointestinal grade 3 or higher toxicity was seen in 4.7% and 3.9% of patients, respectively. A network meta-analysis indicated a similar survival and tumour control for SBRT, SIRT and RFA,[528] suggesting that SBRT, SIRT and TACE may be considered for the treatment of unresectable HCC with curative intent when RFA is not possible.

Is SIRT an acceptable alternative to TACE in patients with single tumours unsuitable for, or recurrent after, ablation?

Recommendation

- SIRT can be considered an alternative to TACE in patients with a single HCC unsuitable for thermal ablation or recurrent after ablation, particularly when the intention is to bridge to transplant or facilitate a subsequent liver resection in patients with initially unresectable HCC **(LoE 3, weak recommendation, strong consensus).**

Four RCTs have compared SIRT *vs.* TACE but only one (PREMIER) recruited more than 50% of patients with single tumours. Among 45 patients with BCLC A or B HCC, TTP was significantly longer with SIRT *vs.* TACE (>26 *vs.* 6.8 months), although OS did not differ (18.6 *vs.* 17.7 months).[529] Meanwhile, a retrospective study comparing segmental TACE and radiation segmentectomy showed that radiation segmentectomy resulted in a higher response rate by mRECIST (84% *vs.*

58%) and longer PFS (564 *vs.* 271 days) than TACE.[530] Robust evidence from large RCTs comparing SIRT *vs.* TACE and ablation is still missing. As mentioned earlier, individual series and a network meta-analysis indicate similar survival and long-term tumour control for SBRT, SIRT and RFA.[528] This suggests that SBRT, SIRT and TACE may be considered for the treatment of unresectable HCC with curative intent when RFA is not possible. Importantly, large tumour size (>7 cm) is associated with increased risk of adverse events after TACE[531] but not after SIRT.[532]

Furthermore, SIRT has been used to downstage or bridge patients to transplant – especially important if time on the waitlist is >6 months[533] – or resection[534–536] .[537-539] In bridging to LT, initial clinical results indicate better local tumour control, allowing for a higher transplantation rate in comparison to TACE.[529] In downstaging intent, a systematic review demonstrated similar efficacy and post-treatment outcomes for TACE and SIRT.[540] Conversely, better tumour shrinkage enabling LT has been described with SIRT compared to TACE in patients beyond Milan criteria.[537,541,542]

When bridging to resection, the dual aim of so-called radiation lobectomy is to effectively treat the entire tumour volume and to induce atrophy of the treated lobe and compensatory hypertrophy of the untreated lobe.[543] In this way the amount of future liver remnant is increased while tumour response or disease control provides a positive test of time that reduces the chance of early postoperative tumour progression.[544] Among 31 patients treated with LR (16 right hepatectomy, 9 trisegmentectomy, 6 partial hepatectomy) a median of 2.9 months after SIRT, disease control was achieved in all patients, complete and major (50%–99%) pathologic tumour necrosis was observed in 45% and 32% of tumours, median RFS was 34.2 months, and the 3-year survival rate was 86%.[545]

Is EBRT an acceptable alternative to TACE in patients with single tumours unsuitable for, or recurrent after, ablation?

Recommendation

- EBRT can be considered an alternative to TACE in selected patients with single unresectable tumours which are unsuitable for thermal ablation or recurrent after ablation. Patients most likely to benefit from EBRT are those at high risk of complications from TACE/TAE **(LoE 3, weak recommendation, consensus).**

EBRT is associated with prolonged local tumour control in HCC. A single-centre study of 318 patients with 375 nodules (60% BCLC 0 or A) showed that 2 and 5 years after SBRT, local control rates were 94% and 94%, PFS rates were 62% and 13%, and OS rates were 72% and 11%, respectively.[546] A meta-analysis of 32 (mostly Asian) studies involving 1,950 patients with HCC across tumour stages with a median value of median tumour size of 3.3 cm (range 1.6-8.6 cm) showed a pooled 3-year local control rate of 83.9% (86% for tumours <5 cm).[547] In one large single-institution comparison of TACE and SBRT in 209 patients with HCC, propensity score analysis found that 2-year local control rate was higher with SBRT than with TACE (91% *vs.* 23%, p <0.001), with no significant difference in OS after adjustment for age, Child-Pugh score, cirrhosis, LT, time from diagnosis, and minor portal vein invasion (HR 0.76, p = 0.21).[548] At the time of LT, pathologic complete response was observed in 58% of evaluable lesions after SBRT and 24% after TACE (p = 0.054). In a prospective study of 40 patients receiving SBRT as bridging therapy to LT, tumour control rate at 1 year was 92.3% and pathological complete response was observed in 48.1%.[549]

Three small RCTs compared TACE to EBRT. One study of proton RT *vs.* TACE (n = 74, early terminated) reported a similar 2-year OS rate (68% and 65%, respectively), improved PFS with proton RT (median not reached *vs.* 12 months with TACE, p = 0.002) and improved local control with proton RT (HR 5.64; 95% CI 1.78-17.9, p = 0.003), with a cost saving also suggested with proton RT.[550] Furthermore, in patients who went on to undergo LT, pathological complete response was more often seen following proton RT *vs.* TACE (25% *vs.* 10%).[551] In two other small RCTs that were also stopped early due to poor accrual, a benefit of SBRT compared to TACE alone [552] or SBRT following incomplete TAE⧵TACE *vs.* exclusive TAE/TACE[553] was also observed. The TRENDY trial of 30 patients reported a median duration of local control of >40 months post SBRT *vs.* 12 months post TACE (p = 0.075). Median OS was 44.1 months *vs.* 36.8 months, respectively (p = 0.36).[552] In the Italian study of 40 patients, local control was superior following SBRT after TAE/TACE *vs.* TAE/TACE alone (median not reached *vs.* 8 months, p = 0.0002), 2-year PFS was 21% *vs.* 6%, respectively (p = 0.002), and 2-year OS was 64% *vs.* 57%, respectively (p = 0.8).[553] The patient group most likely to benefit from EBRT instead of TACE are patients at high risk of complications from TACE.

In candidates for TACE, should TACE plus EBRT be preferred to TACE alone?

Recommendation

- In candidates for TACE, there is insufficient evidence in Western patients to support the combination of EBRT and TACE in favour of TACE alone. Therefore, combination therapy is not recommended. **(LoE 3, strong recommendation, strong consensus).**

The combination of TACE plus EBRT has been used extensively in Asia and less in Western countries. One small (n = 32) phase II trial run in the US reported a 63% complete response rate in the target lesion and median PFS of 35 months.[554] TACE plus EBRT has not been compared to TACE alone in a RCT. However, a RCT compared intensity modulated EBRT followed by TACE *vs.* TACE followed by EBRT in 120 patients with HCC and portal vein tumour thrombus, with OS as the primary endpoint.[555] OS was longer in patients with EBRT followed by TACE although the difference was not statistically significant (median 15.4 *vs.* 11.5 months, HR = 0.68, 95% CI 0.46–1.01, p = 0.054). PFS was also significantly longer with

this sequence (6.6 *vs.* 4.2 months, HR 0.66, 95% CI 0.46–0.96, $p = 0.030$), suggesting that RT should be delivered before TACE, if the combination is to be used. Thus, EBRT followed by TACE is an option for selected patients who would otherwise be treated with TACE alone. However, it is unknown if TACE and EBRT improves outcomes over EBRT alone.

Should patients not showing an objective response to TACE after one or two treatments be considered TACE refractory and better suited for other therapies?

Recommendation

- In patients with lesions not showing a response to one or two consecutive TACE treatments and with preserved liver function other therapies should be considered **(LoE 3, strong recommendation, strong consensus).**

In large RCTs of TACE in patients with BCLC A and B HCC, response rates vary between 36% and 42%, and median OS ranges from 19 to 31 months.[556–558] Combination systemic therapy, predominantly in patients with BCLC C HCC, is associated with response rates of up to 30% and median survival of up to 21 months.[255,559,560] Objective response is an independent prognostic marker of survival after intra-arterial therapies. Responders have a 42% to 59% reduction in the risk of death compared to non-responders.[503,561,562] Patients with a best overall response of complete response have the best outcome followed by those with partial response, stable disease, and progressive disease.[563,564]

In the clinical trials that have proven the benefit of systemic immunotherapy combinations, OS was similar in those who had undergone TACE compared with those who had not,[559] but eligibility criteria exclude those with altered ECOG performance status or liver function.[255,559] Deterioration of liver function following TACE impairs prognosis.[565,566] Following each TACE session, hepatic function deteriorates from Child-Pugh class A to B in 9-14% and from ALBI grade 1 to 2 in 18-21%.[567] Liver function is an important prognostic factor for systemic therapy and deterioration in liver function associated with repeated TACE may preclude the benefit from subsequent systemic therapy.[568] Therefore, preservation of liver function is an important issue in sequencing intra-arterial and systemic therapy.

Should TACE be considered unsuitable and systemic therapy more appropriate in patients with tumour nodules in >2 liver segments, with diffuse tumours with unclear border, and outside the Up-to-7 criteria?

Recommendation

- TACE/TAE should be preferred to systemic therapy for liver-confined disease when a selective approach is possible (based on low tumour size and number, no infiltrative gross appearance, and preserved portal flow) **(LoE 4, strong recommendation, strong consensus).**

Over the last 40 years, TACE has evolved from a non-selective procedure where the main branches of the hepatic artery were occluded to a superselective technique where only the tumour-feeding arteries are catheterized. This results in fewer complications and better outcomes.[569] Both size and number of tumours have been shown to be prognostic in patients treated with TACE. In a study of 114 UK patients, the risk of death was almost double for tumours >7 cm compared to those ≤7 cm (median OS 6.6 *vs.* 18.0 months, HR 1.99, $p = 0.02$).[570] Among 280 Korean patients, multiplicity was an independent prognostic factor with a HR of 2.32 (95% CI 1.71–3.15) for ≥2 *vs.* single tumours.[571] In an Italian study of 361 patients in which a bootstrap resampling procedure based on Cox regression analysis was used to select the most significant prognostic variables, tumour number was selected in 100% of all repeats.[572] Finally, tumour size and number are combined in the Up-to-7 criterion (tumour number + size of the largest tumour in cm ≥7). Among 131 Austrian patients, median OS was 28.3 months for those within Up-to-7 *vs.* 12.0 months for those beyond Up-to-7 (HR 2.2, 95% CI 1.4-3.4).[573] Worse prognosis is at least in part due to the reduced efficacy of TACE for large or multiple tumours. Among 314 Korean patients, achievement of complete response by mRECIST as the initial response to TACE was the most important prognostic factor.[562] Complete response rate was 83% for patients within Milan, 59% for those beyond Milan but within Up-to-7, and only 14% for those beyond Up-to-7 criteria.

Meanwhile, outcomes after systemic therapy have improved significantly in the past few years. Among 90 intermediate stage, patients with Child-Pugh A cirrhosis beyond Up-to-7 treated with lenvatinib or cTACE and matched by propensity score, those treated with lenvatinib had longer median PFS (median 16.0 *vs.* 3.0 months; $p < 0.001$) and OS (median 37.9 *vs.* 21.3 months; $p < 0.01$).[574] RCTs comparing TACE *vs.* systemic therapy are ongoing.

Should prognostic or predictive scores be used to determine whether patients receive systemic or locoregional therapy?

Recommendation

- Neither prognostic nor predictive scores should be used to support clinical decision-making between embolic and systemic therapy, though these scores may be useful for identifying those patients unlikely to derive meaningful benefit from either **(LoE 3, strong recommendation, strong consensus).**

Therapeutic algorithms recommend TACE/TAE for liver-confined disease in patients not suitable for curative interventions and in the absence of portal vein invasion.[263] But it is acknowledged that such disease is heterogeneous[575] and that patients with more extensive liver-confined disease may achieve better outcomes with systemic therapy.

Scores that assess liver function, including Child-Pugh and ALBI, are prognostic for patients treated with TACE[568,576] and systemic therapy but available data do not support their use for

decision-making on treatment modality. In fact, the majority of RCTs exploring the use of TACE/TAE and systemic therapies, including those with positive results, have only recruited patients with Child-Pugh class A cirrhosis. Several TACE-specific prognostic scores have been developed and are based on pretreatment parameters assessing liver function, tumour burden and tumour biology. HAP, mHAPII and mHAPIII[570–572] or ART[566] scores allow for the stratification of TACE candidates into groups with different prognosis. Similarly, scores like CRAFITY[577] and PNI [578] can stratify patients receiving atezolizumab and bevacizumab into subgroups with different prognosis. However, none of these scores can predict if an individual patient will benefit more from TACE over systemic therapy or vice versa. Demonstrating such capacity would require a trial in which patients selected by the predictive score were randomised to receive TACE or systemic therapy. That said, HAP has shown good prognostic discrimination in patients treated with sorafenib and patients within each HAP score showed worse survival with sorafenib than with TACE.[579] However, selection bias precludes any meaningful interpretation and HAP cannot be recommended for treatment selection.

In patients in the intermediate stage not fit for TACE, is SIRT an acceptable alternative to systemic therapy?

Recommendation

- In patients with multiple tumours in the intermediate stage who are not fit for TACE/TAE or surgery, SIRT cannot currently be recommended as an alternative to systemic therapy, although it is an acceptable option if systemic therapy is contraindicated, provided a lobar approach is possible **(LoE 4, weak recommendation, consensus).**

Two phase III RCTs have failed to show a survival benefit of SIRT compared to sorafenib in patients with intermediate or advanced HCC. In the SARAH trial of 459 French patients with BCLC C HCC, OS was not improved with SIRT *vs.* sorafenib (median OS 8.0 *vs.* 9.9 months, respectively; HR 1.15, 95% CI 0.94-1.4, p = 0.18).[580] In the SIRveNIb study of 360 Asian patients with BCLC B or C HCC, OS was also not improved with SIRT *vs.* sorafenib (median OS 8.8 *vs.* 10.0 months, respectively; HR 1.1; 95% CI 0.9-1.4; p = 0.36).[581] Among patients with BCLC B HCC in the SIRveNIB trial, median OS was 13.5 months with SIRT and 14.8 months with sorafenib.

It has been argued that several issues could have influenced these negative results including the limited experience of some participating centres, poor patient selection and outdated dosimetric procedures.[582] The 20.4 month (95% CI 14.9-24.9) median OS reported among 115 patients with BCLC B in the CIRT registry [583] may reflect these nuances. A single-centre analysis of an experienced group showed that survival was worse in the initial period (2005–2011, 68 patients, median OS 11.2 months) than afterwards (2012-2020, 185 patients, 25.7 months).[584] Clinical trials exploring the role of SIRT in TACE-ineligible patients should take these issues into consideration.

In patients in the advanced stage due to segmental or lobar portal vein invasion but free from extrahepatic spread, is EBRT an acceptable alternative to systemic therapy?

Recommendation

- In patients in the advanced stage due to segmental or lobar portal vein invasion but free from extrahepatic spread, EBRT cannot currently be recommended as an alternative to systemic therapy with immune checkpoint-based combinations, and there is limited data to recommend EBRT or the combination of EBRT with TKIs in preference to TKIs alone **(LoE 3, weak recommendation, consensus).**

Prospective phase I or II trials[585,586] and retrospective studies[587,588] have shown that EBRT and tyrosine kinase inhibitors (TKIs) may be delivered safely to patients unfit for TACE (60-100% with vascular invasion) and result in consistent response rates above 50% and encouraging local control endpoints (v.g., time to local control failure of 14 months[587]). SBRT followed by TKI treatment appears to be associated with less toxicity compared to concurrent use.

Two RCTs have compared EBRT (alone or in combination with TACE) to systemic therapy or to the combination of EBRT plus systemic therapy in patients with macroscopic vascular invasion. In a phase II single-centre RCT, 90 treatment-naive patients with portal vein invasion were randomised to sorafenib or TACE (every 6 weeks) plus hypofractionated EBRT (within 3 weeks after the first TACE) with a primary endpoint of 12-week PFS rate by independent review using RECIST v1.1.[589] TACE + RT resulted in improved 12-week PFS rate (86.7% *vs.* 34.3%; p <0.001); higher response rate at 24 weeks (33.3% *vs.* 2.2%; p <0.001), longer TTP (median 31.0 *vs.* 11.7 weeks, p <0.001) and longer OS (median 55 *vs.* 43 weeks; p=0.04). The NRG/RTOG1112 phase III trial randomised patients with locally advanced HCC to sorafenib *vs.* SBRT followed by sorafenib.[590] The study closed earlier than expected with 177 eligible patients accrued out of the 292 planned. Patients were mainly BCLC stage C (84%) and 74% had vascular invasion (63% had tumour thrombus in the first-order branches or the main trunk of the portal vein). The addition of SBRT was associated with an improvement in OS (median 15.8 *vs.* 12.3, HR 0.77, one-sided p = 0.0554). On a pre-planned multivariable analysis, in addition to performance status, Child-Pugh score, presence of extrahepatic disease and the degree of vascular invasion, the addition of SBRT was associated with improved OS (HR 0.72, 95% CI 0.52-0.99, two-sided p = 0.042). PFS was improved with the addition of SBRT (median 9.2 *vs.* 5.5 months, 95% CI 0.40-0.75, HR 0.55, two-sided p = 0.0001) and there was no difference in the frequency of treatment-related adverse events of CTC grade 3 or higher (47% *vs.* 42%, p = 0.52). These results speak in favour of the safety and potential efficacy of combining SBRT and sorafenib in this setting although the caveats around the only randomised trial preclude a formal recommendation.

In patients in the advanced stage due to segmental or lobar portal vein invasion but free from extrahepatic spread, is SIRT an acceptable alternative to systemic therapy?

Recommendation

- In patients in the advanced stage due to segmental or lobar portal vein invasion but free from extrahepatic spread, SIRT is not recommended as an alternative to systemic therapy **(LoE 3, strong recommendation, consensus).**

As mentioned earlier, the RCTs SARAH [580] and SIRveNIb[581] failed to show a survival benefit of SIRT compared to sorafenib in patients with intermediate or advanced HCC. The proportion of patients in the BCLC C stage was 68% (including 63% with macroscopic vascular invasion) in SARAH and 48% in SIRveNIb. In SARAH, HRs for OS were similar for patients with (1.19, 95% CI 0.92–1.54) or without (1.05 95% CI 0.75–1.47) macroscopic vascular invasion. In SIRveNIb, pre-planned subgroup analyses in the treated population showed that OS was significantly better with SIRT compared to sorafenib in BCLC C (median OS 9.2 *vs.* 5.8 months, HR 0.67, 95% CI 0.4-1.0, $p = 0.047$) but not in patients with portal vein thrombosis (median OS 7.5 *vs.* 4.9 months, HR 0.73, 95% CI 0.4-1.2, $p = 0.20$) or in the intention-to-treat population.

Also discussed earlier, these negative results may not reflect the experience gained over the last years in the way SIRT is performed, particularly regarding patient selection and dosimetric procedures. Along this line, a *post hoc* analysis of the impact of tumour-absorbed dose (estimated from the macroaggregated albumin scan) on outcomes among patients treated with SIRT in the SARAH trial[591] showed that patients who received ≥100 Gy had longer OS than those who received <100 Gy (median OS 14.1 *vs.* 6.1 months, $p < 0.001$) and tumour-absorbed dose was higher in patients with disease control *vs.* progressive disease (median 121 *vs.* 85 Gy, $p = 0.02$). More recently, the DOSISPHERE-01 trial randomised 60 patients with locally advanced HCC without extrahepatic disease eligible for SIRT to receive either standard dosimetry (120 ± 20 Gy) targeted to the perfused lobe or personalised dosimetry (≥205 Gy targeted to the index lesion), with the primary endpoint being investigator-assessed objective response rate (ORR) in the index lesion by EASL criteria at 3 months among actually treated patients.[592] ORR was 71% with personalised dosimetry and 36% with standard dosimetry ($p = 0.0074$). Median OS was 26.6 months (95% CI 13.5–NR) among patients who received a tumour dose of ≥205 Gy *vs.* 7.1 months (95% CI 4.6–14.8) in those who received a tumour dose of <205 Gy (HR 0.33, 95% CI 0.15–0.71, $p = 0.0029$). Serious adverse events were reported in similar proportions in both arms. These encouraging results call for a RCT that compares SIRT (as currently performed) to systemic therapy in this population.

In patients in the intermediate stage with a large tumour burden, should intra-arterial therapy (TACE or SIRT) be combined with systemic therapy?

Recommendation

- In patients in the intermediate stage with a large tumour burden, intra-arterial therapy (TACE/TAE or SIRT) should not be combined with systemic therapy using TKIs. There is insufficient evidence to provide a recommendation for the combination of intra-arterial therapy (TACE/TAE or SIRT) with immunotherapy using checkpoint inhibitors **(LoE 2, strong recommendation, consensus).**

Multiple RCTs investigating the combination of TACE and sorafenib or other TKIs *vs.* TACE alone have failed to show a survival benefit for the addition of such systemic agents to patients eligible for embolisation.[556–558,593] Recently, the TACTICS trial, which included 55% of intermediate-stage patients, showed an improvement in TACE-specific PFS with TACE plus sorafenib *vs.* TACE alone (median 22.8 and 13.5 months, respectively) and no significant OS benefit (median 36.2 *vs.* 30.8 months, respectively).[594] In TACE-specific PFS using the RECICL criteria,[595] progression was defined as the inability of a patient to further receive or benefit from TACE for reasons that included intrahepatic tumour progression (25% increase of viable area in the five largest liver lesions), appearance of macroscopic vascular invasion or extrahepatic disease, but not the appearance of new intrahepatic lesions. The surrogacy for OS of TACE-specific PFS is not widely confirmed and thus no treatment recommendations can be made based on the results of the TACTICS trial. In a meta-analysis of 27 studies that were mostly non-comparative or non-randomised, TACE plus sorafenib resulted in longer TTP and a higher disease control rate but no significant difference in OS.[596] In the LAUNCH phase III RCT (n = 338), an improved OS was observed with lenvatinib plus TACE compared to lenvatinib alone (17.8 *vs.* 11.5 months, HR 0.45; $p < 0.001$) but these were patients eligible for systemic therapy usually in the advanced stage (72% with portal vein invasion, 55% with extrahepatic disease).[597]

In the SORAMIC trial that recruited 424 patients at BCLC stages B or C, combining sorafenib with SIRT did not improve OS compared to sorafenib alone (median 12.1 *vs.* 11.4 months, respectively; HR 1.01; 95% CI 0.81-1.25; $p = 0.95$).[598] The subgroup of patients with diffuse or very large tumours beyond up-to-seven criteria, Child-Pugh score ≤6 and no previous TACE showed a trend towards improved survival with SIRT plus sorafenib (14.5 *vs.* 10.5 months). In the STOP-HCC trial, patients with unresectable HCC were randomised to sorafenib or SIRT followed by sorafenib.[599] The study showed no difference in OS between patients at BCLC stages B or C treated with the combination of sorafenib with SIRT or sorafenib alone (HR 1.08, 95% CI 0.89-1.31) (data accessible at https://clinicaltrials.gov/study/NCT01556490). In an analysis of the per protocol population (222 out of 526 randomised patients),

median OS was 13.2 months with SIRT plus sorafenib and 13.8 months with sorafenib alone despite a longer TTP by RECIST v1.1 of 8.1 *vs.* 5.6 months (HR 0.76, 95% CI 0.59-0.96).

Hypothetically, locoregional treatment might be a good partner for immunotherapy using ICIs. Tumour necrosis induced by TACE might lead to a release of tumour-associated antigens, which could activate the tumour microenvironment and stimulate the specific immune response[600] that will then be stimulated by ICIs. Furthermore, TACE-induced hypoxia increases the production of VEGF,[601] which catalyses tumour growth due to increased re-vascularisation and contributes to an immunosuppressive environment. Hence, there is a strong rationale for combining TACE with ICIs and/or VEGF inhibitors. Several small retrospective studies have reported outcomes in patients with BCLC B or C HCC treated with TACE plus ICIs with or without TKIs in a wide variety of combinations and schedules that make it difficult to draw any definitive conclusion.[602–606] PFS ranged from 8.5 to 16.3 months and OS ranged from 23.3 to 24.8 months.

The double-blind phase III EMERALD-1 trial met its primary endpoint of improved PFS in TACE-eligible patients treated with TACE plus durvalumab and bevacizumab *vs.* TACE plus placebo.[607] Patients were recruited irrespective of tumour size and number provided all lesions could be treated within a 16-week period. In the final analysis for PFS after a median follow-up of 17.4 months in the combination arm, the HR for PFS was 0.77 (95% CI 0.61-0.98), with a median PFS (by RECIST v1.1 using blinded independent central review) of 15 months for TACE plus durvalumab and bevacizumab and 8.2 months for TACE plus placebos. The interim analysis co-occurred but OS was not statistically different, and the trial is ongoing for the final analysis of OS.

The double-blind phase III LEAP-012 trial also met its primary endpoint of improved PFS in TACE-eligible patients treated with TACE plus pembrolizumab and lenvatinib *vs.* TACE plus placebo.[608] Patients were recruited provided all lesions could be treated with TACE in one or two sessions. In the final analysis for PFS after a median follow-up of 25.6 months in the combination arm, the HR for PFS was 0.66 (95% CI 0.51-0.84), with a median PFS (by RECIST v1.1 using blinded independent central review) of 14.6 months for TACE plus pembrolizumab and lenvatinib and 10 months for TACE plus placebos. With only around 30% of death events, OS was not statistically different (HR 0.80, 95% CI 0.57-1.11), and the trial is ongoing for the final analysis of OS.

Radiation therapy may also induce immunogenic cell death and SIRT could therefore be a good partner for ICIs too. A recent study retrospectively analysed the immune tumour microenvironment of tumours resected without preoperative treatment (n = 32) or after preoperative TACE (n = 16) or SIRT (n = 12).[609] SIRT promoted the recruitment of CD3+, CD4+ and CD8+ T cells in the tumour microenvironment, and granzyme B expression compared to TACE or no preoperative treatment. Evaluation of the optimal doses and schedule for SIRT and best immunotherapy to be combined with will require further evaluation in prospective studies. So far, two phase II trials have assessed the combination of SIRT followed 3 weeks later by nivolumab. The NASIR-HCC trial recruited 42 patients who were not candidates for TACE (BCLC A or B beyond the Up-to-7 rule or BCLC C unilobar tumours with segmental or lobar portal vein invasion) and showed an ORR of 38% (12% CR), median TTP of 8.8 months (95% CI 7.0-10.5) and median OS of 20.6 months (95 % CI 17.3-24.0).[610] The CA 209-678 trial recruited 36 patients with mostly BCLC C tumours including 36% with extrahepatic spread, and showed an ORR of 31%, median TTP of 5.6 months (95% CI 2.1–8.8), and median OS of 16.9 months (95% CI 8.1–27.6).[611] Larger non-controlled trials are ongoing.

Systemic therapies

Systemic therapy of HCC is performed using immune therapies (aimed at eliciting an antitumor immune response or strengthening an ongoing one) or targeted therapies (with drugs that target specific molecular pathways that are essential for HCC cell growth). The systemic administration of cytotoxic drugs (that kill dividing cells in a non-selective manner) has not proven any substantial benefit in prospective trials. Immune checkpoints include co-inhibitory molecules expressed by effector lymphocytes that prevent their overactivation. ICIs abrogate this effect and reinvigorate effector cells. ICIs used in RCTs target PD-1 (nivolumab, pembrolizumab, sintilimab) or its ligand PD-L1 (atezolizumab, durvalumab, tislelizumab); and cytotoxic T lymphocyte-associated antigen 4 or CTLA-4 (ipilimumab, tremelimumab). VEGF is produced in the tumour microenvironment by tumour or stromal cells. It favours tumour growth by stimulating angiogenesis and via a number of immune-modulating effects that comprise the inhibition of dendritic cell functions or the generation of immunosuppressive myeloid-derived stromal cells and regulatory T cells, among others. Anti-VEGF drugs may abolish these effects by binding to circulating VEGF (bevacizumab), or by selectively inhibiting its cellular receptors like VEGFR-2 (rivoceranib and ramucirumab). Targeted therapies used in HCC consist of multi-TKIs that share an anti-angiogenic effect through the blockade of the VEGF and platelet-derived growth factor receptors and differ in the inhibition of molecules involved in diverse molecular pathways (RAF, FGFR, RET, KIT, TIE2 or MET, among others). Given the multiple mechanisms of action, the effects of multi-TKIs on the immune system are not fully understood.

By definition, systemic therapies target tumour sites irrespective of their size, number and location in the organism. In HCC, a positive impact on patient survival has only been demonstrated for patients in the most advanced stages, with extrahepatic disease, macroscopic vascular invasion or with a large burden of liver disease that is considered not ideal for locoregional therapies, or for patients who failed to respond to locoregional therapies. Combination immunotherapies and TKIs are the mainstay of systemic therapy of HCC in this setting. Their benefit has been established in large RCTs with control arms that have evolved over time. When making therapeutic decisions, direct cross-trial comparisons may suggest misleading analogies or differences and physicians should pay attention to patient profile, relative contraindications and treatment availability, all in conversation with the patient and, once again, in the setting of an MDT discussion.

Biomarkers are not currently useful in the decision-making process.

Should patients in the advanced stage be offered combination systemic therapy including at least one PD1 or PD-L1 inhibitor?

Recommendation

- In patients with advanced HCC, preserved liver function (Child-Pugh A) and ECOG performance status 0-1, combinations including at least one PD-1 or PD-L1 inhibitor should be offered, provided there are no contraindications **(LoE 1, strong recommendation, strong consensus).**

Sorafenib was approved over a decade ago as the first-line systemic therapy for advanced HCC based on the results of the SHARP[252] and Asia Pacific[612] trials. Subsequently, lenvatinib was shown to be non-inferior to sorafenib in the REFLECT trial[253] and both have been regarded as standard-of-care first-line therapy. Most recently, three global RCTs have demonstrated the superiority of regimens containing ICIs targeting the PD-1/PD-L1 axis compared to sorafenib or to the investigators choice between lenvatinib or sorafenib.

IMbrave 150 was a global study which randomised 501 patients to the combination of atezolizumab and bevacizumab given 3 weekly or sorafenib in a 2:1 ratio.[256] The co-primary endpoints were OS and PFS and both were met. Atezolizumab plus bevacizumab provided superior OS *vs.* sorafenib (HR 0.58, 95% CI 0.42-0.79; p <0.001) and PFS (HR 0.59, 95% CI 0.47-0.76; p <0.001). The independently assessed response rate for atezolizumab plus bevacizumab was 27.3% and that for sorafenib was 11.9% according to RECIST v1.1 criteria. On further follow-up the median OS was reported as 19.2 months for atezolizumab plus bevacizumab and 13.4 months for sorafenib.[559]

The HIMALAYA trial evaluated the combination of tremelimumab and durvalumab *vs.* sorafenib in a randomised global study which also included a third arm with single agent durvalumab.[257] The so-called STRIDE regimen comprised a single priming dose of tremelimumab plus durvalumab given at 4 weekly intervals. Overall, 1,171 patients were randomised 1:1:1 and the primary endpoint of OS for STRIDE *vs.* sorafenib was met. STRIDE provided superior OS *vs.* sorafenib (median OS 16.43 *vs.* 13.77 months; HR 0.78, 95% CI 0.65-0.93; p = 0.0035). The independently assessed response rate for STRIDE and sorafenib using RECIST v1.1 was 20.1% and 5.1%, respectively. PFS was not statistically significantly different with a HR 0.9 (95% CI 0.77-1.05). OS was noninferior with durvalumab monotherapy compared to sorafenib (HR 0.86; 95.67% CI, 0.73 to 1.03; noninferiority margin, 1.08).

In the CheckMate 9DW trial, 668 patients were randomised 1:1 to the combination of nivolumab and ipilimumab or the investigator's choice of lenvatinib (85%) or sorafenib (15%).[613] Ipilimumab was given for up to four 3-weekly courses and nivolumab was given for a maximum of 2 years. The primary endpoint of OS was met. Nivolumab plus ipilimumab provided a superior OS *vs.* sorafenib (median OS 23.7 *vs.* 20.6 months; HR 0.79; 95% CI 0.65–0.96; p = 0.0180). Using RECIST v1.1, the independently assessed response rate (36% *vs.* 13%; p <0.0001), complete response rate (7% *vs.* 2%) and duration of response (median 30.4 *vs.* 12.9 months) were all higher with nivolumab plus ipilimumab than with lenvatinib or sorafenib.

A fourth trial was conducted exclusively in China in which the combination of the PD-1 inhibitor sintilimab was combined with the bevacizumab biosimilar (IBI305) and compared with sorafenib in an open-label randomised phase II-III study.[614] The study met its primary endpoint; sintilimab plus the bevacizumab biosimilar provided superior OS *vs.* sorafenib (HR 0.57, 95% CI 0.43–0.75; p <0.0001) providing conceptual confirmation of the IMbrave 150 trial, although its relevance to the global population is not clear. Finally, in a trial conducted in a predominantly HBV-infected (74%) population in which 82% were recruited in Asia, the combination of camrelizumab and rivoceranib (a TKI that selectively inhibits VEGFR2 and only mildly inhibits c-Kit and c-SRC) was shown to provide superior OS compared to sorafenib (HR 0.62, 95% CI 0.49-0.80).[615]

The combination of PD-1 or PD-L1 inhibitors with multi-TKIs has been explored in both the COSMIC 213 and the LEAP-002 trials. In COSMIC-312, the combination of cabozantinib and atezolizumab was compared with sorafenib and in LEAP-002, the combination of pembrolizumab and lenvatinib was compared with lenvatinib. Whilst the PFS endpoint was met for COSMIC-312, the interim analysis for OS was not encouraging (HR 0.90, 96% CI 0.69–1.18; p = 0.44).[616] LEAP-002 also failed to meet its primary OS endpoint despite a response rate of 26.1% by RECIST v1.1 and median OS of 21.2 months (HR 0.84, 95% CI 0.708-0.997).[560]

Single agent PD-1 inhibitors have not been shown to be superior to sorafenib in prolonging OS. Nivolumab failed to meet its primary endpoint of superiority in CheckMate 459[617] but durvalumab and tislelizumab have both demonstrated non-inferiority to sorafenib.[255,618] In the presence of combination therapy, the role of single agent PD-1 inhibitors is likely to be confined to those patients that have contraindications to combination therapy.

Based on the results of the global IMbrave 150 and HIMALAYA trials, combination therapy containing PD-1 or PD-L1 inhibitors should be considered first-line standard of care for those without contraindications to ICIs (and bevacizumab). There is no evidence to support the use of one option in preference to the other. Sorafenib and lenvatinib remain first-line options in these patients and both single agent durvalumab and tislelizumab may also be considered. It is important to note that all positive trials reported to date have included only those patients with Child-Pugh class A liver disease and performance status 0-1. The benefit beyond these criteria is unproven.

Should aetiology influence the choice of systemic immunotherapy?

Recommendation

- The choice of systemic therapy should not be influenced by aetiology **(LoE 1, strong recommendation, strong consensus).**

The aetiology of liver disease is usually reported in clinical trials of systemic therapy for advanced HCC, and clinical outcomes according to aetiology are increasingly reported in

subgroup analyses. This has allowed aetiology to be evaluated as a potential stratification factor for treatment selection. For TKIs, no consistent pattern has emerged. A combined analysis of the SHARP [252] and Asia Pacific[612] studies of sorafenib suggested a greater survival benefit in those patients infected with HCV[619] whilst for cabozantinib, those with HCV infection had the worst outcomes.[620] For regorafenib [621] and lenvatinib,[253] those with a background of HBV infection had greater benefit. At best, these findings can be regarded as hypothesis generating and prospective evaluation would be required to confirm these associations.

For ICIs, the association of outcome with aetiology is similarly inconsistent. Preclinical experiments have suggested that MASH-induced HCC may be resistant to ICIs and a meta-analysis of the CheckMate 459, IMbrave 150 and Keynote-240 trials suggested no benefit of checkpoint inhibitor over control therapy.[622] Since then, five additional randomised trials have been reported in which ICI monotherapy or ICI-based combinations have been compared with sorafenib or lenvatinib.[255,615,616,618] In subgroup analysis of the HIMALAYA trial, those with HCV infection appeared to have least benefit from the STRIDE regimen[255] and in the RATIONALE 301 trial, those with HBV infection had the least apparent benefit from tislelizumab.[618] Moreover, the initial large phase Ib/II studies of nivolumab and pembrolizumab demonstrated broadly similar response rates across those with HBV, HCV and non-viral aetiologies.[623,624] Interestingly, an update of the IMbrave 150 trial also showed similar response rates across aetiologies; 27% in patients with non-viral liver disease, 32% in HBV infection and 30% in HCV infection.[559] An updated meta-analysis including the recently published trials has confirmed the benefit of ICI-based therapy in those with non-viral liver disease and demonstrated variable outcomes across trials based on aetiology.[625] The lack of differentiation between causes of non-viral liver disease limits interpretation of the data and separation into those with more common aetiologies such as alcohol or MASLD may be helpful, although, in practice, there is frequent overlap between multiple aetiologies.

Should second-line TKI therapy be recommended following progression on first-line combination PD-1/PD-L1-containing therapy?

Recommendation

- Following discontinuation of the combination of ICI-based combinations due to tumour progression or treatment-related adverse events, TKIs can be considered in selected patients **(LoE 4, weak recommendation, strong consensus).**

To date, no RCTs have reported the clinical outcomes of second-line therapy following first-line treatment with PD-1/PD-L1-containing combinations. One phase II study has studied 47 patients refractory to prior ICI-based treatment who received cabozantinib as a second- or third-line therapy.[626] The median OS was 9.9 months (95% CI 7.3-14.4) in the entire cohort and 14.3 (95% CI 8.9-NR) months when used in the second line.

Post-progression treatment was frequently administered in the recently reported trials of combination therapy and in most cases a TKI was given. In IMbrave 150, 36% received systemic therapy after discontinuation of atezolizumab plus bevacizumab of whom 32% received TKIs.[559] Similarly, in HIMALAYA, 40.7% received second-line therapy following the STRIDE regimen of whom 36.4% received TKIs.[255] Interestingly, subsequent TKI therapy was also given after combinations which contained TKIs. In LEAP-002, 44.1% had subsequent therapy after lenvatinib and pembrolizumab, and this was a TKI in 35% of cases.[560] In COSMIC 312, post-progression therapy was less common at 20% but in 14% it was a TKI.[616] In most cases the relative outcome of these post-progression subgroups has not been reported but in a *post hoc* exploratory analysis of IMbrave 150, the median OS for 60 patients treated with 'other' therapies post-progression was 6.8 months compared with 2.0 months for those that received no treatment.[627] Such analysis is subject to considerable selection bias as is the case for those retrospective analyses so far reported which in general report similar OS with sorafenib or lenvatinib ranging from 7.5 to 17 months.[628–631] Currently, there are no approved first-line combinations containing TKIs and, given the proven efficacy of lenvatinib and sorafenib and their distinct mechanism of action, it is unlikely that a second-line, placebo-based randomised trial will be acceptable to clinicians and patients. Ongoing trials such as IMbrave 251 (NCT04770896), will at least provide some robust prospective data on second-line TKI therapy and the basis for a control arm in future trials.

Should patients with mildly decompensated cirrhosis be offered systemic therapy?

Recommendation

- Patients with decompensated cirrhosis should not be routinely treated with systemic therapy outside a prospective clinical trial. However, systemic therapy may be considered in carefully selected patients with mild liver impairment (Child-Pugh 7-8) **(LoE 3, weak recommendation, strong consensus).**

The SHARP trial set the standard for design of phase III trials in advanced HCC. Critically, recruitment was limited to those with preserved liver function as defined by Child-Pugh class A to reduce the effect of competing risk of death due to background liver disease. Since then, all subsequent trials resulting in drug approval have restricted recruitment to patients with Child-Pugh A. The REACH trial of ramucirumab initially included those with Child-Pugh B liver disease but an increase in adverse events in this subgroup resulted in an amendment to exclude them from further enrolment and they were not included in the final analysis.[632] A subsequent analysis compared the 78 patients with Child-Pugh B to the 565 with Child-Pugh A and confirmed a higher incidence of grade 3 or higher treatment-emergent adverse events for the Child-Pugh B sub-group and no significant difference in survival compared with placebo.[633] Notably, the median OS for patients with a Child-Pugh score of 5 was 11.66 months compared with

4.57 months for the Child-Pugh B cohort. REACH is the only prospective randomised trial data which allows for robust analysis of the efficacy of systemic therapy in patients with Child-Pugh B.

However, there are numerous prospective and retrospective field of practice cohort studies that confirm the poor survival of patients with Child-Pugh B, which is typically less than half that reported in the Child-Pugh A population. For sorafenib, the median OS in patients with Child-Pugh B ranges from 3.6 to 6 months compared with 9.5 to 13.6 months for Child-Pugh A.[634–639] A meta-analysis comprising 33 studies compared the outcome for sorafenib between Child-Pugh A (n = 6,820) and B (n = 1,684). The estimated median OS was 8.8 months and 4.6 months, respectively.[640] Similarly, two retrospective studies have reported outcomes of lenvatinib with median OS of 17.8 months and 21 months for Child-Pugh A but 8.8 months and 9 months for Child-Pugh B, respectively.[641,642] A small retrospective study of cabozantinib reported median OS of 9.7 months *vs.* 3.2 months for those with Child-Pugh A *vs.* B.[643]

Patients with impaired liver function treated with ICIs also do poorly with median survivals of 7.3-7.6 months for nivolumab[644,645] and 6-6.7 months for atezolizumab and bevacizumab.[646,647] Regarding safety, the rates of all grade and grade 3 or 4 adverse events in a prospective cohort of 49 patients with Child-Pugh B recruited in the CheckMate040 trial were comparable to those in patients with Child-Pugh A.[644] Clearly patients with Child-Pugh B liver disease and HCC present an unmet need but current data do not support the unrestricted use of any approved therapies in this setting. Appropriately designed trials are needed to develop a robust evidence base for this group.

Should patients with recurrence post-transplant be offered systemic therapy if surgical and locoregional interventions are not feasible

Recommendation

- In patients with recurrent disease following transplantation, which is not amenable to surgical or locoregional therapy, systemic therapy with sorafenib or lenvatinib can be considered. ICIs are not recommended in view of the risk of organ rejection **(LoE 4, weak recommendation, strong consensus).**

Patients with HCC recurrence after LT have been systematically excluded from all clinical trials of systemic therapies. In three retrospective European studies, median OS of sorafenib-treated patients ranged between 19 and 21 months.[648–650] However, in a large Korean study of 232 patients, median OS was only 11.8 months and survival rates were not different according to sorafenib therapy.[651] Tolerability is an issue when sorafenib is used in the post-transplant setting. Dose reduction is needed in 30% to 68% of patients[648,650] and the maximum tolerated dose was 200 mg BID in a phase I trial of adjuvant sorafenib in patients at high risk of recurrence,[652] with grade 3-4 hypertension, hand-foot syndrome and diarrhoea all occurring in >10%. The results are similar for lenvatinib. In a retrospective study of 45 patients with recurrent HCC after LT who received lenvatinib, median PFS and OS were 7.6 and 14.5 months, respectively, and dose reduction or interruption occurred in 49%.[653] Finally, in a multicentre retrospective study of 81 LT recipients with HCC recurrence who tolerated but discontinued sorafenib, receiving regorafenib (n = 36) was an independent predictor of reduced mortality (HR 0.37; 95% CI 0.16-0.89; p = 0.02); the median OS of regorafenib-treated patients was 13.1 months and the regorafenib dose was reduced in 61% of patients.[654]

Immune checkpoint molecules are important players in graft tolerance.[655] Consequently, ICIs carry a risk of inducing graft rejection. In a pooled analysis of 52 patients treated with ICIs after LT for recurrent HCC or other malignancies, acute graft rejection occurred in 29% and was associated with a 46% mortality rate.[656] Rejection rate was lower with CTLA-4 inhibitors (1/5 patients) than with PD-1 inhibitors (14/46) but the low number of patients in the former group precluded any conclusion. Given the relatively low number of patients with HCC recurrence post-LT and the large number of confounding factors, prospective studies are strongly encouraged to increase our understanding of the safety and efficacy of ICIs in this population.

Should patients who develop oligometastatic progression on systemic therapy be offered local therapy while continuing existing systemic therapy

Recommendation

- In patients demonstrating a sustained response to systemic therapy, an isolated site of disease progression may be treated with local therapy while continuing systemic therapy **(LoE 5, weak recommendation, strong consensus).**

Oligometastasic HCC progression is defined as progression of a limited number of metastatic foci. The upper limit to the number of metastases is not well defined and more often includes up to 5.[657] In a propensity-matched study of patients with HCC and 1–4 lung oligometastases, the number of metastases did not worsen the apparent benefit from local therapy.[658] A recent meta-analysis supports the application of local treatment for HCC oligometastases.[659] Only studies with at least five cases treated with local modalities were considered and a total of 10 studies involving 527 patients were included. Most patients received EBRT or RFA. Pooled ORRs of comparative series favoured the use of local treatment (4.664, 95% CI 2.595–8.380, p <0.001, I^2 ~0.0%). Pooled rates of 1-year OS were 71.8% (95% CI 59.0–81.9; I^2 = 81.5%), and pooled 2-year OS rates were 43.3% (95% CI 29.1–59.6; I^2 = 85.4%). In a phase II trial including 40 patients with a controlled primary HCC and 1–5 previously untreated metastatic lesions treated with ablative SBRT (62 lesions), the 2-year rates of local progression, objective response and disease control were 91.1%, 75.8%, and 98.4%, respectively.[660] Little is known about patients with oligometastatic progression who continue systemic therapy and receive local therapy in addition. Case reports demonstrate promising tumour control in individual and selected patients.

Should patients with sustained response to ICIs be discontinued from treatment after 2 years

Recommendation

- The consequences of discontinuing ICIs in those patients with a sustained response are currently unknown. The decision to discontinue can be made in discussion with the patient based on available knowledge of risks and benefits **(LoE 4, weak recommendation, strong consensus).**

Treatment was maintained until disease progression or unacceptable toxicities in pivotal clinical trials of immunotherapy combinations approved in HCC.[255,559] However, long-term use of ICIs is associated with an increased risk of toxicities, the need for continued medical visits and procedures, and an important financial burden to healthcare providers. Treatment discontinuation in the absence of tumour progression or toxicity may be considered in patients with stable disease or partial response, but more frequently in those with complete response. Indeed, the increasing rates of complete responses to systemic therapy (8% in the Imbrave150 trial,[559] 11.7% in the HIMALAYA trial[255] and 7% in the CheckMate 9DW trial[613] or systemic therapy followed by locoregional therapy with curative intent (*e.g.* LR, LT or RFA) have stimulated discussions regarding whether drug-free status can be obtained.[661]

In a cohort study of 107 evaluable patients in the intermediate stage treated with atezolizumab plus bevacizumab, "clinical" complete response (defined as complete response per mRECIST v1.1, continuous normalisation of AFP, AFP-L3 and PIVKA-II lasting ≥12–24 weeks, and complete disappearance of intranodular arterial flow by CEUS) were observed in 35 patients after locoregional therapy (7 resection, 12 percutaneous ablation, 15 superselective TACE). Such therapies were applied to a selected group of patients with RECIST-based partial response (n = 25), stable disease (n = 12) or slow progressive disease (n = 2) after ≥6 cycles, drug discontinuation due to toxicity (n = 1), or PET-positive HCC (n = 7).[662] Three additional patients achieved clinical complete response with atezolizumab plus bevacizumab only. Systemic therapy was discontinued in 25/38 (66%) patients and maintained in the rest. Recurrence was not observed in patients who were in a drug-free state and occurred as new sites of disease in three patients on continued therapy. Prospective trials including non-Asian patients are required before such criteria can be considered in clinical practice.

Should patients continue systemic therapy beyond progression

Recommendation

- In the absence of an evidence-based subsequent therapy, a patient may continue systemic therapy beyond progression if the patient is perceived to be deriving ongoing clinical benefit **(LoE 3, weak recommendation, consensus).**

Treatment beyond progression with ICIs in patients with HCC is generally safe and may benefit a subset of patients due to later-onset tumour responses or disease stability. In fact, treatment beyond progression was allowed in the pivotal clinical trials of immunotherapy combinations.

In the Imbrave 150 trial, patients could continue treatment beyond progression per RECIST v1.1 if they met the criteria of evidence of clinical benefit as determined by the investigator and absence of signs and symptoms indicating unequivocal disease progression, decline of ECOG performance status that could be attributed to disease progression, and tumour progression at critical anatomical sites that could not be managed by protocol-allowed interventions.[559] Of the 336 patients enrolled in the atezolizumab plus bevacizumab arm of IMbrave150, 236 (70%) experienced progressive disease. On or after the first progression, these patients then received atezolizumab with or without bevacizumab (n = 130), other non-atezolizumab therapies (n = 60) or no treatment (n = 46). Median OS after progressive disease in these groups was 14.5 months (95% CI 11.5–16.7), 6.8 months (95% CI 4.9–11.5), and 2.0 months (95% CI 1.6–3.0), respectively. Any comparison between arms should be made with great caution given the implicit patient selection bias.

In the HIMALAYA trial, patients with progression by RECIST v1.1 could continue receiving treatment if they did not have clinical progression (*i.e.* investigator determination that the patient was no longer benefiting from treatment). Furthermore, patients with progressive disease could receive a second dose of tremelimumab. Out of the 388 patients receiving tremelimumab plus durvalumab, 184 (47.4%) were treated beyond RECIST progression and 31 (8%) received an additional dose of tremelimumab.[257] The OS of this subgroup of patients was not reported but the proportion of patients treated beyond progression was similar in the subset of patients that survived for more than 3 years.[255]

Assessment of clinical endpoints in research and practice

There is a general agreement that OS is the most relevant and objective patient outcome in cancer therapy. Other endpoints may serve as potential surrogates for OS or may provide complementary information related to treatment efficacy. PFS and ORR are particularly interesting in this regard. From a clinical trial perspective, they allow for an earlier identification of efficacy. It is important for the clinician to make a fair assessment of the value of these measures.

Which radiological criteria should be used to assess response to systemic therapy in clinical trials

Recommendation

- RECIST v1.1 should be the primary means by which to assess response in clinical trials evaluating systemic therapy. mRECIST and iRECIST can be reported as secondary assessments where appropriate **(LoE 1, strong recommendation, consensus).**

RECIST v1.1 criteria were designed and are most commonly used to assess tumour response across tumour types.[663] The largest tumour diameter of each lesion is measured in a predefined number of tumour sites and changes are classified based on predetermined ranges. Thermal or chemical ablation and intra-arterial embolising procedures aim to induce extensive acute tumour necrosis, and tumour shrinkage is delayed and may never be complete. To address this issue, the EASL

criteria introduced the assessment of viable tumour defined as those areas that show contrast uptake in dynamic CT or MRI.[142] In the mRECIST criteria, it is the largest diameter of viable, contrast-enhanced tumour that is measured.[664] mRECIST is now considered the standard tool for assessing imaging endpoints in clinical trials of locoregional therapies and a consistent correlation between ORR by mRECIST and OS has been observed in this setting. In a meta-analysis including 1,357 patients, HR for OS in mRECIST responders *vs.* non-responders was 0.39 (95% CI 0.26–0.61, p <0.0001).[665]

Given the anti-angiogenic effect of TKIs, it was hypothesised that mRECIST could also be used to evaluate their efficacy. The mechanisms of action of systemic therapies nevertheless differ substantially from locoregional therapies, and acute tumour necrosis is not expected. Due to their anti-angiogenic effects, TKIs may induce a vascular shutdown and this explains at least in part the higher response rates reported with mRECIST. In a phase III trial comparing brivanib *vs.* placebo in advanced HCC, mRECIST response showed promising results as a surrogate of OS (R = −0.92; 95% CI −1 to −0.73, p <0.001).[666] In a phase III study of lenvatinib *vs.* sorafenib, ORR by both mRECIST and RECIST v1.1 showed an association with OS (HR 0.61 and 0.50, respectively) and they both served as independent predictors of OS in multivariable analysis.[667] Similar studies in clinical trials of ICIs have not been reported so far. On the other hand, progression is captured similarly by RECIST v1.1 and mRECIST criteria and there is no difference between the two criteria when assessing TTP or PFS. Finally, iRECIST[668] has not been properly evaluated in HCC.

RECIST v1.1 has been used for response evaluation in all pivotal trials of systemic therapies approved worldwide, it is easier to use and has a good interobserver agreement[669] and is not affected by the heterogeneity in contrast enhancement that usually occurs in advanced HCC. A demonstration of a significant added value would be needed to recommend mRECIST over RECIST v1.1 in advanced HCC treated with systemic therapies.

Is progression-free survival an appropriate surrogate for overall survival in advanced HCC?

Recommendation

- Overall survival should remain the primary endpoint for randomised-controlled trials in advanced HCC **(LoE 1, strong recommendation, strong consensus).**

As mentioned, OS has been considered the gold standard endpoint for phase III clinical trials but reasons have been advanced to support the development of surrogate endpoints. These include a desire to reduce the size, cost and duration of trials, to obtain regulatory approval as early as possible and to accelerate the sequential development of new therapies.[670] There is also concern that crossover and post-progression therapies may be a confounding factor for OS. Criteria to establish the strength of surrogacy have been defined by the Institute of Quality and Efficiency in Health Care based on weighted Pearson correlation coefficients (*i.e.*, low: R ≤0.7; moderate/medium: 0.7 <R <0.85; high: R ≥0.85)[671] and to date, three meta-analyses have been performed which explore the surrogacy of PFS for OS. The first included 21 randomised phase III trials of which 12 were first-line and 9 second-line.[672] Interventions evaluated included multi-TKIs, SIRT and cytotoxic chemotherapy but not ICIs. A moderate correlation was found between the HR for PFS and OS with a weighted Pearson coefficient of 0.84. However, among the seven studies with significant HR for PFS only three met their OS endpoint. Consequently, a PFS HR of ≤0.6 was recommended as a threshold to predict a positive outcome with respect to OS. But recent phase III trials of ICIs have demonstrated that the relationship between PFS and OS HR is less reliable. The HIMALAYA trial met its primary OS endpoint reporting a HR of 0.78 for STRIDE *vs.* sorafenib but the HR for PFS was 0.906. Conversely, the COSMIC-312 trial reported a promising HR for PFS of 0.63 but failed to meet its OS endpoint at interim analysis with an HR for OS of 0.908.

Two meta-analyses have compared median PFS and OS rather than HRs and therefore included single-arm studies in addition to randomised trials. One evaluated 49 trials including phase I/II to phase III of which 11 included ICIs and 38 TKIs.[673] The overall correlation between median PFS and OS was weak (R^2 = 0.20). However, the correlation improved when comparing 12 month restricted mean survival time for PFS and OS (R^2 = 0.58) and the correlation was greater for ICIs (R^2 = 0.80) compared with multi-TKI trials (R^2 = 0.61). Overall, the authors concluded that the relationship between PFS and OS was variable and depended on treatment class and evaluation time point. The second is a meta-analysis of 26 trials including 41 treatment arms.[674] All studies included ICIs either as monotherapy or in combination. Overall, the weighted Pearson correlation coefficient for median PFS and OS was low (R = 0.62). Sensitivity analysis suggested liver function and line of treatment did not impact the result.

In summary, the analyses published to date have applied differing methodology to varying data sets which include a wide range of trial phases, lines of treatment and drug classes. Overall, there is at best a moderate correlation between PFS and OS, but a wide variation is seen between individual trials suggesting that PFS is not a robust surrogate for OS. The identification of a surrogate is most important for first-line trials where OS is longest. For advanced HCC, the OS in recent trials remains around 20 months. By comparison with other tumours this is relatively short, and OS remains appropriate under these circumstances.

Appendix. Delphi round agreement on the recommendations of the present clinical practice guidelines.

Recommendation	Consensus
Patients with HBV infection should be treated with nucleoside or nucleotide analogues to reduce the risk of developing HCC (both *de novo* and recurrence) and the type and time of treatment should follow EASL guidelines on HBV infection **(LoE 2, strong recommendation).**	100%
Patients with HCV infection and liver fibrosis should be treated with direct-acting antivirals to reduce the risk of cirrhosis-related complications, including HCC **(LoE 2, strong recommendation).**	100%
Patients with HBV and HCV co-infection can be treated following the same criteria as for mono-infected patients **(LoE 3, weak recommendation).**	100%
Weight loss in patients with obesity, alcohol cessation, and tobacco cessation are recommended to reduce the risk of liver-related and other adverse outcomes and may be recommended to reduce the risk of HCC **(LoE 3, weak recommendation).**	100%
Coffee consumption may be recommended to reduce the risk of HCC **(LoE 3, weak recommendation).**	94%
Owing to a lack of evidence, the use of statins, aspirin and metformin cannot currently be recommended to reduce the risk of HCC development **(LoE 3, weak recommendation).**	96%
High-risk seronegative people should be vaccinated against HBV to decrease HCC incidence and HCC-related death and improve overall survival **(LoE 3, strong recommendation).**	100%
Patients with cirrhosis should be offered surveillance for HCC unless they have a relatively high risk of death from non-HCC causes, or they could not be offered a curative-intent treatment for HCC (*e.g.*, patients with Child-Pugh class C cirrhosis ineligible for liver transplantation) **(LoE 2, strong recommendation).**	96%
Patients with chronic liver disease and advanced fibrosis without cirrhosis have a higher risk of HCC than the general population, but HCC surveillance cannot currently be recommended in this group owing to insufficient evidence **(LoE 3, weak recommendation).**	95%
An ultrasound examination of the liver every 6 months is recommended for screening of HCC. The combined use of ultrasound with AFP increases sensitivity while decreasing specificity and is a reasonable option. There is limited data to support the use of other promising imaging modalities such as abbreviated MR or serum biomarkers **(LoE 3, strong recommendation).**	78%
The LI-RADS should be used to favour standardisation in the acquisition, description and reporting of liver imaging examinations **(LoE 3, strong recommendation).**	96%
Non-invasive diagnosis of HCC should be based on the LI-RADS CT/MR v2018 or the LI-RADS CEUS v2017 criteria. With CT/MRI, the following major imaging features are combined to reach the diagnosis: tumour size, rim and non-rim arterial hyperenhancement, peripheral and non-peripheral washout (in the portal venous or delayed phases on CT and MRI using extracellular contrast agents or gadobenate dimeglumine, or in the portal venous phase only with MRI using gadoxetic acid), enhancing capsule and threshold growth. With CEUS, non-rim arterial hyperenhancement with late-onset (>60 s) and washout of mild intensity are combined to reach the diagnosis **(LoE 1, strong recommendation).**	95%
The LR-5 category and the 2018 EASL algorithm have similar performance for the non-invasive diagnosis of HCC. However, LI-RADS should be preferred because it introduces valuable refinements (*e.g.*, LR-M and LR-TIV categories) and allows for an estimation of the probability of HCC in nodules that do not meet the LR-5 category **(LoE 3, strong recommendation).**	100%
Multiphasic CT or dynamic contrast-enhanced MRI are recommended, without preference, for the non-invasive diagnosis of HCC **(LoE 1, strong recommendation).**	90%
Extracellular contrast agents should be favoured over gadoxetic acid for the non-invasive diagnosis of HCC using MRI **(LoE 1, strong recommendation).**	91%
CT or MRI should be preferred over CEUS as a first-line examination for the non-invasive diagnosis of HCC because of their higher sensitivity and their utility for analysis of the whole liver **(LoE 3, strong recommendation).**	100%
When used for the non-invasive diagnosis of HCC, CEUS should be performed according to the LI-RADS technical recommendations **(LoE 4, strong recommendation).**	95%
The non-invasive criteria should only be applied to patients with cirrhosis, chronic HBV infection or a history of HCC. In other patients, the diagnosis of HCC should be confirmed by biopsy **(LoE 1, strong recommendation).**	88%
Pathological diagnosis of HCC should be based on the International Consensus recommendations using the required histological and immunohistochemical analyses **(LoE 1, strong recommendation).**	100%
If a biopsy is obtained, relevant prognostic features should be reported, including tumour differentiation and HCC subtyping per the WHO classification **(LoE 1, strong recommendation).**	100%
In patients undergoing tumour biopsy for the diagnosis of HCC, it is suggested to simultaneously obtain a sample of the non-tumoural liver parenchyma to facilitate the diagnosis **(LoE 3, weak recommendation).**	84%
Until therapeutic decisions can be reliably informed by molecular analysis of tumours, routine molecular analysis is not recommended **(LoE 3, strong recommendation).**	100%
Gadoxetic acid-enhanced MRI is suggested in patients who are candidates for curative-intent treatments (*i.e.*, transplantation, liver resection, thermal or radiation ablation) as it may improve local tumour staging **(LoE 3, weak recommendation).**	75%
18F-FDG and 18F–FCH PET/CT are not recommended for tumour staging **(LoE 3, strong recommendation).**	96%
Measurement of AFP once a definitive HCC diagnosis has been made is recommended as it may provide useful prognostic information **(LoE 3, strong recommendation).**	96%
The BCLC classification is recommended for tumour staging and provides important prognostic information **(LoE 1, strong recommendation).**	91%
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 patient's comorbidities to ensure perioperative mortality is lower than 3% and morbidity is lower than 20% **(LoE 2, strong recommendation).**	100%
Clinically significant portal hypertension (HVPG >10 mmHg) and Child-Pugh class B cirrhosis are not absolute contraindications for limited resections approached with minimally invasive techniques. However, the risks and benefits of resection should be weighed against those of alternative options such as LT or locoregional therapies. **(LoE 3, weak recommendation).**	96%
Clinically significant portal hypertension and Child-Pugh class B cirrhosis should be regarded as an absolute contraindication to major resections (*i.e.*, >2 segments) **(LoE 3, strong recommendation).**	96%

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Recommendation	Consensus
Advanced age should not be considered as an absolute contraindication to liver resection **(LoE 3, strong recommendation).**	80%
Since patients with MASLD and HCC may experience better long-term survival outcomes but higher perioperative morbidity compared to those with viral aetiologies, a thorough pre-operative assessment of metabolic-related conditions should be performed in such patients and pre-operative optimisation of modifiable metabolic-related risk factors is recommended **(LoE 3, strong recommendation).**	96%
Liver resection is recommended as the preferred therapeutic option in patients with single HCC (with or without satellites) arising on a non-cirrhotic liver **(LoE 3, strong recommendation).**	92%
Multifocal tumours involving multiple segments require bridging or downstaging therapies to allow a positive test of time before considering surgical resection **(LoE 3, weak recommendation).**	80%
Liver transplantation is not recommended in patients without cirrhosis who have unresectable HCC that is beyond the Milan criteria. Exceptions should be based on sustained response to non-surgical therapies and assessment of transplant benefit **(LoE 4, weak recommendation).**	96%
Liver resection, particularly by minimally invasive means, and thermal ablation are recommended, without preference, in compensated patients with cirrhosis and a solitary HCC ≤2 cm who are otherwise not candidates for liver transplantation. Ablation should be preferred when a major hepatectomy is needed **(LoE 2, strong recommendation).**	100%
No one thermal ablation technique (radiofrequency or microwave) is recommended over the others **(LoE 2, strong recommendation).**	96%
Liver resection is recommended for single HCC >2 cm in patients with cirrhosis when hepatic function is preserved and sufficient remnant liver volume can be maintained **(LoE 2, strong recommendation).**	86%
Owing to insufficient evidence, resection cannot currently be recommended over locoregional therapies or vice versa for patients with cirrhosis and multiple tumours when resection is feasible after multiparametric assessment **(LoE 2, weak recommendation).**	100%
In properly trained centres, liver resection should be performed via laparoscopic or minimally invasive approaches whenever feasible, especially for tumours in anterolateral and superficial locations **(LoE 3, strong recommendation).**	100%
Neoadjuvant therapies should only be considered in the context of prospective studies, as evidence of a survival advantage with pre-surgical treatments is lacking **(LoE 3, strong recommendation).**	100%
Patients who achieve downsizing/downstaging after locoregional treatment should be considered for liver resection or transplantation **(LoE 2, strong recommendation).**	100%
Patients who achieve downsizing/downstaging after systemic treatment may also be considered for liver resection or transplantation, preferably in prospective studies **(LoE 3, weak recommendation).**	92%
Adjuvant treatment after resection or ablation is not recommended **(LoE 2, strong recommendation).**	95%
Resected patients with pathological findings associated with a high risk of recurrence other than Milan criteria (*i.e.*, satellites, micro-vascular invasion, poor differentiation) may be considered for liver transplantation if a predicted transplant benefit in survival can be shown and adequate observation time (>6 months) has elapsed **(LoE 4, weak recommendation).**	91%
Liver resection should not be considered as a downstaging procedure for HCC beyond Milan criteria to meet liver transplantation eligibility criteria **(LoE 4, strong recommendation).**	83%
Patients with HCC within Milan criteria who are unsuitable for resection (due to tumour location, marginal liver function or other liver-related contraindications) should be considered for liver transplantation. An ablate-and-wait strategy can be recommended for solitary HCC ≤2 cm **(LoE 2, strong recommendation).**	96%
Patients with HCC beyond the transplant criteria adopted by each centre should be considered for liver transplantation after successful downstaging to within Milan criteria. Patients who do not achieve downstaging are poor candidates for liver transplantation **(LoE 2, strong recommendation).**	96%
The choice of downstaging strategies should be based on patient and tumour characteristics and no single locoregional procedure is recommended over the others. There is insufficient evidence to recommend systemic therapy as a downstaging treatment **(LoE 3, strong recommendation).**	96%
AFP >1,000 ng/ml should be considered an absolute contraindication to liver transplantation regardless of tumour burden. Patients downstaged to within Milan criteria should have an AFP level ≤1,000 ng/ml for at least 3 months before they are listed **(LoE 3, strong recommendation).**	95%
Pre-transplant locoregional therapies should be considered, if not contraindicated due to liver dysfunction, in patients who will likely remain on the waitlist for >6 months **(LoE 4, strong recommendation).**	100%
Prioritising a cadaveric graft allocation for patients with or without HCC within a common waitlist is complex, and no system can serve all regions. Prioritisation criteria for HCC should at least include tumour burden, AFP, waiting time and response to tumour treatment **(LoE 4, strong recommendation).**	100%
Transplant benefit for patients with HCC should be considered in combination with the conventional transplant principles of urgency and utility in the allocation policies of donated organs in each region **(LoE 4, strong recommendation).**	100%
Living donor liver transplantation should be considered for selected patients with HCC, if performed in experienced centres according to the local context of waitlist time and providing adherence to donor-recipient double equipoise principles **(LoE 3, strong recommendation).**	100%
Any approach aimed at widening the availability of liver grafts (*e.g.* marginal cadaveric grafts from donation after brain death or cardiac death, the use of machine perfusion and dynamic preservation techniques) should be considered in patients with HCC **(LoE 3, strong recommendation).**	96%
In candidates for TACE, DEB-TACE and cTACE should be considered equivalent **(LoE 2, strong recommendation).**	100%
In candidates for TACE, bland TAE should be considered an alternative to cTACE or DEB-TACE **(LoE 1, strong recommendation).**	75%
Radiation segmentectomy can be considered an alternative to percutaneous ablation for single tumours within Milan criteria that are unsuitable for resection or transplantation, when there is a significant risk of post-ablation recurrence based on size (>3 cm) or location (v.g. in contact with large vessels) **(LoE 3, weak recommendation).**	96%
EBRT can be considered an alternative to percutaneous ablation for single tumours within Milan criteria unsuitable for resection or transplantation, when there is a significant risk of post-ablation recurrence based on size (>3 cm) or location (v.g. in contact with large vessels) **(LoE 4, weak recommendation).**	88%

(*continued on next page*)

(*continued*)

Recommendation	Consensus
SIRT can be considered an alternative to TACE in patients with a single HCC unsuitable for thermal ablation or recurrent after ablation, particularly when the intention is to bridge to transplant or facilitate a subsequent liver resection in patients with initially unresectable HCC **(LoE 3, weak recommendation).**	96%
EBRT can be considered an alternative to TACE in selected patients with single unresectable tumours which are unsuitable for thermal ablation or recurrent after ablation. Patients most likely to benefit from EBRT are those at high risk of complications from TACE/TAE **(LoE 3, weak recommendation).**	83%
In candidates for TACE, there is insufficient evidence in Western patients to support the combination of EBRT and TACE in favour of TACE alone. Therefore, combination therapy is not recommended. **(LoE 3, strong recommendation).**	96%
In patients with lesions not showing a response to one or two consecutive TACE treatments and with preserved liver function other therapies should be considered **(LoE 3, strong recommendation).**	100%
TACE/TAE should be preferred to systemic therapy for liver-confined disease when a selective approach is possible (based on low tumour size and number, no infiltrative gross appearance, and preserved portal flow) **(LoE 4, strong recommendation).**	96%
Neither prognostic nor predictive scores should be used to support clinical decision-making between embolic and systemic therapy, though these scores may be useful for identifying those patients unlikely to derive meaningful benefit from either **(LoE 3, strong recommendation**	96%
In patients with multiple tumours in the intermediate stage who are not fit for TACE/TAE or surgery, SIRT cannot currently be recommended as an alternative to systemic therapy, although it is an acceptable option if systemic therapy is contraindicated, provided a lobar approach is possible **(LoE 4, weak recommendation).**	92%
In patients in the advanced stage due to segmental or lobar portal vein invasion but free from extrahepatic spread, EBRT cannot currently be recommended as an alternative to systemic therapy with immune checkpoint-based combinations, and there is limited data to recommend EBRT or the combination of EBRT with TKIs in preference to TKIs alone **(LoE 3, weak recommendation**	90%
In patients in the advanced stage due to segmental or lobar portal vein invasion but free from extrahepatic spread, SIRT is not recommended as an alternative to systemic therapy **(LoE 3, strong recommendation).**	86%
In patients in the intermediate stage with a large tumour burden, intra-arterial therapy (TACE/TAE or SIRT) should not be combined with systemic therapy using TKIs. There is insufficient evidence to provide a recommendation for the combination of intra-arterial therapy (TACE/TAE or SIRT) with immunotherapy using checkpoint inhibitors **(LoE 2, strong recommendation).**	82%
In patients with advanced HCC, preserved liver function (Child-Pugh A) and ECOG performance status 0-1, combinations including at least one PD-1 or PD-L1 inhibitor should be offered, provided there are no contraindications **(LoE 1, strong recommendation).**	100%
The choice of systemic therapy should not be influenced by aetiology **(LoE 1, strong recommendation).**	100%
Following discontinuation of the combination of ICI-based combinations due to tumour progression or treatment-related adverse events, TKIs can be considered in selected patients **(LoE 4, weak recommendation).**	100%
Patients with decompensated cirrhosis should not be routinely treated with systemic therapy outside a prospective clinical trial. However, systemic therapy may be considered in carefully selected patients with mild liver impairment (Child-Pugh 7-8) **(LoE 3, weak recommendation).**	100%
In patients with recurrent disease following transplantation, which is not amenable to surgical or locoregional therapy, systemic therapy with sorafenib or lenvatinib can be considered. ICIs are not recommended in view of the risk of organ rejection **(LoE 4, weak recommendation).**	100%
In patients demonstrating a sustained response to systemic therapy, an isolated site of disease progression may be treated with local therapy while continuing systemic therapy **(LoE 5, weak recommendation).**	95%
The consequences of discontinuing ICIs in those patients with a sustained response are currently unknown. The decision to discontinue can be made in discussion with the patient based on available knowledge of risks and benefits **(LoE 4, weak recommendation).**	100%
In the absence of an evidence-based subsequent therapy, a patient may continue systemic therapy beyond progression if the patient is perceived to be deriving ongoing clinical benefit **(LoE 3, weak recommendation).**	87%
RECIST v1.1 should be the primary means by which to assess response in clinical trials evaluating systemic therapy. mRECIST and iRECIST can be reported as secondary assessments where appropriate **(LoE 1, strong recommendation).**	92%
Overall survival should remain the primary endpoint for randomised-controlled trials in advanced HCC **(LoE 1, strong recommendation).**	100%

Abbreviations

AASLD, American Association for the Study of Liver Diseases; ADC, apparent diffusion coefficient; BCLC, Barcelona Clínic Liver Cancer; CPGs, Clinical Practice Guidelines; CT, computed tomography; DAA, direct-acting antivirals; DCP, des-gamma carboxy-prothrombin; EASL, European Association for the Study of the Liver; EBRT, external beam radiation therapy; ECA, extracellular contrast agents; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HKLC, Hong-Kong Liver Cancer; HOPE, hypothermic oxygenated machine perfusion; HR, hazard ratio; HVPG, hepatic venous pressure gradient; ICIs, immune checkpoint inhibitors; LR, liver resection; LT, liver transplant(ation); MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MDT, multidisciplinary team; MELD, model for end-stage liver disease; MILS, minimally invasive liver surgery; mRECIST, modified RECIST; MRI, magnetic resonance imaging; NUCs, nucleoside/nucleotide analogues; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PHLF, post-hepatectomy liver failure; RCT, randomised-controlled trial; RFS, recurrence-free survival; RR, relative risk; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy; TAE, transarterial embolisation; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation; TKIs, tyrosine kinase inhibitors; TTP, time-to-progression; UNOS, United Network for Organ Sharing; VEGF, vascular endothelial growth factor.

Conflict of interest

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

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Supplementary data

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